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OMEGA-3 FATTY ACIDS AND CARDIOVASCULAR HEALTH: A NARRATIVE REVIEW

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Abstract

Omega-3 polyunsaturated fatty acids (PUFAs) have attracted considerable attention because of their protective effects against cardiovascular disease (CVD), one of the leading causes of morbidity and mortality worldwide. This narrative review provides a comprehensive overview of the role of omega-3 fatty acids in cardiovascular health, with particular emphasis on alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Relevant literature was retrieved from PubMed, Google Scholar, and Sci-Hub to summarize current evidence regarding dietary sources, physiological mechanisms, clinical outcomes, and therapeutic recommendations. ALA is primarily obtained from plant-based foods such as flaxseed, chia seeds, walnuts, soybean, and canola oil, whereas EPA and DHA are mainly derived from fatty fish, seafood, fish oil, breast milk, and marine microorganisms. Evidence indicates that omega-3 PUFAs exert cardioprotective effects through multiple mechanisms, including anti-inflammatory, antithrombotic, antiarrhythmic, triglyceride-lowering, and endothelial function-enhancing activities, as well as modulation of gene expression and membrane fluidity. Clinical studies demonstrate that increased intake of EPA and DHA is associated with reduced risks of myocardial infarction, major adverse cardiovascular events (MACE), coronary heart disease, and cardiovascular mortality. High-dose EPA therapy, particularly 4 g/day, has shown significant reductions in cardiovascular events among high-risk individuals. Studies recommend regular consumption of fatty fish and appropriate omega-3 supplementation, particularly for individuals with hypertriglyceridemia or elevated cardiovascular risk. Nevertheless, inconsistencies regarding optimal dosage, formulation, duration of supplementation, and comparative efficacy of EPA alone versus EPA plus DHA remain. Further large-scale, well-designed clinical trials are needed to establish standardized recommendations and clarify the long-term cardiovascular benefits of omega-3 fatty acids across diverse populations.

INTRODUCTION

Omega-3 fatty acids, also known as omega-3 oils, n-3 fatty acids, and ω-3 fatty acids, are distinguished from other fatty acids by their double bond in their molecular structure, three atoms away from the terminal methyl

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group [1]. Docosahexaenoic acid (DHA) contains 22 carbon atoms, whereas eicosapentaenoic acid (EPA) contains 20. At least two double bonds are present in PUFAs, and EPA and DHA have five and six double bonds, respectively. omega-3 (ω-3, n-3) indicates that the first double bond is located at the third carbon from the methyl end (HC3-C-C=). [2]. Biomedical kits with a simple design, low cost, and high reliability are essential for the future development of point-of-care medicine. Reducing the complexity of a biosensing design can greatly lower its cost while improving its robustness [3].

Most PUFAs, including alpha-linolenic acid (ALA), are not produced by the human body and must thus be consumed through the diet. As a result, they are regarded as fatty acids that need to be obtained from food [4]. Grain and plant seeds contain omega-3 fatty acids in the form of ALA, which can be converted to EPA and DHA [5]. Furthermore, the availability of important dietary fatty acids affects this conversion process. Marine life is rich in omega-3 fatty acids. Numerous species of fish naturally contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [2], [6, 7].

Globally, cardiovascular disease (CVD) is the leading cause of death, accounting for approximately 75% of deaths in low- and middle-income countries according to the World Health Organization [8]. As CVDs significantly contribute to the rising costs of healthcare, they place a major socioeconomic burden on the entire population[9]. The Global Burden of Disease study found that there were 523 million CVD cases globally in 2019, as opposed to 271 million in 1990 [10], [11].

Early observational studies showing a correlation between marine diet and a lower incidence of cardiovascular illness sparked interest in n-3 PUFAs as possible treatments for lowering cardiovascular risk [12]. In the latter part of the 1970s, it was first noted that there was a relationship between higher fish consumption and decreased cardiovascular mortality [13]. Eating two–three meals of fish per week is associated with a lower incidence of coronary heart disease (CVD), myocardial infarction (MI), stroke, and heart failure than eating less fish according to systematic analyses of prospective observational studies [14]. Meta-analyses of observational studies have associated increases in dietary ALA with a 10% reduction in the risk of all cardiovascular diseases and a 20% reduction in the risk of fatal coronary heart disease [15], [16]. As a result, omega-3 PUFA have been approved as therapeutic and preventive measures for the management of several cardiovascular illnesses [17]. Numerous guidelines endorsing the use of omega-3 PUFA supplements have been released [18], and they were soon commonly prescribed by cardiologists and other medical professionals. Furthermore, as food has always been a hot topic in the media, suggestions have been widely accepted, making over-the-counter omega-3 PUFA supplements the most popular worldwide [19], [20].

The current review examines the data supporting the benefits of omega-3 fatty acids for the cardiovascular system from epidemiological research, clinical trials, and meta-analyses. Furthermore, it explores the physiological processes, such as anti-inflammatory, anti-thrombotic, and antiarrhythmic activities, by which these fatty acids achieve their cardioprotective benefits. This review highlights the knowledge gaps that

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currently exist in the field, possible directions for future studies, and practical ramifications for dietitians who wish to incorporate omega-3 fatty acids into their recommendations to promote heart health.

Methodology

The data used in this study were retrieved from published articles on SciHub, PubMed, and Google Scholar. Keywords such as omega-3 fatty acids, sources of omega-3 fatty acids, omega-3 fatty acids, heart health, anti-inflammatory action of omega-3 fatty acids, health advantages of omega-3 fatty acids, omega 3 supplements, dietary guidelines of omega 3, EPA, ALA, DHA, and PUFAs were used to search for the topic. One thousand and forty-four papers were downloaded and examined. The inclusion criteria were (1) studies having the role of omega 3 fatty acid in cardiovascular health or mortality effects on all-cause mortality, cardiac death, fatal/nonfatal myocardial infarction (MI), major adverse cardiovascular events (MACE), or fatal/nonfatal stroke; (2) human studies; and (4) articles only in English were included in this review. Exclusion criteria were as follows: (1) animal studies, (2) studies depicting omega 3 affects in other than cardiovascular diseases, and (3) studies in languages other than English. Publications referenced in the initial search articles were also manually selected because of their applicability to the subject.

Omega-3 Fatty Acid Types and Dietary Sources

α-linolenic acid (ALA; 18:3 ω-3), stearidonic acid (SDA; 18:4 ω-3), eicosapentaenoic acid (EPA; 20:5 ω-3), docosapentaenoic acid (DPA; 22:5 ω-3), and docosahexaenoic acid (DHA; 22:6 ω-3), are examples of omega-3 polyunsaturated fatty acids (PUFAs) [5]. Omega 3 found in plant seeds and grains is known as ALA. These fatty acids can then be transformed into EPA and DHA. It is crucial to include LC ω-3 PUFAs in the daily diet, because the body can only produce these fats at best at rates of less than 4% from ALA [21]. Green leafy vegetables, flaxseed, walnuts, soybean, and canola oils contain alpha-linolenic acid (ALA) [13].Two excellent sources of EPA, DHA, and ALA derivatives are breast milk and fish oils from seafood, such as salmon, mackerel, sardines, anchovies, herring, rainbow trout, and algae. The plant known as *sacha inchi*, or SI (*Plukenetia volubilis*), is an oleaginous plant that produces high-protein seeds and oil. It is deemed underused because of its high protein content and concentration of polyunsaturated fatty acids (PUFAs). The bioactive ingredients in *sacha inchi* seeds contribute to their recent rise in popularity, especially ALA, which acts as a precursor to EPA and DHA under normal physiological conditions [22]. Microalgae holds great promise for the production of nutrient-dense meals and feed additives. Microalgae offer a different method to obtain polyunsaturated fatty acids (PUFAs) [23]. As novel sources of ω-3 LC-PUFAs, oleaginous microalgae are potential substitutes for fish and seafood [24]. Studies have been conducted on the production of omega-3 LC-PUFAs in a variety of marine species. These organisms include marine algae such as *Crypthecodinium,*

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Thraustochytrids, Ulkenia, and *Schizochytrium* species, as well as marine bacteria such as *Phaeodactylum tricornutum, Nannochloropsis* species, and *Desmodesmus* species. Bivalves may concentrate EPA and DHA from phytoplankton, which makes them good providers of high-quality lipids [25].

Fatty fish cold-water marine oily fish, particularly wild species such as mackerel, herrings, sardines, salmon, tuna, and trout, are good sources of omega-3 polyunsaturated fatty acids (PUFAs) [13]. This can be explained by the fact that most of their diet is composed of phytoplankton and zooplankton, which are abundant sources of -3 PUFAs [13].

Gut microbiota

In recent years, there has been a substantial increase in the interest in the growing field of study concerning the function of gut bacteria in omega-3 biosynthesis and cardiovascular health [26], [27]. The intestinal microflora has several roles, but among the most important ones are the metabolism of nutrients and xenobiotics, preservation of gut mucosal integrity, metabolism of bile salts, vitamin production, immune system control, and biosynthesis of FAs [28]. Gut symbiotic bacteria metabolize dietary precursors such as alpha-linolenic acid (ALA) to synthesize short-chain fatty acids (SCFAs) [29], [30]. Six SCFAs are created in the intestinal lumen by bacteria that ferment the undigested carbohydrates. These SCFAs are taken up by host cells, and then oxidized. Energy is released in this reaction, which can be used locally in the colon as well as systemically when the portal circulation carries energy to the liver [31]. *Bacteroides, Bifidobacterium,* and *Lactobacillus* are among the bacteria that have been found to be capable of this conversion process. Gut bacteria may influence the total omega-3 status of the body through this conversion [32]. Maintaining a balance between the composition and activities of the intestinal microbiota is crucial because failure to do so might result in a condition known as gut "dysbiosis," which has been linked to a number of human illnesses, including cardiovascular disease (CVD) [32], [33]. Additionally, GM has shown that it can metabolize cardiovascular medications, which changes the medicines' effects and bioavailability [34], [35]. According to a study by Cui et al., there were notable variations in bacterial makeup between control individuals and patients with chronic heart failure [36]. A high intake of saturated fats and trans fats is associated with an increase in pro-inflammatory bacteria, while a high intake of MUFAs and PUFAs enhances the production of short-chain fatty acid (SCFA)-producing bacteria [37].

The human gut microbiome (GM) has been a promising new area of research and a possible treatment for cardiovascular disorders in recent years [26], [27]. Additionally, GM has shown that it can metabolize cardiovascular medications, which changes the medicines' effects and bioavailability. [34] [35]. According to a study by Cui et al., there were notable variations in bacterial makeup between control individuals and patients with chronic heart failure [36] and myocardial ischemia/reperfusion [38].

Influence on Omega-3 Absorption and Metabolism: The absorption and metabolism of omega-3 fatty acids are influenced by gut bacteria [39]. They have the ability to alter the expression of genes related to fatty acid

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metabolism, which can affect how well the body absorbs and uses omega-3 fatty acids [40]. Furthermore, certain gut flora create bioactive lipids and short-chain fatty acids (SCFAs), which are metabolites of omega-3 fatty acids that may be advantageous for cardiovascular health.

Modulation of Inflammation and Cardiovascular Health: Because their well-known anti-inflammatory properties, omega-3 fatty acids are essential for preserving cardiovascular health [41]. Through a number of processes, such as the synthesis of chemicals that interact with the immune system and the function of the gut barrier, gut microbiota can affect the inflammatory response both in the gut and throughout the body [42] Omega-3 fatty acids has the potential to mitigate inflammation and minimize the risk of cardiovascular diseases, including atherosclerosis, hypertension, and coronary artery disease, by fostering a balanced population of gut flora [43].

Regulation of Lipid Metabolism and Lipid Profile: The Lipid profile and lipid metabolism are critical components of cardiovascular health that are influenced by gut flora [44]. Research has indicated that certain microorganisms in the gut are linked to modifications in fat metabolism, such as increased bile acid production, which affects cholesterol absorption and synthesis. Gut microbiota may affect blood lipid levels and help avoid cardiovascular illnesses by regulating lipid metabolism [44].

Overall, new research indicates that maintaining a healthy gut microbiota through dietary interventions, such as consuming omega-3-rich foods and probiotics, may have positive effects on cardiovascular health, even though the precise mechanisms by which the gut microbiota influences omega-3 production and cardiovascular health remain unclear. Further research is needed to completely comprehend the intricate interactions between gut bacteria, omega-3 fatty acids, and CVDs [43].

Omega-3 fatty acid Physiological Mechanisms of action

The beneficial effects of n-3 PUFAs are attributed to various mechanisms of action. Indeed, they have an antiarrhythmic and antithrombotic action, reduce plasma triglyceride levels, resolve inflammatory states, regulate the expression of several genes and transcription factors, and act on membrane fluidity by influencing signal transduction, stimulating neuronal growth, influencing neurotransmitter release, and facilitating glucose uptake from the endothelial cells into the brain [45]. In the treatment of CVD, n-3 PUFAs fatty acids (ω-3) have the same effects as many antioxidants; in fact, they protect endothelial cells and cardiomyocytes from damage and cell death [14], [46]. Omega-3 LCPUFA are also an important precursor of eicosanoids, resulting in reduced blood clotting and increased blood flow. DHA is a precursor of docosanoids such as resolvins and maresins, resulting in anti-inflammatory effects and neuroprotective effects that protect neurons [47].

The metabolites of omega-3 play an important role in the synthesis of different inflammatory mediators, such as prostaglandins (PG), leukotrienes (LT), thromboxanes (TX), protectins, and resolvins. Omega-3 fatty acids (FAs) play a role in the host cellular membrane by regulating membrane fluidity and intricate lipid raft

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assembly in the cell membrane [48]. Omega-3 FAs improve macrophage function by secreting cytokines and chemokines, promoting phagocytosis, and activating macrophages by polarization [49]. This study showed that fish oil enhances the antiviral response by inducing interferon (IFN), which inhibits viral replication. Omega-3 FAs also downregulate nuclear factor-kappa Beta (NF-κB). NF-κB is considered a transcription factor involved in cell signaling that initiates an inflammatory response by the innate immune system [49], [50], [51].

Anti-Inflammatory Effects of Omega-3 fatty acids

The progression of inflammation in the blood vessels and endothelial dysfunction causes atherosclerotic lesions in the arteries, which further induces stroke and myocardial dyslipidemia, as indicated by elevated concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG), as well as low concentrations of high-density lipoprotein cholesterol (HDL-C), which continues to be a major CVD risk factor [52]. PUFA, especially alpha-linolenic acid, help regulate blood plasma TG levels in patients with dyslipidemia, lower blood pressure, and protect against coronary heart disease [52]. Several studies have shown that PUFA protect the blood vessels and heart by regulating membrane phospholipids, thereby improving cardiac mitochondrial function and energy production, and reducing TG concentrations [53]. Omega-3 PUFAs alter the production of inflammatory, vasodilatory, and anti-aggregatory signaling molecules, which reduces inflammation, prevents thrombosis, and maintains the balance of atherosclerotic plaques [46]. The significance of omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) in preventing and treating illnesses, such as coronary artery disease, has been well researched because of their anti-inflammatory properties [54, 55].

Han *et al.* reported that ALA suppresses the biosynthetic pathway of cholesterol and TG by regulating the expression of sterol regulatory element-binding proteins 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase, sterol regulatory element-binding protein 1c (SREBP-1c), and acetyl-CoA carboxylase, illustrating that partial replacement of lard with flaxseed oil can significantly alleviate atherosclerosis symptoms, improve oxidative stress, reduce lipid and inflammatory abnormalities, and promote cardiovascular health [56], [57]. Long-chain PUFAs, such as ALA, EPA, and DHA, detach from membrane phospholipids and undergo oxidation into their respective lipid mediators using oxygenase enzymes. ALA also produces other octadecadienoid (C_{18}) lipid mediators, which have metabolic functions in inflammation. PUFAs regulate inflammation, immunity, blood vessels, platelets, synaptic plasticity, cellular growth, pain, and sleep. Especially for inflammation, immunity, blood vessels, and platelets, derivatives of n-3 PUFAs inhibit inflammation and platelet aggregation, and enhance vasodilation [58], [59]. After ingestion of PUFAs, the activity of glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) is enhanced, and the generation of the free radical metabolite malondialdehyde (MDA) decreases, thus achieving free radical scavenging, reducing cell damage, and improving tissue and organ function [60]. Glutathione (GSH)-dependent peroxidase glutathione peroxidase 4 (GPX4), the activity of which is particularly important for the effects of

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polyunsaturated fatty acids (PUFAs) on lipid modules. GPX4 was identified as a target protein whose inhibition triggers uncontrolled PUFA oxidation and fatty acid radical production, leading to ferroptosis in the heart [61]. Clinical studies have shown that EPA-only treatment can reduce inflammatory markers and gene expression related to cardiovascular diseases. EPA has also demonstrated a decrease in inflammatory mediators compared to DHA in cellular studies. The study suggests that while reducing triglyceride levels may not directly correlate with cardiovascular benefits, EPA-only formulations have pleiotropic effects and reduce composite cardiovascular events [8].

Anti-Thrombotic Effects of Omega-3 fatty acids

Omega-3 fatty acids have cardioprotective, anti-inflammatory, antidiabetic, and antineoplastic effects [45]. A study conducted by Mason explored the mechanisms of action of omega-3 fatty acids in athero-thrombotic cardiovascular disease. Omega-3 fatty acid consumption has been shown to lower triglyceride levels and may reduce the risk of cardiovascular mortality and morbidity. EPA and DHA exhibit similar effects on triglyceride levels but may differ in their effects on lipid oxidation, cell function, and membrane structure [8]. It is known that n-3 PUFAs can inhibit normal platelet function, indicating platelet involvement in EPA- and DHA-mediated cardioprotection. Numerous studies indicate that platelets treated with EPA and DHA show a reduction in the rate of thrombin formation and exposure to platelet phosphatidylserine. This treatment reduces thrombus formation and modifies the processing of thrombin precursor proteins [62]. An additional result indicated that when whole blood was treated with ω-3, there was more occlusion time and less fibrin accumulation under flow conditions. Moreover, in vitro studies have shown that n-3 PUFAs reduce, without eliminating, the pro-coagulant ability of platelets, which represents one of the cardioprotective mechanisms of ω-3 in subjects fed a diet rich in EPA and DHA [63], [64, 65].

Antiarrhythmic Effects of Omega-3 fatty acids

By altering cellular and tissue responses, EPA and DHA provide more conducive environments for development, growth, and health maintenance. Omega-3 polyunsaturated fatty acids change the cellular membrane structure, prevent oxidation, and exert an antiarrhythmic effect [66]. Additionally, this tactic involved modifying the potassium, sodium, and calcium channels, which showed antiarrhythmic effects and decreased the synthesis of thromboxane, in addition to having beneficial effects on heart rate variability. These polyunsaturated fats (PUFAs) limit atrioventricular conduction, significantly reduce the likelihood of a prolonged QT interval, and make cardiac cells less impulsive by changing ion channels [19].

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Myocardial cells situated at the edge of the ischemic area are more susceptible to stimulation and have a somewhat depolarized resting potential. This can result in ventricular fibrillation. Therefore, an increase in omega-3 polyunsaturated fatty acids (PUFAs) balances the increased excitability of partially depolarized cells in the ischemic myocardium. Therefore, there is a longer refractory period and a higher threshold voltage needed for cellular depolarization, which reduces the likelihood of spontaneous or premature depolarization [67].

Docosahexaenoic acid (DHA) has the highest degree of unsaturation and unique stereochemical structure. Owing to their special makeup, neurons can effectively conduct signals that prevent blood vessels and cardiac spasms. Moreover, DHA has antiarrhythmic effects [47]. These antiarrhythmic actions are due to processes that include the reduction of thromboxane formation and regulation of sodium, potassium, and L-type calcium channels. They also considerably reduce the chance of a prolonged QT interval and delayed atrioventricular conduction [68]. Omega-3 polyunsaturated fatty acids (PUFAs) have a strong affinity for the peroxisome proliferator-activated receptor (PPAR), which promotes improved beta oxidation and fatty acid metabolism. This process is precisely how they lower their TG levels [69].

Epidemiological Evidence of Omega-3 fatty acids as cardio protective agent

AbuMweis et al. performed a meta-analysis to evaluate the impact of supplements containing EPA and DHA on the risk factors associated with cardiovascular disease. Compared to the control groups, the administration of EPA and DHA supplements resulted in a significant decrease in triglyceride levels. This study revealed higher levels of low-density and high-density lipoprotein cholesterol. The claims regarding the lipid-lowering, blood pressure-lowering, antiarrhythmic, and anti-inflammatory properties of EPA and DHA supplements were validated by the analysis of randomized placebo-controlled blinded clinical trials [66]. In the prevention of venous thrombosis embolism (VTE) following surgery, Bonutti et al. demonstrated the synergistic anti-thrombotic effect of a combined therapy employing aspirin and fish oil with anti-thrombotic and anti-inflammatory activities. A high consumption of marine omega-3 polyunsaturated fatty acids (PUFAs) in the diet was linked to a lower risk of VTE; according to the research of Isaksen et al. consuming omega-3 polyunsaturated fats (PUFAs) has been linked to a decreased incidence of VTE and recurrent VTE, according to another study. The potential of omega-3 polyunsaturated fatty acids to lower the risk of deep vein thrombosis and pulmonary embolism following surgery has also covered[70].

The goal of a study by Lazaro et al. was to determine whether dietary alpha-linolenic acid (ALA), the main plant-derived omega-3 fatty acid, is linked to a better prognosis for patients with heart failure (HF). The rates of all-cause mortality, CV-related mortality, first-HF hospitalizations, and the composite outcome of CV death

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and HF hospitalization were all significantly lower according to the researchers. Ultimately, patients with heart failure (HF) who had serum phospholipid levels with ALA levels in the lowest 25% range had a worse prognosis than those with the highest levels during the intermediate-term follow-up period [71].

Nelson and Raskin examined the clinical value of the eicosapentaenoic acid (EPA): arachidonic acid (AA) ratio in cardiovascular disease. Patients with chronic heart failure and dyslipidemia who underwent EPA therapy had a greater left ventricular ejection fraction (LVEF) than those in the control group. The EPA: AA ratio was significantly higher and positively correlated with the LVEF in the EPA-treated group. Higher EPA: AA ratios were associated with a decrease in the thickness of the left ventricular wall in diabetic patients, whereas lower ratios were associated with a higher risk of death in hospitalized patients with decompensated heart failure. In a variety of clinical contexts, the EPA: AA ratio has proven to be a reliable predictor of future cardiovascular events [72].

A predefined independent examination of 3,146 randomly assigned patients in the US showed that EPA ethyl ester (IPE) therapy indicated a significant 31% relative risk reduction and 6.5% absolute risk reduction in the important composite endpoint and outcome. Furthermore, compared to the placebo, IPE had a 31% decreased risk of cardiovascular death, nonfatal MI, and nonfatal stroke. Furthermore, in this study, the all-cause mortality of the IPE group was considerably lower than that of the placebo group's [73].

Three recently completed major clinical trials that showed the benefits of omega-3 fatty acid consumption for CVD were examined by Kris-Etheron et al. These clinical trials amply illustrated the advantages of consuming omega-3 fatty acids in one's diet with regard to reducing the risk of heart attacks and other major cardiovascular events, as well as cardiovascular disease-related death [74]. The effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on cardiovascular risk variables were examined in a recent review by Fatahi et al. Clinical trial results suggest that DHA may be a better candidate than EPA in lowering cardiovascular risk factors. Additionally, a paired meta-analysis that directly compared the effects of DHA and EPA on insulin and blood sugar levels showed a significant difference between the two, even though the results had no effect on overall risk factors. The findings showed that both EPA and DHA exhibited comparable effects on the examined markers, with only slight variations in plasma glucose, insulin, and LDL-C [75]. The effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on the omega-3 index and the risk of cardiovascular disease are inversely related, according to a meta-analysis of 10 studies, which was reviewed recently by Fatahi et al. According to a study, the strongest protection against CVD is provided by red blood cell omega-3 membrane concentrations of over 8%, while the lowest protection is provided by concentrations of less than 4% [76]. Recent clinical studies have demonstrated that EPA ethyl esters can reduce the risk of cardiovascular diseases [77].

The Vitamin D and Omega-3 Trial (VITAL) fatty acid (n−3 FA) trials for cardiovascular disease (CVD) prevention were reviewed by Bassuk et al. When it came to myocardial infarction and repeated hospitalizations for heart failure, African Americans benefited from treatment the most. When VITAL was

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combined with high-risk or secondary preventive studies, meta-analyses showed a decrease in the risk of coronary heart disease, but not stroke [78].

Many meta-analyses investigating the relationship between different types of fatty acids, especially n-3 fatty acids, and the consequences of cardiovascular disease were conducted by Innes and Calder. Based on data from 16 trials including over 422,000 participants, the meta-analysis showed a 13% reduction in risk for those with greater dietary intake of EPA + DHA compared to those with lower intake. Moreover, individuals with higher circulation levels of EPA, DHA, and EPA + DHA, respectively, showed risk reductions of 22%, 21%, and 25%, according to data from 13 trials including over 20,000 participants. People with higher dietary intake of EPA + DHA had an 18% decreased risk of any coronary heart disease incident, according to another study of prospective cohort study. Furthermore, there were notable decreases in the risks of coronary mortality, sudden cardiac death, and fatal coronary events, which were 23%, 19%, and 47%, respectively. These findings generally suggest that increased EPA and DHA intake or levels are associated with a decreased risk of coronary events [79].

Qi et al. reviewed the advantages of omega-3 supplementation. Nineteen eligible randomized control trials (RCTs) with 116,498 individuals were included in the review. Treatment with omega-3 polyunsaturated fatty acids significantly reduced revascularization and cardiovascular death (CV mortality). However, it is associated with an increased rate of atrial fibrillation (AF). Omega-3 PUFA supplementation increased the frequency of atrial fibrillation, even though it reduced CV mortality and revascularization [80].

Using significant RCTs, Bae et al. conducted a meta-analysis to resolve this discrepancy and evaluate the biochemical and clinical effects of LC ω-3 PUFAs. RCTs with at least 500 participants and at least one year of follow-up were considered. Supplementing with LC ω-3 PUFA had a positive impact on CV death and fatal or nonfatal MI according to 17 trials with 143,410 participants. Better outcomes for 3-point MACE, CV mortality, and fatal or nonfatal MI were found in RCTs that focused solely on EPA. Hospitalization for heart failure, all-cause mortality, and fatal or non-fatal stroke did not show any advantages. Notably, research on EPA alone and in conjunction with DHA revealed a much higher risk of new-onset atrial fibrillation [81]. Table 1 shows the studies on omega 3 fatty acids and their effects on cardiovascular health.

A meta-analysis of 12 papers including 29913 patients' randomized control trials, was conducted by Chao et al. Conversely, among patients with coronary artery disease (CAD), omega-3 FAs decreased the rates of hospitalization for heart failure or unstable angina pectoris, revascularization, myocardial infarction, and all-cause mortality. In subgroups of intervention with EPA and baseline triglyceride levels ≥1.7 mmol/L, the beneficial effects of omega-3 FAs on MACEs were substantial [90].

Dugre et al. assessed the benefits and harms of lipid-lowering therapies used to prevent or manage cardiovascular diseases, including omega-3 supplements, bile acid sequestrants (BAS), fibrates, ezetimibe, niacin, proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, and statins. A total of 76 systematic

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reviews were reviewed. Omega-3 combination supplements had no effect on MACE or all-cause mortality but significantly reduced cardiovascular mortality. Eicosapentaenoic acid ethyl ester alone significantly reduced MACE and cardiovascular mortality. The addition of statins to eicosapentaenoic acid ethyl ester provides additional MACE risk reduction but has no effect on all-cause mortality [91].

Table 1: Studies on omega 3 fatty acids and cardiovascular health

Reference	**PUFAs used in study**	**Indicators**	**Result**
[78]	effects of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) on cardiovascular risk factors were compared	plasma glucose, insulin, and LDL-C,	both EPA and DHA display similar activities
[79]	ALA	Plasma LDL-C	Reduced Plasma LDL-C
[77]	neutral forms of n-3 PUFA and IPE compared	differential bioavailability	IPE exerts high differential bioavailability and biological effects
[77]	IPE compared with EPA/DHA, or EPA/DHA ethyl ester	red blood cell omega-3 membrane concentration	EPA ethyl ester can reduce the risk of cardiovascular disease
[72]	eicosapentaenoic acid (EPA) and arachidonic acid (AA) compared	Left ventricular ejection fractions (LVEF).	EPA:AA ratio was considerably greater and had a positive correlation with LVEF

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[78]	Vitamin D and Omega-3 Trial	Atrial fibrillation	reduction in coronary risk
[79]	n-3 fatty acids, with the outcomes of coronary disease	coronary mortality, and sudden cardiac death	higher intake or levels of EPA and DHA are linked to a lower risk of a variety of coronary events
[80]	omega-3 supplementation	Cardiovascular mortality (CV mortality) and revascularization	significantly declined as a result of omega-3 PUFA treatment
[73]	EPA ethyl ester (IPE) treatment	nonfatal MI, or nonfatal stroke	31% relative risk reduction
[82]	2,700 mg of DHA and EPA daily for 10 weeks.	sudden heart death	DHA lowered 5.6% risk of sudden heart death EPA lowered 3.3% risk of sudden heart death
[83]	Seafood (EPA) and plant-derived n-3(ALA) polyunsaturated fatty acids (PUFA)	atherosclerotic cardiovascular disease, acute major ischemic events	A high consumption of EPA decreased risk of total ASCVD and acute major ischemic events. no significant association was observed for the plant-derived ALA[83].

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[66]	supplements containing EPA and DHA	triglyceride levels	EPA and DHA supplements have lipid-lowering, blood pressure-lowering, antiarrhythmic, and anti-inflammatory activities
[74]	EPA and DHA	CVD	lowered the risk of heart attacks, cardiovascular events, and mortality from CVD
[84]	low-dose omega-3 fatty acids therapy	cardiac arrhythmias	reduction in sudden death from cardiac arrhythmias
[85]	n-3 PUFA	cardiovascular mortality	notable effect on cardiovascular mortality when used 8 grams/day
[86]	ALA	all-cause mortality, cardiovascular disease (CVD),	5% decreased risk of both all-cause and CVD mortality.
[71]	alpha-linolenic acid (ALA),	serum phospholipids heart failure (HF)	statistically significant reductions in the rates of all-cause mortality, CV-related mortality, first HF hospitalizations,
[87]	EPA ethyl ester (IPE) treatment1.8 g/d with statin alone	acute cardiovascular conditions	decrease in ventricular arrhythmias
[88]	EPA at doses of 600 mg/d or 1800 mg/d, or DHA at a dose of 600 mg/d,	postprandial triglyceride (TG)	DHA exhibited significant reductions in postprandial triglyceride (TG)

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[81]	EPA supplementation	Fatal or nonfatal MI	EPA alone showed better results for 3-point MACE, CV death, and fatal or nonfatal MI
[89]	EPA administered alone	MACE and MI	EPA showed 25% and 30 % reduction in MACE and MI respectively when used 1 g per day
[90]	EPA and baseline triglyceride levels ≥1.7 mmol/L	hospitalization for heart failure or unstable angina pectoris, revascularization, myocardial infarction, and all-cause mortality	omega-3 FAs decreased the rates of hospitalization for heart failure or unstable angina pectoris, revascularization, myocardial infarction, and all-cause mortality
[91]	Omega 3 supplements and IPE alone	major adverse cardiovascular events (MACE), cardiovascular mortality, all-cause mortality	Omega-3 combination supplements had no effect on MACE or all-cause mortality but significantly reduced cardiovascular mortality. IPE alone significantly reduced MACE and cardiovascular mortality.

Dosage and Duration Effects of Omega-3 fatty acids

Bork et al. investigated the connection between the development of acute major ischemic episodes and atherosclerotic cardiovascular disease (ASCVD) and the consumption of seafood and plant-derived n-3 polyunsaturated fatty acids (PUFA). Alpha-linolenic acid (ALA), an n-3 PUFA produced from plants, and docosahexaenoic acid (DHA), the principal marine n-3 PUFA, were measured during the recruitment phase using a validated dietary frequency questionnaire. Using multivariable analyses that included established risk

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variables, they found no correlations between ALA consumption and the incidence of acute major ischemic events or total ASCVD; however, they found evidence of inverse associations between EPA, DHA, and EPA + DHA intake and these events. Interestingly, a high intake of marine n-3 PUFAs was associated with a lower incidence of acute major ischemic episodes and overall ASCVD, whereas no significant correlation was found with ALA40 produced from plants [83].

In a review focusing on DHA, Borgaonkar and Patil emphasized the advantages of omega-3 fatty acids. A total of 154 obese adults participated in one trial and received 2,700 mg DHA daily for ten weeks. the omega-3 index, a blood test for omega-3 levels associated with a 5.6% decrease risk of sudden cardiac death, increased as a result. A daily dose of EPA only resulted in a 3.3% increase in the omega-3 index in these subjects. Moreover, blood triglycerides decreased more in the DHA group than in the EPA group by 13.3%, as opposed to 11.9%. Additionally, DHA was associated with a 7.6% rise in "good" HDL cholesterol whereas EPA was associated with a small decline. It is important to remember that DHA tends to increase the low-density lipoprotein (LDL levels [82].

Associations between food consumption, tissue alpha-linolenic acid (ALA) biomarkers, and the risk of death from various causes, including cardiovascular disease (CVD) and all-cause mortality. Interestingly, there was a significant correlation between a higher intake of ALA and lower consumption and a decreased risk of death from all causes, cardiovascular disease, and coronary heart disease (CHD). The dose-response analysis showed that a 5% lower risk of both all-cause and CVD mortality was linked to every additional 1 g/day of ALA intake, which was equivalent to one tablespoon of canola oil or 0.5 ounces of walnuts. Furthermore, a lower risk of dying from CHD was associated with ALA blood concentrations that increased by one standard deviation, as reported by a study of dosage response. The findings of this study indicate that dietary ALA intake is linked to a slightly higher risk of mortality from cancer-related causes and a lower risk of death from all-cause, CVD, and CHD [86].

Xie et al. conducted an extensive analysis of the literature. Major adverse cardiovascular events (MACEs) might be more significantly affected by a higher consumption of -3 PUFA. There was a noticeable impact on cardiovascular mortality when the researchers extended the duration of the intervention and raised the daily dose in individuals at risk of cardiovascular disease. However, when subgroup analyses considered greater dosages and longer intervention periods (daily dose intervention time > 8 g/day), a reduction in MACEs and all-cause mortality was more evident. Furthermore, the dose-response meta-analysis revealed a decrease of 8.99% in all-cause deaths and 13.05% in MACEs. This meta-analysis revealed a robust link between significant doses and long-term interventions with ω-3 PUFA supplementation and MACEs, as well as cardiovascular or all-cause mortality, after combining the most recent randomized controlled trials [85].

Asztalos et al. employed widely available doses in the general population to explore the effects of inflammatory biomarkers on cardiovascular disease (CVD) risk. In a six-week blinded randomized experiment, 121 healthy participants were given a placebo consisting of olive oil (6 g/d), EPA at dosages of 600 mg/d or 1800 mg/d,

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DHA at a dose of 600 mg/d, or a combination of the two. The DHA group showed significant reductions in postprandial triglyceride (TG) levels, but significant increases in postprandial low-density lipoprotein cholesterol (LDL-C) and fasting levels compared to the placebo group. However, there were no notable changes in inflammatory markers. The group received 600 mg/d EPA, but no discernible effects were observed. However, there were notable decreases in the concentration of lipoprotein-associated phospholipase A2 (Lp-PLA2) in the high-dose EPA group. The benefits of 1800 mg/day of EPA on reducing CVD risk may stem, at least partially, from the reduction of Lp-PLA2 levels without having a negative impact on LDL-C levels. Conversely, DHA increased LDL-C levels but decreased postprandial TG levels. These dietary fatty acids have different effects on cardiovascular risk factors, according to previous findings [88]. Examining the connection between fish oil intake and decreased risk of cardiovascular events and cardiovascular disease mortality was the aim of a study conducted by Jain et al. Three notable clinical trials that highlighted the benefits of omega-3 fatty acids on the cardiovascular system were included. omega-3 fatty acids have been shown to significantly reduce all-cause mortality and the risk of sudden death from cardiac arrhythmias in patients with established coronary heart disease. Moreover, studies have shown that omega-3 fatty acids have a positive effect on the metabolism of high-density lipoprotein (HDL) cholesterol. This meta-analysis demonstrated that the incidence of sudden death significantly decreased when low doses were used [84].

With a focus on the influence of dosage, type of n-3 PUFA, and varying CV risk at baseline, Casual et al. investigated the effect of n-3 PUFA administration on CV outcomes in published randomized clinical trials (RCTs). Sixteen RCTs with 81,073 individuals were included in the meta-analysis. The risks of MI, MACE, and cardiac death were significantly reduced when n-3 PUFA was added. Only RCTs that recruited patients for secondary prevention showed a decrease in the risk of cardiac mortality and MI in subgroup analysis (-21 % and -31%, respectively). Furthermore, the risk of cardiac mortality (-35%), MACE (-24 %), and MI (-33 %). Lastly, compared with EPA administered alone (8%), EPA + DHA supplementation was only significantly related to a lower incidence of cardiac mortality. On the other hand, EPA supplementation alone appears to be more effective than EPA + DHA supplementation in terms of reducing the risk of MI (-30%) or MACE (-25%) [89].

Safety Considerations of Omega-3 fatty acids in the natural environment

Omega-3 fatty acids, also known as polyunsaturated fatty acids (PUFAs), are abundant. The GRAS (generally regarded as safe) supplement category includes omega-3 FAs [92]. The American Heart Association (AHA) recommends supplementation with EPA and DHA in the form of fish oil at a level of 2-4 g/day for patients with hypertriglyceridemia. Recent American and European guidelines have stated that prescribing omega-3 fatty acids (EPA + DHA or EPA only) at a dose of 4 g/day (>3 g/day total EPA + DHA) is an effective and safe option for reducing triglycerides, as monotherapy or as an adjunct to other lipid-lowering agents. It is

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imperative that the amount of capsules intended for daily consumption in all patients with CVD corresponds to the recommended dosage of EPA and DHA [92].

Numerous studies have also demonstrated that increased linolenic acid and LA content can prevent and cure CVD by lowering the plasma concentrations of TC, LDL-C, VLDL, apolipoprotein B, and apolipoprotein A-1 [93]. When partially substituting saturated fat in a high-fat diet, PUFAs have been found in a recent study to be successful in decreasing plasma and liver cholesterol, as well as boosting HDL/LDL ratios [94], [52].

Recommended Intake and Supplementation: The World Health Organization (WHO) suggests that individuals consume 200–500 mg of EPA + DHA daily, whereas the National Institute of Medicine (NAM) states that 10% of the ALA intake should come from EPA + DHA [95]. To meet the daily needs of 250 mg EPA and DHA, it is recommended to consume two to three meals of fatty fish each week. It is generally agreed that for optimal nutrition, a minimum daily intake of 250 mg of EPA and DHA is required; however, the exact amount needed for certain populations or health situations is unknown and, in many circumstances, is likely to surpass the recommended minimum intake [96]. For example, consuming rice bran oil, flaxseed oil, or pomegranate seed oil can provide more phytosterols and unsaturated fatty acids, which can help reduce CVD. The Panel on Dietetic Products, Nutrition, and Allergies (NDA) of the European Food Safety Agency (EFSA) states that the overall amount of fat consumed should not exceed 20–35% of energy (E%) [97]. For ALA, the Adequate Intake (AI) was fixed at 0.5 E%. The EFSA Panel recommends that adults consume 250 mg/d of EPA plus DHA and babies (>6 months) and young children (<24 months) should consume 100 mg/d of EPA plus DHA to the health advantages of avoid sudden heart attacks and coronary heart disease [97]. To ensure that pregnant and lactating women received an adequate amount of omega-3 VLC-PUFAs, the panel also advised the addition of 100–200 mg of preformed DHA. The World Health Organization (WHO) also suggested adding 200–500 mg EPA + DHA to adult women [98]. The WHO also suggests that vegetarians who do not eat fish should ensure adequate intake of plant sources of ALA [99].

People must consume both PUFAs in the highly recommended n-6/n-3 ratio of 4-5/1 in order to reduce all of the risks associated with the overconsumption of n-6 PUFAs [58], [100]. This is due to either estrogen-catalyzed conversion or an increased need for EPA and DHA during pregnancy and fetal development [100]. The ability of adult males to convert ALA to DHA is either nonexistent or very low [101]. The researchers hypothesized that boys' low-to-absent conversion meant that pre-formed DHA intake from food may be more "critical for maintaining adequate DHA concentrations in young men" than in women [101, 102].

Higher n-6/n-3 ratios in modern diets lead to larger quantities of LA- and AA-derived lipid mediators [58], [100]. English walnuts are an exception, with values of 9 g ALA and 38 g LA per 100 g chopped English walnuts and a dietary n-6: n-3 ratio of 4:1. Most other nuts were high in LA and not very high in ALA. The seeds of chia and flax (linseed) are rich in ALA. In 100 grams, chia has 17.8 g of ALA and 5.84 g of LA; in 100 grams of flaxseed, there are 53.37 g of ALA and 14.25 g of LA; in 100 grams of hemp seeds, there are

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8.864 g of ALA and 1.34 g of LA. Supplements containing EPA and DHA from marine algae or flax (linseed) oil have lower levels of LA than other oils [103], [104].

Incorporating Omega-3 Fatty Acids into Dietary Plans

Factors that were positively associated with n-3 LCPUFA levels included age, female sex (women under 50 years old), wine consumption, and the triacylglycerides (TAG) form; factors that were negatively associated with n-3 LCPUFA levels included genetics, BMI, and smoking. Human health depends on omega-3 fatty acids such as EPA and DHA, which are mostly found in marine foods such as fish oil. Depending on their chemical composition, omega 3 supplements can appear in various ways when consumed. These forms consist of phospholipids, triacylglycerides (TAG), and ethyl ester (EE) [105].

The naturally occurring fats and oils in living organisms are called triacyl glycerides (TAG). They were composed of three chains of fatty acids joined to a glycerol backbone. The main dietary lipids found in foods such as nuts and fish are TAGs. Omega-3 fatty acids and ethanol are synthesized to produce ethyl ester (EE) versions of omega-3 fatty acids. TAG forms of omega-3 fatty acids are more bioavailable than EE forms, according to some studies [106], [107],[108]. When ethanol is applied to omega-3 fatty acids in fish oil, an ethyl ester form is produced. Although EE forms are frequently included in omega-3 supplements, their bioavailability is lower than that of the triglyceride forms because the body must first convert them back to the triglyceride form before absorption can occur. However, in many instances, this difference may not be clinically meaningful [109].

The phospholipid form of omega-3 fatty acids, which are present in krill oil supplements, is also thought to have good bioavailability. Studies have indicated that phospholipid forms may be easier for cells to absorb than other forms, which may have advantages over other forms; however, further research is required in this area [106]. The phospholipid form of omega-3 fatty acids, which are present in krill oil supplements, is also thought to have good bioavailability. Studies have indicated that phospholipid forms may be easier for cells to absorb than other forms, which may have advantages over other forms; however, further research is required in this area [110].

In conclusion, the ethyl ester (EE) forms of triglycerides are not always as bioavailable as chemically bonded (TAG) forms in omega-3 supplements, but the difference may not always be clinically relevant. There could also be benefits associated with phospholipid forms, but further study is required to completely comprehend them.

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Counseling Strategies for Patients

The best medical nutrition therapies for CVD prevention are those that encourage a healthy diet in terms of both quantity and quality of calories and support long-term patient adherence [111] . The replacement of saturated fats with unsaturated fats lowers the risk of CVD. Dietary Approaches to Stop Hypertension (DASH) and the Mediterranean Diet have the strongest evidence for preventing cardiovascular disease (CVD) [112], [111, 113]. The intake of lipids influences how a long-term low-carbohydrate diet affects the risk and mortality of CVD [114, 115].

Intermittent fasting may lower overall calorie intake, help patients who are pre-obese or obese lose weight, and improve metabolic parameters linked to CVD (such as blood pressure, lipids, insulin sensitivity, and inflammatory markers) [116]. Eating fewer large meals throughout the day is not as nutritious as eating several smaller meals. Consuming nutritious whole foods (fruits and vegetables, for example), high levels of vitamin D and calcium are linked to a lower risk of CVD [116]. Consuming foods high in omega-3 fatty acids is associated with a lower risk of cardiovascular disease (CVD) [117]. Taking supplements that combine EPA and DHA may also lower the risk of CVD events [118], [119], The potential benefit of omega-3 fatty acid consumption on CVD may vary depending on baseline risk, statin use and the composition of the supplement [120]. Sclerostin is a small protein expressed by osteocytes and bone cells that plays an important role in the regulation of bone remodeling. A humanized antibody against sclerostin for postmenopausal osteoporosis therapy was approved by the U.S. Food and Drug Administration (FDA) in April 2019 and demonstrated a protective role in the cardiovascular system. It could inhibit inflammatory cytokines and chemokines to prevent both aortic aneurysm (AA) and atherosclerotic development, and protect the cardiovascular system [10].

In addition to heredity, unhealthy eating habits, inactivity, and tobacco use can have a separate impact on the risk of CVD [121]. Adopting a positive lifestyle is linked to a roughly 50% decrease relative risk of coronary heart disease compared with adopting a negative lifestyle [122]. Educating patients on evidence-based meal planning and dietary practice guidelines is one way to implement healthy nutrition. The other is to refer patients to a dietitian nutritionist for medical nutrition therapy, which can assist in the management of CVD risk factors and lower CVD risk [123] ,[124].

Gaps in Research and Future Directions: According to recent studies, n-3 PUFA are bonded to EPA ethyl esters (IPE). appear to have distinct biological effects and bioavailability after eating compared to neutral forms of omega-3 polyunsaturated fatty acids [125]. Most clinical trials have employed neutral forms of n-3 PUFA supplementation, either as free fatty acids or attached to ethyl esters or triacylglycerides (TAG). According to recent studies, n-3 PUFA attached to polar lipids (PL), including phospholipids, appear to have distinct biological effects and bioavailability when consumed than when n-3 PUFA are in a neutral state. In this review, we address the potential health advantages of marine PL rich in n-3 PUFA, which appear to

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surpass those of neutral n-3 PUFA. To fully understand the biological actions of marine n-3 PL and its potential applications in functional foods and nutraceuticals, extensive research is necessary [126].

Unexplored aspects of cardiovascular disease: Nevertheless, there has been conflicting research on the efficacy of plant-based ALA. Although some studies have suggested that ALA may be beneficial for heart health, others have not produced meaningful results. Consequently, further investigation is required to elucidate the role of ALA in the prevention of cardiovascular diseases [127]. Better outcomes for 3-point major adverse cardiovascular events (MACE), CV death, and fatal or nonfatal MI were observed in RCTs that focused solely on EPA. Hospitalization for heart failure, all-cause mortality, and fatal or non-fatal stroke did not show any advantages. Notably, research on EPA alone and in conjunction with DHA revealed a markedly higher risk of atrial fibrillation with a recent beginning. Therefore, well-designed research is required to explore the underlying processes responsible for the different effects of EPA and DHA on cardiometabolic disorders [128].

Potential Areas for Future Investigation

One can benefit from omega-3 essential nutrients and lower the risk of heart disease by eating more nuts, seeds, and fatty fish. Further research is required to completely comprehend the pathways via which omega-3 affects heart health. Subsequent investigations should examine the ideal quantity and length of omega-3 supplementation, along with any possible correlations between omega-3 and additional dietary or lifestyle elements that may impact heart health. We can learn more about how to prevent cardiovascular diseases by pursuing research on the connection between omega-3 fatty acids and cardiovascular health.

Owing to the greater n-6/n-3 ratio in contemporary diets, more LA-derived proinflammatory molecules are produced than n-3 PUFA-derived proinflammatory molecules, which have anti-inflammatory properties. Consequently, it is becoming increasingly important to maintain a balanced ratio of these two PUFA families in diet and daily consumption to support both the prevention of the genesis of contemporary chronic diseases and the healthy development and function of the human body [58].

Variations in LC ω-3 PUFA types (EPA plus DHA or EPA alone), doses, and comparators (corn oil, mineral oil, or other substances) have contradictory results and require further research in this area [129].

The precise mechanisms by which the gut microbiota influences omega-3 production and cardiovascular health are still being clarified. Further research is needed to completely comprehend the intricate interactions between gut bacteria, omega-3 fatty acids, and CVDs [43].

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Conclusion

Omega-3 PUFA have been approved as therapeutic and preventive measures for the management of several cardiovascular illnesses. α-linolenic acid (ALA; 18:3 ω-3), eicosapentaenoic acid (EPA; 20:5 ω-3), and docosahexaenoic acid (DHA; 22:6 ω-3) are examples of omega-3 polyunsaturated fatty acids (PUFAs). Green leafy vegetables, flaxseed, walnuts, soybean, and canola oils all contain alpha linolenic acid (ALA), and English walnuts, chia seeds, and flax (linseed) are rich in ALA. ALA is transformed into EPA and DHA. EPA and DHA sources are breast milk and fish, seafood, fish oil, oleaginous microalgae, marine bacteria, and bivalves, which are potential substitutes for fish and seafood. Gut symbiotic bacteria metabolize dietary precursors such as ALA for the synthesis of short-chain fatty acids (SCFAs). Recent research indicates that consuming omega-3-rich foods has positive effects on cardiovascular health. The beneficial effects of n-3 PUFAs are due to a set of various mechanisms of action (antiarrhythmic, antithrombotic, reduced plasma triglyceride levels, resolved inflammatory states, regulation of the expression of several genes and transcription factors, and action on membrane fluidity by influencing signal transduction).

The risks of myocardial infarction, MACE, and cardiac death were significantly reduced when n-3 PUFA was added. The effects of EPA and DHA on the omega-3 index and risk of cardiovascular disease are inversely related. Lower EPA: AA ratios were associated with a higher risk of death in hospitalized patients with decompensated heart failure. EPA ethyl ester (IPE) therapy had a 31% decreased risk of cardiovascular death, nonfatal MI, and nonfatal stroke. Increased EPA and DHA intake and levels are associated with a decreased risk of coronary events. IPE exerts differential bioavailability and biological effects. High intake of marine n-3 PUFAs is associated with a lower risk of acute major ischemic episodes and overall CVDs, while no discernible correlation was observed with plant-derived ALA[83][83][83]. The dose-response analysis showed that a 5% lower risk of both all-cause and CVD mortality was linked to every additional 1 g/day of ALA intake, which was equivalent to one tablespoon of canola oil or 0.5 ounces of walnuts. EPA showed 25% and 30 % reductions in MACE and MI, respectively, when used 1 g per day. Notable reductions in MACEs and all-cause mortality were observed with higher dosages and longer intervention periods (daily dose intervention time > 8 g/day). Daily DHA and EPA use for ten weeks resulted in higher blood triglycerides levels in the DHA group than in the EPA group. combination of EPA and DHA was more effective.

Recent American and European guidelines have stated that prescribing omega-3 fatty acids (EPA + DHA or EPA only) at a dose of 4 g/day (>3 g/day of total EPA + DHA) is an effective and safe option for reducing triglycerides. To meet the daily needs of EPA and DHA, it is recommended to consume two–three meals of fatty fish each week. The World Health Organization (WHO) has also suggested adding 200–500 mg of EPA + DHA to adult women. The WHO also suggests that vegetarians who do not eat fish should ensure adequate intake of plant sources of ALA. Adult males' ability to convert ALA to DHA is either nonexistent or very low; therefore, pre-formed DHA intake from food is more critical for maintaining adequate DHA concentrations in young men than in women. Supplements with chemically bonded triacylglycerides (TAG)

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are more bioavailable than the ethyl ester (EE) forms. The potential benefit of omega-3 fatty acid consumption on CVD may vary depending on the baseline risk, statin use, and composition of the supplement. Dietary Approaches to Stop Hypertension (DASH) and the Mediterranean Diet have the strongest evidence for preventing cardiovascular disease (CVD). Variations in LC ω-3 PUFA ideal quantity, length of omega-3 supplementation, types (EPA plus DHA or EPA alone), doses, and comparators (corn oil, mineral oil, or other substances), and any possible correlations between omega-3 and additional dietary or lifestyle elements that may impact heart health have contradictory results and need more research in this area.

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