Kurdistan Regional Government- Iraq

Ministry of Higher Education & Scientific Research

Salahaddin University – Erbil

Directorate of Higher Education & Postgraduate Studies

Education College

Chemistry Department

Role of Omega-3 Fatty acid in Cardio Vascular diseases

A Review Article in (Biochemistry)

Prepared by:

Hardam Mohammed Salih Hasan

Supervised by:

Asst. Prof. M. Lutfiaa Mohammed Hassan

(2023-2024)

Role of Omega-3 Fatty acid in Cardio Vascular diseses

[a] Hardam Mohammed Salih Hasan, [b] Lutfia Mohammed Hassan

[a] Chemistry Department, Education College, Salahaddin University -Erbil,
hardam.salih@su.edu.krd

[b] Chemistry Department, Education College, Salahaddin University -Erbil,
Lutfia.hasan@su.edu.krd

Abstract

Cardioceuticals are dietary supplements that encompass essential nutrients such as vitamins, minerals, omega-3 fatty acids, and antioxidants like alpha-lipoic acid in balanced proportions. These supplements offer comprehensive cardiovascular protection by mitigating common risk factors for cardiovascular disease, including elevated levels of low-density lipoprotein cholesterol and triglycerides, as well as factors contributing to blood coagulation. Omega-3 fatty acids, in particular, have been demonstrated to significantly lower the risk of sudden death due to cardiac arrhythmias and reduce overall mortality in individuals with known coronary heart disease. They are also effective in treating hyperlipidemia and hypertension, without notable drug interactions. The American Heart Association advises individuals without a history of coronary heart disease to consume two servings of fish per week, while those with known coronary heart disease should consume at least one serving of fish daily.

A daily intake of roughly 1 gramme of both docosahexaenoic acid and eicosapentaenoic acid is advised for cardiovascular protection; greater dosages (2-4 grammes per day) are needed to lower increased triglyceride levels.

Keywords: CVD Cardiovascular disease, Omega3 fatty acids, Eicosopentaenoic acid, Docosahexaenoic acid.

Contents

1. Introduction

Omega-3 (Ω-3) fatty acids, also known as polyunsaturated fatty acids (PUFAs), can be found in plants, animals, and marine sources. These fatty acids are crucial for various metabolic activities, but mammals are unable to produce them internally (Harris *et al.*, 2008). The distinguishing factor of Ω-3 fatty acids is the existence of a double bond located three carbon atoms away from the omega (methyl) end of the molecule (Reimers and Ljung, 2019). Omega-3 fatty acids consist of both short-chain and long-chain forms. Plants generate short-chain Ω-3 fatty acids, including linoleic acid (18:2n-6) and alpha-linolenic acid (ALA; 18:3n-3), which can be found in nuts, seeds, and seed oils (Shahidi and Ambigaipalan, 2018). Mammals lack the ability to synthesize α-linolenic acid or linoleic acid. Long-chain fatty acids, such as DHA (20:6n-3) and EPA (20:5n-3), are mostly obtained from fatty fish species such as mackerel, halibut, herring, salmon, and tuna (Bradberry and Hilleman, 2013), These fatty acids, as a group, are referred to as marine n-3 fatty acids (Calder, 2015). Due to the absence of the required enzymes in mammalian cells, the formation of a double bond at the Ω-3 and Ω-6 locations is not possible. As a result, these fatty acids are classified as essential and need to be acquired from the diet (Calvo *et al.*, 2017).

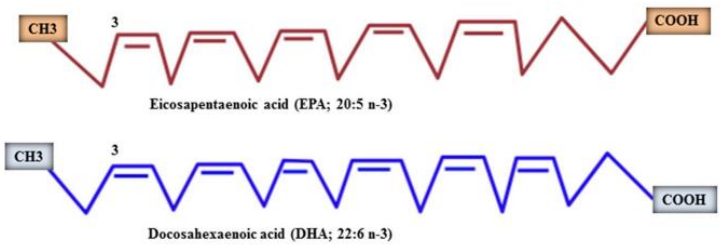

Fig1. The molecular makeup of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), the two most significant Ω-3 fatty acids

Fish oil dietary supplements (DS) are readily available over-the-counter at pharmacies and other retail establishments throughout the United States. They consist of the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The American Heart Association (AHA) advises those with elevated triglyceride levels to eat 2-4 grams of DHA and EPA daily (Kris-Etherton, Harris and Appel, 2002). as well as prescription At a dose of 4 g/day, OM3FA products are recommended as a dietary supplement to patients with severe

hypertriglyceridemia (500 mg/dL) should have reduced triglyceride levels (Sperling and Nelson, 2016).

Many patients choose to use fish oil dietary supplements instead of prescription omega-3 fatty acid (OM3FA) drugs, and certain managed care organizations may even deny coverage for prescription OM3FA products unless the patient has previously experienced unsuccessful results with fish oil dietary supplements. While DS (dietary supplements) are readily accessible, they are not regulated as pharmaceuticals and are not available without a prescription. Consequently, their safety, efficacy, and quality remain uncertain.. (Hilleman and Smer, 2016). To achieve the desired levels of OM3FAs recommended by healthcare professionals or the American Heart Association, patients may be required to consume ten or more capsules of fish oil dietary supplements per day. However, this might potentially cancel out any perceived cost benefits compared to prescription drugs and result in higher consumption of saturated fats and oxidized lipids (Zargar and Ito, 2011).

Cardioceuticals refer to dietary supplements that enhance and protect the heart. Vitamins provide antioxidant properties that are beneficial for the heart. However, it is important to note that they do not offer comprehensive cardioprotection. This level of protection is provided by cardioceuticals. This is accomplished by reducing cholesterol levels, avoiding the formation of blood clots in the walls of the arteries, enhancing the delivery of oxygen, limiting oxidation, and maintaining a normal heartbeat. Cardioceuticals must address substantial risk factors such as reactive oxygen species effects, oxidative damage, and low-density lipoprotein (LDL) cholesterol levels. In persons suffering from cardiovascular disease, they mitigate the risk of sudden death, myocardial infarctions, arrhythmias, and cerebrovascular accidents. These dietary supplements can inhibit the progression of atherosclerotic plaque formation (Jain, 2015).

Cardiovascular disease (CVD) is the primary cause of death globally, responsible for over 75% of fatalities in low- and middle-income countries, as reported by the World Health Organization. Genetic and epidemiologic research provides evidence that high levels of triglycerides (TG) are a significant risk factor for cardiovascular disease (CVD). It has been observed that the penetration of TG and TG-rich lipoproteins (TGRL) into the intimal space is linked to the initiation and progression of atherosclerotic plaque formation (Fig. 2). Even after accounting for other risk variables, it is challenging to determine the extent to which TGs serve as a distinct risk factor. Mendelian genetic studies may not always provide definitive evidence of causal relationships due to the potential for polymorphisms to have complex or counteracting impacts on the progression of the disease. Furthermore, fenofibrates and niacin, which are

commonly used medications, have not been successful in reducing the risk of cardiovascular disease in patients who are already being treated with statins, even if they effectively cut triglyceride levels (Mason, Sherratt and Eckel, 2023).

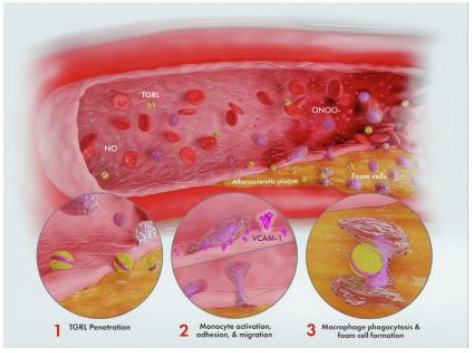

Fig. 2. Triglyceride-rich lipoproteins, or TGRLs, have atherogenic pathways.

2. History

The identification of the significance of polyunsaturated fatty acids (PUFA) for human health occurred in the start of the 20th century and continues to be relevant today. A significant scientific connection between the initial group of researchers studying "vitamin F" and the present generation of professionals in the field of "omegas" can be attributed to the late biochemist Ralph Holman (Leaf, 2008).

Initial evidence suggesting the potential benefits of fish oil fatty acids for coronary heart disease came from the observation that Greenland Eskimos, who consume a diet rich in n-3 fatty acids, experience a reduced mortality rate from coronary heart disease compared to Danes and Americans. Human diets rely on two categories of extended-chain polyunsaturated fatty acids: n-3 fatty acids, present in marine vertebrates, and n-6 fatty acids, present in plant seeds. Further proof of the positive effects of omega-3 fatty acids on health is provided by a study conducted in 1989. The study revealed that individuals who had recently experienced a heart attack and consumed fish oil had a 29% reduced risk of fatal ventricular arrhythmias (Leaf, 2008).

3.Types and Structures of Omega-3 fatty acid

Omega-3 fatty acids, which are polyunsaturated fatty acids, have a double bond located three carbons away from the methyl end of the carbon chain. The three predominant types of omega-

3 fatty acids found in food are docasahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and alpha linolenic acid (ALA) (Bultosa, 2015).

Alpha linolenic acid (ALA) is a compound consisting of an 18-carbon chain with three cis double bonds. The initial one is located in the omega-3 position, specifically the third carbon atom counting from the methyl end.

Eicosapentaenoic acid (EPA) is a 20-carbon fatty acid that contains five cis double bonds. The first double bond is located in the omega-3 position, specifically the third carbon from the methyl end.

Docasahexaenoic acid, also known as DHA, is a 22-carbon molecule that contains six cis double bonds. The initial double bond is located at the omega-3 position, specifically the third carbon from the methyl end.

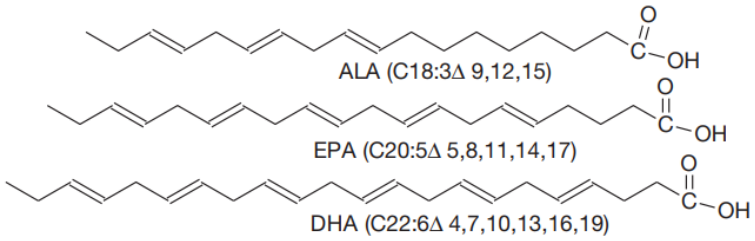

Fig 3. ALA, EPA, and DHA are the three omega-3 fatty acids' chemical structures.

4. Source of Omega-3

The optimal daily dosage of omega-3 fatty acids for promoting and sustaining good health is between 200 mg to 1 g. Although lower amounts of omega-3 fatty acids possess antioxidant capabilities, greater concentrations can lead to oxidative damage. Flaxseed, canola oil, almonds, and fatty fish are the main dietary sources of ALA, which acts as a precursor for the synthesis of long chain PUFAs in the human body. Seafood, including fish, contains larger amounts of omega-3 fatty acids compared to other types of food. However, the levels of these fatty acids differ among species. In standard fish oil, omega-3 fatty acids constitute around 30% of the total fatty acid content (Punia et al., 2019).

Plant-based sources of omega-3 fatty acids, denoted as Ω-3, include soybean, flaxseed, chia, hemp, linseed, rapeseed (canola oils), and tree nuts. Alpha-linolenic acid is the primary form of omega-3 fatty acids that is present in plants. Substituting preformed $\mathscr{L}$-3 EPA and DHA with plant-based $\mathscr{L}$-3 is not advised since plant $\mathscr{L}$-3 has little ability to convert into these two crucial fatty acids. Additional research is required to fully understand the role of plant-based omega-3

fatty acids and their potential health benefits. Algae, for example, naturally contains omega-3 fatty acids (EPA and DHA) and may serve as a sustainable supply of these nutrients (Mozaffarian and Wu, 2011).

5. Metabolism

ALA, the least intricate member of the physiologically active fatty acid group, undergoes limited metabolism to the more biologically potent EPA and DHA. The conversion of linoleic acid to arachidonic acid and ALA acid to EPA is competitive due to the involvement of the same enzymes. The small intestine produces bile, which emulsifies fat to facilitate its digestion and absorption. ALA, triglycerides from various meals are consumed, hydrolyzed, and then absorbed and transported to bodily tissues through plasma in the small intestine (Punia et al., 2019).

Afterwards, they undergo oxidation to produce ATP. Additionally, esterification takes place, involving triglycerides and phospholipids, which are crucial for the structure and function of omega-6 and omega-3 fatty acids. Finally, longer and saturated chain molecules are produced (Fig. 3). The primary omega-3 fatty acid is ALA, which is found in plant oils. It is then followed by DHA and EPA, which are found in marine oils. Mammals consume ALA, a shorter chain fatty acid with 3 double bonds and 18 carbons, which they can subsequently convert into EPA, a fatty acid with 20 carbons and 5 double bonds, as well as DHA, a fatty acid with 22 carbons and 6 double bonds (Punia et al., 2019).

The desaturase enzyme in humans competes with omega-6 and omega-3 fatty acids, hence decreasing the effectiveness of converting ALA to EPA and DHA. However, DHA remains necessary for optimal brain function. Additionally, their research findings indicate that EPA and DPA aid in the transformation of ALA in the diet into DHA. Stearidonic acid is the initial product generated by the Δ6-desaturase enzyme when it metabolizes ALA. It can then be extended to become eicosatetraenoic acid. The Δ5-desaturase enzyme is utilized to further desaturate the mixture, resulting in the production of eicosapentaenoic acid (EPA) and docosapentaenoic acid (DPA).

Desaturation and elongation processes occur in the formation of several omega-3 fatty acids when ALA is converted to DHA (Fig. 4). The speaker explains that desaturase enzyme synthesizes docosahexaenoic acid (DHA) by catalyzing the desaturation of docosapentaenoic acid (DPA) at the Δ-4 position. In addition, elongase has the ability to extend it to tetracosapentaenoic acid, whereas desaturase can introduce unsaturation to form tetracosahexenoic acid. Peroxisomal oxidation subsequently transforms it into DHA. After

being consumed, ALA undergoes a slower conversion into EPA and DHA. (Figs. 5 and 6) (Punia et al., 2019).

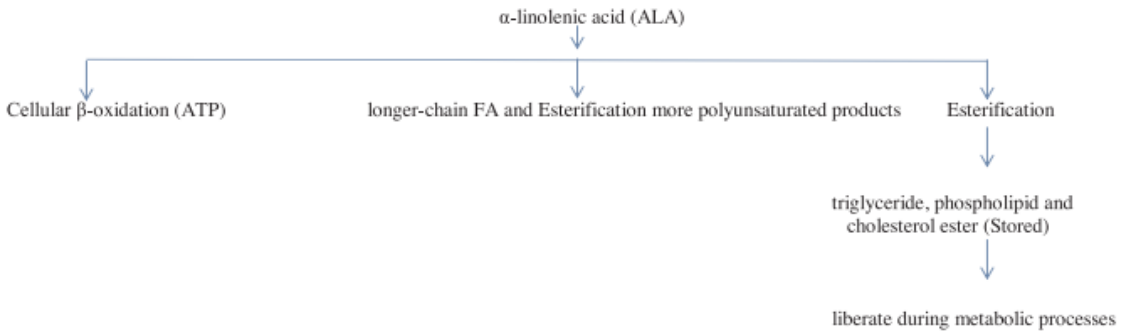

Fig. 4. ALA fatty acids Metabolism

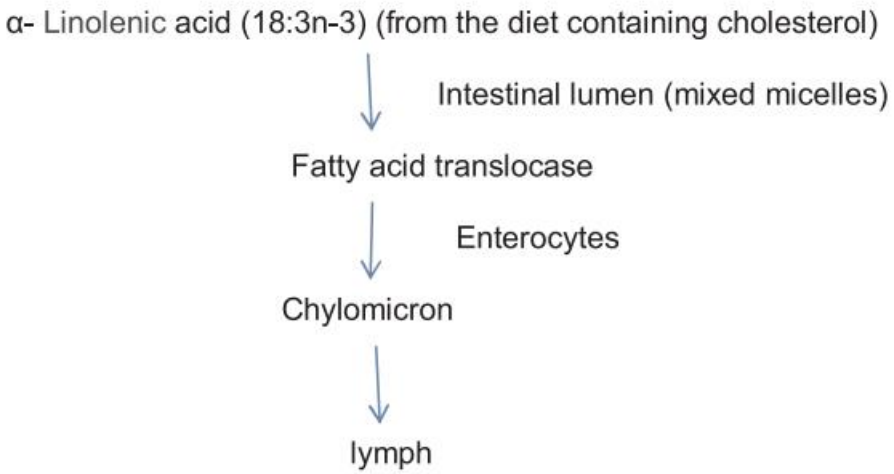

Fig. 5. ALA fatty acids Absorption.

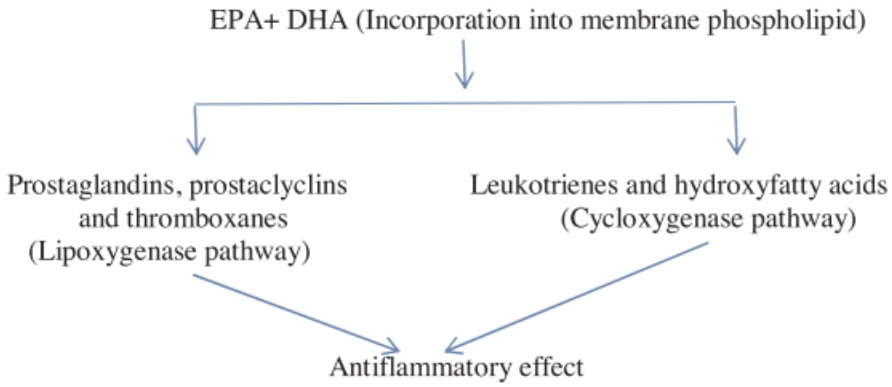

Fig. 6. Anti-inflammatory mechanism of eicosanoids.

6. Bio Availability

Various vegetable oils, such as chia, perilla, linseed, and walnut oils, include the primary polyunsaturated oil ALA, albeit in lesser amounts. Previously, it was believed that consuming sufficient amounts of ALA might provide the necessary long-chain omega-3 fatty acids. Bioavailability refers to the extent and speed at which a substance is absorbed by the digestive system and enters the portal circulation. However, based on the existing facts, it is necessary to challenge this assumption because there is little conversion of ALA into the physiologically essential LC n−3 FA, specifically eicosapentaenoic acid (EPA, 20:5n−3) and docosahexaenoic acid (DHA, 22:6n−3) (Schuchardt and Hahn, 2013).

Many factors influence the bioavailability of long chain n−3 FA. The concurrent consumption of food, particularly its fat content, and the presence of other components influence the uptake of LC n−3 FA in addition to the type of chemical connection. For instance, calcium ions and FFA can combine to form a complex that lowers the availability of FFA. (Schuchardt and Hahn, 2013). The forms in which omega-3 fatty acids are found—ethyl ester (EE), triacylglycerides (TAG), phospholipid (PL), and free fatty acids (FFAs)—have an impact on their bioavailability. Diets richer with the ester form of omega-3 fatty acids have lower bioavailabilities than FFA. LC n−3 FA availability is dependent on numerous factors. Generally speaking, ethylesters of long chain n−3 FA can be used less successfully than triacylglyceride-bound versions (Schuchardt and Hahn, 2013).

Following ingestion, enzyme activity lowers the content of ALA intracellularly and releases dihydrolipoic acid (DHLA) into the extracellular milieu (Bilska and Wlodek, 2005). Research findings indicate that the β-oxidation pathway has a significant impact on the body's overall utilization of ALA. The high rate of oxidation of ALA has been seen to lead to restricted bioavailability 85% of the ingested ALA has disappeared. DHA, in contrast, is considerably more readily available but is not efficiently utilized as a substrate for beta-oxidation activities in mitochondria and peroxisomes(Libinaki and Gavin, 2017).

The positioning of fatty acids on the glycerol molecule of triglycerol affects their ability to be absorbed and utilized by the body. The sn-2 location is the most desirable due to its higher absorbability, leading to increased bioavailability(Tengku-Rozaina and Birch, 2013).

It was shown that the body stores twice as much DHA (86%) compared to ALA (30%) from the overall intake. After consuming ALA, the body expelled 59% of the ALA, stored 21.2% of it, eliminated 0.4%, and recognized long chain derivatives (EPA, DPA, and DHA) of the total ALA (Poumès-Ballihaut *et al.*, 2001).

Milk is notable for its excellent bioavailability because its fat is distributed in tiny micelles. The reduced dimensions of fat globules in homogenized bovine milk, with an average size ranging from 1 to 3 μm, might enhance the absorption and accessibility of lipid-soluble compounds such as vitamin E and omega-3 fatty acids (Visioli et al., 2000). Empirical data suggests that omega-3 fatty acids derived from fish are more effectively incorporated into plasma lipids in comparison to their consumption in the form of capsules. Moreover, there is a clear correlation between the consumption of EPA and DHA through capsules and the subsequent elevation of their levels in the bloodstream.(Visioli *et al.*, 2003).

7. Comparetive Biophysical and Antioxidant properties of omega-3 Fatty acid

The specific cellular effects of EPA and DHA are governed separately and indirectly by the length of their hydrocarbon chains and the number of double bonds they possess. Compared to EPA, DHA has a total of two additional carbon atoms and six additional double bonds. The structural characteristics of these two fatty acids influence their interaction with the surrounding membrane lipids, which might potentially modify the creation of membrane lipid rafts and signal transduction pathways (Figure 7). Due to its long hydrocarbon chain and many double bonds, EPA assumes an elongated conformation when it integrates into lipoprotein particles and cellular membranes, as per the EPA's adoption. The presence of conjugative resonance stabilization in EPA allows for the stabilization of unpaired electrons across many conjugated double bonds. This structural characteristic enables EPA to effectively scavenge reactive oxygen species (ROS). The number is 36. Patients with elevated triglycerides who were given prescription EPA (2–4 g/d) had dramatically reduced plasma levels of oxLDL compared to those who got a placebo. Oxidative modification of LDL can potentially contribute to the development of vascular inflammation, impaired functioning of the endothelium, and other factors involved in the formation of atherosclerotic plaques. Oxidatively modified LDL, rather than native LDL, has the ability to stimulate the formation of foam cells (Mason, Libby and Bhatt, 2020)

Elevated levels of oxLDL and other lipid oxidation products are associated with heightened risks of myocardial infarction, vascular surgeries, metabolic syndrome, and the severity of acute coronary syndromes. In laboratory trials, EPA demonstrates strong antioxidant effects in model membranes and different lipoprotein particles that contain apolipoprotein B. This sets it apart from other substances that likewise reduce triglyceride levels. EPA's shorter carbon chain and lower number of double bonds enable it to exhibit longer-lasting antioxidant activity in

comparison to DHA. DHA has a tendency to interact with the phospholipid head group region in the hydrocarbon core of the membrane, causing disorder. On the other hand, EPA takes on a stretched orientation within cell membranes. The antioxidant effects of EPA are especially evident in the presence of hyperglycemia, which promotes the generation of reactive oxygen species (ROS) and carbonyl species. In addition, the antioxidant effects of EPA are increased in laboratory conditions when an active metabolite of atorvastatin is present. This leads to enhanced interactions with cell membranes, which in turn stabilizes free radicals in a way that is either synergistic or additive, unlike DHA which does not display this effect (Mason, Libby and Bhatt, 2020).

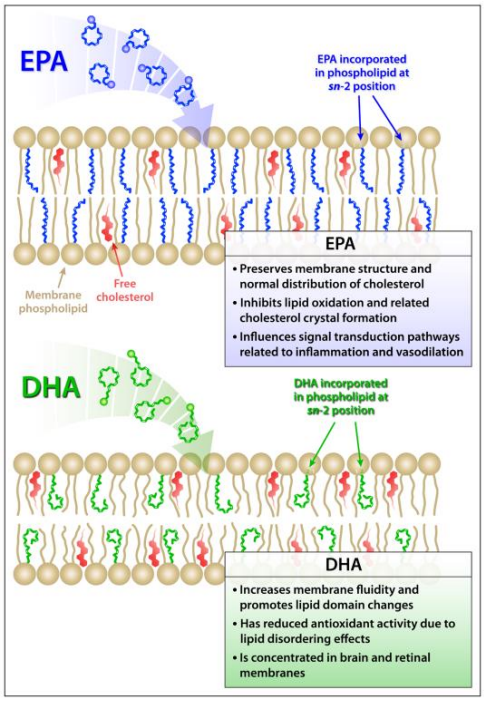

Fig 7. Omega-3 fatty acid interactions with molecular membranes.

8. Health benefits

Multiple epidemiological studies have demonstrated a correlation between the consumption of a diet abundant in omega-3 fatty acids (FA) and a decrease in the likelihood of developing cardiovascular illnesses, specific types of cancer, inflammation, high blood pressure, and the promotion of children's health. This evidence has generated a heightened interest in integrating omega-3-rich foods into dietary practices. Due to the health benefits associated with omega-3 fatty acids, it is advisable to increase the consumption of ALA in one's diet. Table 1 provides a concise overview of the interconnected health benefits.

Table 1 α-Linolenic acid (ALA) Health benefits.

Health benefits	Reference
(CV) Cardiovascular benefits	(Mason, Sherratt and Eckel, 2023)
Hypertension	(Colussi *et al.*, 2016)
Maternal and Child health	(Best *et al.*, 2016)
Blood cholesterol	(Zibaeenezhad *et al.*, 2017)
Cancer	(Theinel *et al.*, 2023)
Anti-inflammatory	(Akerele and Cheema, 2016)

8.1 Cardiovascular diseases

The main factors contributing to coronary heart disease (CHD), which is the leading cause of death worldwide and a detrimental mental condition, are currently food patterns, heredity, and modern way of life. The potential advantage of including long-chain omega-3 polyunsaturated fatty acids (omega-3 PUFA) dietary supplements to prevent cardiovascular disease (CVD) has been a topic of vigorous discussion in recent years. The pioneering British scientist, Sinclair, was the first to propose the preventive impact of omega-3 fatty acids in reducing the occurrence of coronary heart disease (CHD). Research conducted on Greenland Inuits, who have a higher intake of fish oil, has yielded data supporting this advantage.

In addition, several researchers have undertaken pioneering research on Greenland Eskimos, which suggests that a high intake of EPA and DHA may protect them against congestive heart failure. Flaxseed is an excellent source of polyunsaturated fatty acids (PUFA) and possesses qualities that protect the heart. The findings of the Gruppo Italiano per lo Studio della Sopravivenza nel'Infarto Miocardico (GISSI)-Prevenzone trial, initially released in 1999, demonstrated a reduced risk of the primary combined outcome of mortality, non-fatal myocardial infarction (MI), and stroke in a cohort of individuals who had recently experienced a MI and were randomly allocated to receive treatment with omega-3 polyunsaturated fatty acids (PUFA) (850 mg/d EPA + DHA as ethyl esters). The primary focus of study has been on

EPA and DHA due to their shown ability, as shown by several studies undertaken by researchers, to reduce the risk of cardiovascular disease. (Vedtofte *et al.*, 2014).

Kaur et al. conducted a substantial clinical trial in which more than a thousand patients were administered a daily dose of 1 g of omega-3 fatty acids (FAs). The findings demonstrated a significant decrease in mortality (20%), cardiovascular ailments (30%), and heart failure (45%). Omega-3 fatty acids exert their inhibitory effects by lowering circulating triacylglycerol levels, platelet activity, and the generation of adhesion vascular molecules (Vanschoonbeek, de Maat, & Heemskerk, 2003). Furthermore, it has been discovered that omega-3 fatty acid-enriched triacylglycerol is effectively removed from the bloodstream, showing reduced reliance on apolipoprotein E-dependent pathways and lipoprotein lipase activity for its elimination (Qi *et al.*, 2002).

On an practical result, Bowen et al. (Bowen, Harris and Kris-Etherton, 2016) It has been determined that omega-3 fatty acids reduce the risk of coronary heart disease and overall mortality. The 2016 guidelines for cardiovascular disease prevention by the European Atherosclerosis Society and European Society of Cardiology (Piepoli *et al.*, 2016) stated that the question of whether omega-3 FAs have a protective impact is up for debate, and the 2016 guidelines for managing dyslipidemia (Catapano *et al.*, 2016) suggested that additional data was required to support the prescription of omega-3 FA supplements in order to demonstrate their effectiveness in preventing clinical consequences.

In contrast, the American Heart Association recommende (Siscovick *et al.*, 1995) Individuals who have a past medical record of coronary heart disease (CHD), heart failure, and decreased ejection fractions are highly suitable candidates for the use of omega-3 fatty acids (FA) as a preventive measure against CHD. The present meta-analysis's results, however, do not endorse the suggestions to administer 1 g/d of omega-3 fatty acids to individuals with a previous history of coronary heart disease (CHD) as a preventive measure against vascular events, such as nonfatal myocardial infarction (MI) and fatal CHD. Additional trial findings are necessary to ascertain the impact of higher dosages (3-4 g/d) of omega-3 fatty acids on the risk of major vascular events.As reported by Abbasi (Abbasi, 2018) and Aung et al. (Aung et al., 2018) Omega-3 fatty acids have not shown any therapeutic effects in preventing death from coronary heart disease or any other form of heart disease in individuals with a history of vascular sickness. The current definition of the Omega-3 Index includes the presence of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) in erythrocytes, but excluding docosapentaenoic acid (DPA). DPA, similar to EPA and DHA, is present in fish and various

fish oils. However, it is challenging to find sources that are rich in DPA. The Omega-3 Index refers to the proportion of eicosapentaenoic acid (EPA) and docasahexaenoic acid (DHA) present in erythrocytes (RBCs) (von Schacky and Harris, 2018). Von Schacky and Harris proposed the idea (Harris and Von Schacky, 2004) In 2004, a new risk factor for cardiovascular events, including sudden cardiac death, was discovered. Individuals with either elevated or normal cholesterol levels. Choi and Kim (Kim HyeKyeong and Choi Haymie, 2001) During an in vivo study, the subjects were given corn oil, perilla oil, and fish oil. The results showed that consuming ALA through diet led to a decrease in lipid levels after a meal, while increasing the levels of DHA and EPA.

9. Conclusion

Omega3 (FA) faty acids play a crucial role in the health of human, particularly in cardiovascular protection. While essential for various metabolic processes, they can't be synthesized by mammals, necessitating dietary intake. Fish oil dietary supplements are widely available as sources of omega 3- fatty acids, yet concerns persist regarding their purity, efficacy and adherence to stated content.

Cardioceutical, which encompass omega 3- fatty acids among other nutrients, offer comprehensive heart protection, addressing various risk factors associated with cardiovascular disease. Despite advancements in station therapy for reducing LDL cholesterol levels, residual cardiovascular risk remains, often linked to elevated triglycerides. Omega-3 fatty acid, particularly EPA and DHA, have shown promise in mitigating this risk, though outcomes vary depending on formulation and dosage.

Further research into the distinct biological actions of EPA and DHA may offer new insights into cardiovascular disease prevention and treatment strategies.

10. References

Abbasi, J. (2018) 'Another nail in the coffin for fish oil supplements', *JAMA*, 319(18), pp. 1851–1852.

Akerele, O.A. and Cheema, S.K. (2016) 'A balance of omega-3 and omega-6 polyunsaturated fatty acids is important in pregnancy', *Journal of Nutrition & Intermediary Metabolism*, 5, pp. 23–33.

Aung, T. *et al.* (2018) 'Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77 917 individuals', *JAMA cardiology*, 3(3), pp. 225–233.

Best, K.P. *et al.* (2016) 'Omega-3 long-chain PUFA intake during pregnancy and allergic disease outcomes in the offspring: a systematic review and meta-analysis of observational studies and randomized controlled trials', *The American journal of clinical nutrition*, 103(1), pp. 128–143.

Bilska, A. and Wlodek, L. (2005) 'Lipoic acid-the drug of the future', *Pharmacol Rep*, 57(5), pp. 570–577.

Bowen, K.J., Harris, W.S. and Kris-Etherton, P.M. (2016) 'Omega-3 fatty acids and cardiovascular disease: are there benefits?', *Current treatment options in cardiovascular medicine*, 18, pp. 1–16.

Bradberry, J.C. and Hilleman, D.E. (2013) 'Overview of omega-3 fatty acid therapies', *Pharmacy and Therapeutics*, 38(11), p. 681.

Bultosa, G. (2015) *Functional Foods: Overview*. 2nd edn, *Encyclopedia of Food Grains: Second Edition*. 2nd edn. Elsevier Ltd. Available at: https://doi.org/10.1016/B978-0-12-394437-5.00071-1.

Calder, P.C. (2015) 'Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance', *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids*, 1851(4), pp. 469–484.

Calvo, M.J. *et al.* (2017) 'Omega-3 polyunsaturated fatty acids and cardiovascular health: A molecular view into structure and function', *Vessel Plus*, 1(3), pp. 116–128.

Catapano, A.L. *et al.* (2016) '2016 ESC/EAS guidelines for the management of dyslipidaemias', *Polish Heart Journal (Kardiologia Polska)*, 74(11), pp. 1234–1318.

Colussi, G. *et al.* (2016) ‘Omega-3 polyunsaturated fatty acids in blood pressure control and essential hypertension’, *Update on essential hypertension* [Preprint].

Harris, W.S. *et al.* (2008) ‘Omega-3 fatty acids and coronary heart disease risk: clinical and mechanistic perspectives’, *Atherosclerosis*, 197(1), pp. 12–24.

Harris, W.S. and Von Schacky, C. (2004) ‘The Omega-3 Index: a new risk factor for death from coronary heart disease?’, *Preventive medicine*, 39(1), pp. 212–220.

Hilleman, D. and Smer, A. (2016) ‘Prescription Omega-3 Fatty Acid Products and Dietary Supplements Are Not Interchangeable.’, *Managed care (Langhorne, Pa.)*, 25(1), pp. 46–52.

Jain (2015) ‘441-445’, pp. 441–445.

Kaur, N., Chugh, V. and Gupta, A.K. (2014) ‘Essential fatty acids as functional components of foods-a review’, *Journal of food science and technology*, 51, pp. 2289–2303.

Kim HyeKyeong, K.H. and Choi Haymie, C.H. (2001) ‘Dietary α-linolenic acid lowers postprandial lipid levels with increase of eicosapentaenoic and docosahexaenoic acid contents in rat hepatic membrane.’

Kris-Etherton, P.M., Harris, W.S. and Appel, L.J. (2002) ‘Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease’, *circulation*, 106(21), pp. 2747–2757.

Leaf, A. (2008) ‘Historical overview of n− 3 fatty acids and coronary heart disease’, *The American journal of clinical nutrition*, 87(6), pp. 1978S-1980S.

Libinaki, R. and Gavin, P.D. (2017) ‘Changes in bioavailability of omega-3 (DHA) through Alpha-Tocopheryl Phosphate Mixture (TPM) after oral administration in rats’, *Nutrients*, 9(9), p. 1042.

Mason, R.P., Libby, P. and Bhatt, D.L. (2020) ‘Emerging Mechanisms of Cardiovascular Protection for the Omega-3 Fatty Acid Eicosapentaenoic Acid’, *Arteriosclerosis, Thrombosis, and Vascular Biology*, 40(5), pp. 1135–1147. Available at: https://doi.org/10.1161/ATVBAHA.119.313286.

Mason, R.P., Sherratt, S.C.R. and Eckel, R.H. (2023) ‘Omega-3-fatty acids: Do they prevent cardiovascular disease?’, *Best Practice and Research: Clinical Endocrinology and Metabolism*, 37(3), p. 101681. Available at: https://doi.org/10.1016/j.beem.2022.101681.

Mozaffarian, D. and Wu, J.H.Y. (2011) ‘Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events’, *Journal of the American College of*

Cardiology, 58(20), pp. 2047–2067.

Piepoli, M.F. *et al.* (2016) '2016 European Guidelines on cardiovascular disease prevention in clinical practice', *Polish Heart Journal (Kardiologia Polska)*, 74(9), pp. 821–936.

Poumès-Ballihaut, C. *et al.* (2001) 'Comparative bioavailability of dietary α-linolenic and docosahexaenoic acids in the growing rat', *Lipids*, 36(8), pp. 793–800.

Punia, S. *et al.* (2019) 'Omega 3-metabolism, absorption, bioavailability and health benefits–A review', *PharmaNutrition*, 10(July), p. 100162. Available at: https://doi.org/10.1016/j.phanu.2019.100162.

Qi, K. *et al.* (2002) 'Omega-3 triglycerides modify blood clearance and tissue targeting pathways of lipid emulsions', *Biochemistry*, 41(9), pp. 3119–3127.

Reimers, A. and Ljung, H. (2019) 'The emerging role of omega-3 fatty acids as a therapeutic option in neuropsychiatric disorders', *Therapeutic advances in psychopharmacology*, 9, p. 2045125319858901.

von Schacky, C. and Harris, W.S. (2018) 'Why docosapentaenoic acid is not included in the Omega-3 Index', *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 135, pp. 18–21.

Schuchardt, J.P. and Hahn, A. (2013) 'Bioavailability of long-chain omega-3 fatty acids', *Prostaglandins, leukotrienes and essential fatty acids*, 89(1), pp. 1–8.

Shahidi, F. and Ambigaipalan, P. (2018) 'Omega-3 polyunsaturated fatty acids and their health benefits', *Annual review of food science and technology*, 9, pp. 345–381.

Siscovick, D.S. *et al.* (1995) 'Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest', *Jama*, 274(17), pp. 1363–1367.

Sperling, L.S. and Nelson, J.R. (2016) 'History and future of omega-3 fatty acids in cardiovascular disease', *Current medical research and opinion*, 32(2), pp. 301–311.

Tengku-Rozaina, T.M. and Birch, E.J. (2013) 'Enrichment of omega-3 fatty acids of refined hoki oil', *Journal of the American Oil Chemists' Society*, 90(8), pp. 1111–1119.

Theinel, M.H. *et al.* (2023) 'The effects of omega-3 polyunsaturated fatty acids on breast cancer as a preventive measure or as an adjunct to conventional treatments', *Nutrients*, 15(6), p. 1310.

Vanschoonbeek, K., de Maat, M.P.M. and Heemskerk, J.W.M. (2003) 'Fish oil consumption and reduction of arterial disease', *The Journal of Nutrition*, 133(3), pp. 657–660.

Vedtofte, M.S. *et al.* (2014) 'Association between the intake of α-linolenic acid and the risk of CHD', *British journal of nutrition*, 112(5), pp. 735–743.

Visioli, F. *et al.* (2000) 'Very low intakes of n-3 fatty acids incorporated into bovine milk reduce plasma triacylglycerol and increase HDL-cholesterol concentrations in healthy subjects', *Pharmacological Research*, 41(5), pp. 571–576.

Visioli, F. *et al.* (2003) 'Dietary intake of fish vs. formulations leads to higher plasma concentrations of n− 3 fatty acids', *Lipids*, 38, pp. 415–418.

Zargar, A. and Ito, M.K. (2011) 'Long chain omega-3 dietary supplements: a review of the National Library of Medicine Herbal Supplement Database', *Metabolic syndrome and related disorders*, 9(4), pp. 255–271.

Zibaeenezhad, M.J. *et al.* (2017) 'Comparison of the effect of omega-3 supplements and fresh fish on lipid profile: a randomized, open-labeled trial', *Nutrition & diabetes*, 7(12), p. 1.