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Review Article

Cardiovascular Importance of Omega-3 Fatty Acids: A Depth Review

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Abstract

Omega-3 fatty acids are a class of polyunsaturated fats that are present in many dietary sources. They have attracted a lot of interest in the field of cardiovascular health. This extensive study offers a detailed examination of the cardiovascular significance of omega-3 fatty acids, looking at its function in the prevention and treatment of cardiovascular disorders. The introduction of the review explains the various kinds of omega-3 fatty acids, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that are present in fatty fish and supplements. Their anti-inflammatory, antiarrhythmic, and lipid-lowering actions are some of the mechanisms of action that are being examined. It provides insights into the effect of omega-3 fatty acids on risk factors for cardiovascular illnesses, such as hyperlipidemia, hypertension, and endothelial dysfunction. The study of epidemiological research randomized controlled studies, and meta-analyses are crucial. The review looks into how omega-3 fatty acids could help to lower the risk of serious heart attacks such as myocardial infarction, stroke, and sudden cardiac death. Also covered in depth are the effects of omega-3 supplementation on known cardiovascular diseases including atherosclerosis and heart failure. Omega-3 fatty acid safety, doses, and sources are examined, addressing queries about toxicity and recommended dietary ranges. The review's conclusion highlights the expanding body of research that shows omega-3 fatty acids have positive cardiovascular effects and the possibility that these organic substances might be useful supplements to traditional cardiovascular treatments. In boosting heart health, it emphasizes the need of a balanced diet, lifestyle changes, and the prudent use of omega-3 supplements. With a thorough analysis of their methods of action and effects on cardiovascular risk factors and outcomes, this in-depth study highlights the cardiovascular significance of omega-3 fatty acids. Healthcare professionals, researchers, and those looking to improve their cardiovascular health by dietary and supplement changes can all benefit from the data reported in this analysis.

Keywords: Omega-3 fatty acids, Eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), Cardiovascular, low-density lipoproteins (LDL).

Introduction

It is becoming more widely known that frequent fish eating, or the addition of fish oils rich in long-chain omega-3 polyunsaturated fatty acids (n-3 PUFAs) to one's diet, reduces the risk of coronary heart disease (CHD) and guards against sudden cardiac death. Hugh Sinclair, a British physiologist, initially proposed the idea that fish fatty acids may have cardio protective effects in the early 1940s.

He contended that the rise in Western illnesses like CHD may be due to a possible fatty acid deficit(Albert et al., 2002)(Hu et al., 2002). Researchers have recently tested the omega-3 fatty acids (n3-FAs), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), to see if they can lower the risk of cardiovascular disease (CVD) in those who have taken statins.

The World Health Organization (WHO) reports that atherothrombotic cardiovascular disease (CVD) is now the main cause of death worldwide, with low- and middle-income nations being disproportionately affected(Kaptoge et al., 2019). CV risk continues despite low-density lipoproteins (LDL) being well controlled with oral and non-oral therapies, possibly in part because of high triglyceride (TG)-rich lipoproteins (TGRLs), a dyslipidemia that is particularly common in individuals with diabetes and metabolic syndrome(Ganda et al., 2018)(Libby, 2015). Increased CV risk is associated with TGRL concentrations and the accompanying proteins apolipoprotein C3 (ApoC3) and angiopoietin-like 3 (ANGPTL3), which restrict lipoprotein lipase (LPL) function and cause TGRL levels to rise. Human mendelian randomization studies firmly establish the link between TGRL and atherosclerotic events, but they cannot establish the independence of TGs as a risk factor on its own since variations frequently have pleiotropic effects that may affect disease aetiology(Burgess et al., 2014)(Ference et al., 2019).

In individuals with well-controlled LDL-C levels and excessive TGs, randomised CV studies have evaluated n3-FAs for residual risk reduction. The outcomes of these trials have been wildly disparate, despite similar and successful TG reductions.

Icosapent ethyl (IPE), an ethyl ester formulation of eicosapentaenoic acid (EPA), has been shown to have advantages, but not those of more conventional mixed n3-FA preparations or other TG-lowering medicines(Mason et al., 2022)(Mason & Eckel, 2021). Compared to DHA, EPA keeps the usual phospholipid packing restrictions, competes with arachidonic acid for cyclooxygenase (COX), and improves endothelial function when combined with a high intensity statin(Sherratt et al., 2022).

The European Society for Cardiology, national cardiac societies, and the American Heart Association/American College of Cardiology most recently recommended consuming 1 g/day of the marine omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for secondary prevention, cardiovascular prevention, treating myocardial infarction after it has occurred, and preventing sudden cardiac death(Howard, 2007)(De Backer et al., 2004).

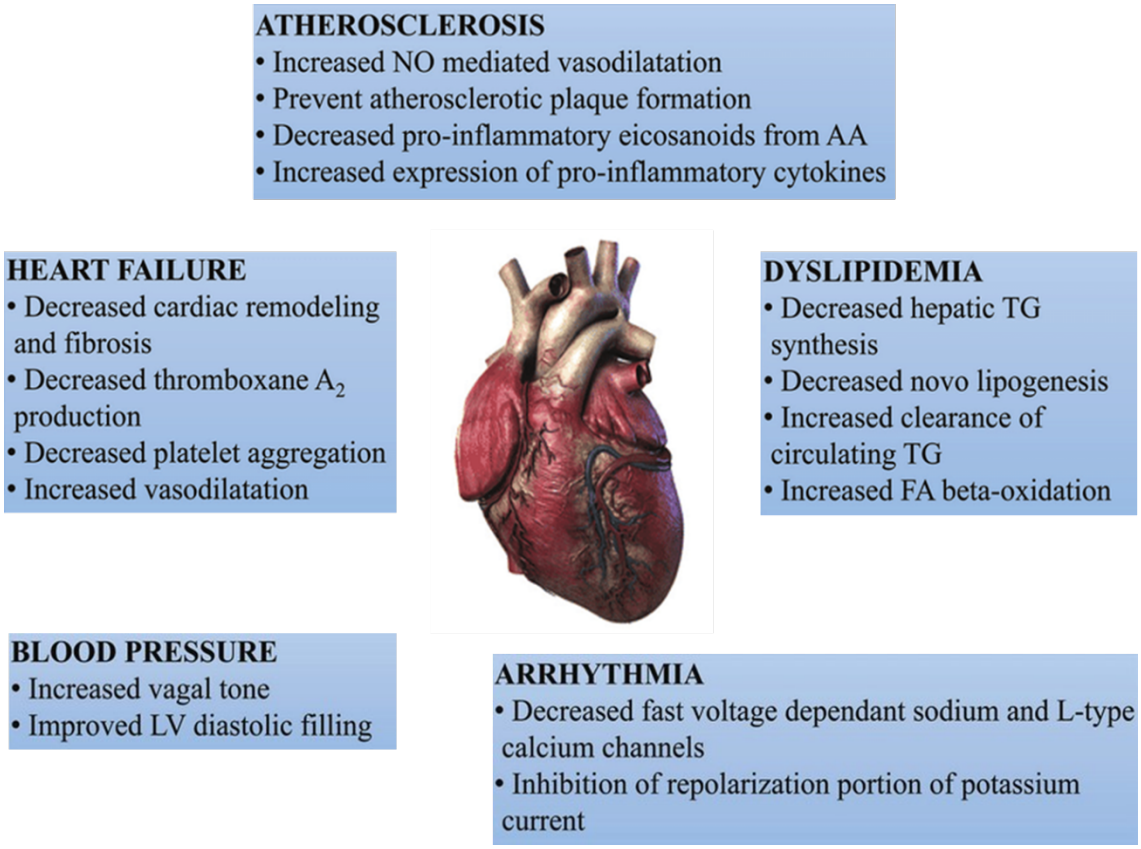

Figure 1: The cardiovascular effects of omega-3 polyunsaturated fatty acids

1.1. Epidemiologic studies

The risk of sudden cardiac mortality and heart illness is often lower among those who consume fish. When the omega-3 fatty acid content of the fish ingested is taken into consideration, this link tends to be greater in studies(Zhang, 2015). However, strong concentration-risk dependency is seen when looking at biomarkers of omega-3 fatty acids: People with 6.5% more omega-3 fatty acids in their red blood cell membranes than those with 3.3% do so at 90% lower risk of abrupt cardiac mortality. These statistics are from a case-control study that was conducted in Seattle on matched controls and victims of sudden cardiac death. Similar findings have been observed in the Physicians' Health Study: After adjusting for confounders, doctors with whole blood omega-3 fatty acid levels of 6.87% had 90% lower risk of sudden cardiac death than doctors with whole blood levels of 3.58%(Harris, 2005)(Siscovick et al., 1995)(Friedman et al., 2013). Omega-3 fatty acids are likewise linked to lowered risk in various parts of the vasculature: The risk of stroke was 0.48 (95% confidence range 0.21-1.06) in women who consumed fish five or more times per week, compared to 1.0 in those who did so less frequently (less than once per month)(Iso et al., 2001).

1.2. Omega-3 and cardiovascular health

Numerous epidemiological, observational, experimental, and randomised controlled experiments carried out over the past three decades have proven the beneficial cardiovascular benefits of the long chain omega 3 fatty acids DHA and EPA(Kris-Etherton et al., 2003)(Kones et al., 2018). These advantages appear to be principally brought about by the DHA and EPA enrichment of membrane phospholipids, which enhances artery and endothelial function, decreases platelet aggregation, enhances autonomic tone, raises arrhythmic thresholds, and lowers blood pressure(Anand et al., 2008)(Ventura et al., 1993). Additionally, interleukin 6, interleukin 1, and tumour necrosis factor production are all pro-inflammatory cytokines that may be suppressed by omega 3 fatty acids. Omega 3 fatty acid dosages of 8g daily or greater enhance body composition and have anti-inflammatory benefits in heart failure patients. Omega 3 fatty acids also have positive benefits on lipid profiles, and the DHA advises individuals with excessive triglyceride levels to take 2-4 g of DHA and EPA daily(Zhao et al., 2007)(Lavie et al., 2009).

Omega 3 fatty acid therapy after a myocardial infarction decreased 2-year all-cause mortality by 29%, according to a randomized controlled research done in the late 1980s (the Diet and reinfarction trial [DART]). Fish oil capsules (about 900mg of DHA + EPA per day) and oily fish (about 300 g per week, yielding around 1 g of EPA/DHA per day) both provided the same effect(Burr et al., 1989). Large-scale trials have more recently looked at the impact of omega 3 fatty acid supplementation on CHD risk. 11,323 individuals who had a myocardial infarction during the previous three months were randomly allocated to receive or not receive 850 mg of DHA and EPA daily. Additionally, all patients received the best possible treatment through pharmaceutical therapy and dietary changes. By the end of the 3.5 year experiment, individuals who got omega 3 therapy had a 21% lower relative risk of mortality from any cause and a 45% lower relative risk of sudden cardiac death(Yokoyama et al., 2007). 18,645 individuals with hypercholesterolemia were given a statin alone or a statin combined with a highly concentrated version of ePa at a dosage of 600 mg three times per day. The ePa group's relative risk of major adverse cardiovascular events was lowered by 19% during the course of the 5-year follow-up(GISSI-HF investigators, 2008).

A randomized control study has not yet been conducted to determine the effects of omega 3 fatty acids in the primary prevention of cardiovascular mortality. Although the secondary prevention cohort (n = 3,664) and the primary prevention cohort of the Jelis (n = 14,981 hypercholesterolemia, statin treated patients) both experienced a similar relative risk reduction (18% vs. 19%), the latter group's reduction was statistically significant (P=0.048) while the former's was not. The consistency in effect sizes shows that the primary prevention cohort's lack of statistically significant impact was due to sample size and not to a difference in efficacy(Saito et al., 2008).

1.3. Fish or fish oils?

An omega 3 fatty acid formulation at a dosage of 4 g per day has been authorised by the FDA for the treatment of individuals with extremely high triglyceride levels. The greatest available concentration of omega 3 acid ethyl esters, including both DHA and EPA, is found in this formulation, which is only accessible in the US with a prescription.

Because fish oil supplements lack some essential minerals including vitamin D, selenium, and naturally occurring antioxidants that are present in oily fish, some experts recommend using dietary sources of fatty fish as the primary supply of omega 3 fatty acids. Indeed, despite the fact that omega 3 fatty acids have not continually been demonstrated to lower C reactive protein levels, obese, insulin-resistant patients experienced significant drops in C reactive protein levels after 4 weeks on a diet supplemented with cod protein when compared to those on diets containing

comparable amounts of other types of protein(Madsen et al., 2007)(Balk et al., 2006)(Ouellet et al., 2008).

Additionally, selenium, which is found in fish in variable amounts, is regarded to have antioxidant characteristics, the capacity to lessen the negative effects of methyl mercury, and to be beneficial for the cardiovascular system. Selenium is antithrombotic, lowers lipid peroxidation, myocardial infarct size, and ischemia-induced ventricular arrhythmias, enhances recovery from ischemia or reperfusion damage, and guards against free radicals(Brown & Arthur, 2001)(Mozaffarian, 2009)(Flores-Mateo et al., 2006).

1.4. Omega-3 fatty acids and human nutrition

PUFAs are crucial fatty acids for human nutrition and may be further subdivided into omega-3 (n-3) and omega-6 (n-6), based on where their first double bond is positioned in the carbon molecule. The n-3 PUFAs have their first double bond at the third carbon molecule, while the n-6 PUFAs have it at the sixth. Arachidonic acid may be created by elongating and desaturating linoleic acid, which is the main n-6 PUFA in humans. Alphalinolenic acid, on the other hand, can be transformed into the longer-chain EPA PUFA by elongating and desaturating it. Omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) are not interchangeable in the human body; they are necessary fatty acids and significant parts of nearly all cell membranes. Due to the biological effects of their metabolites, the metabolisms of fatty acids of the n-3 and n-6 families (arachidonic acid) are of special interest(Lo et al., 2022).

Example: Arachidonic acid-derived eicosanoids are pro-inflammatory and pro-aggregatory agonists, but n-3 PUFA-derived eicosanoids often suppress platelet aggregation and are anti-inflammatory(Simopoulos, 1991)(Simopoulos, 2003).

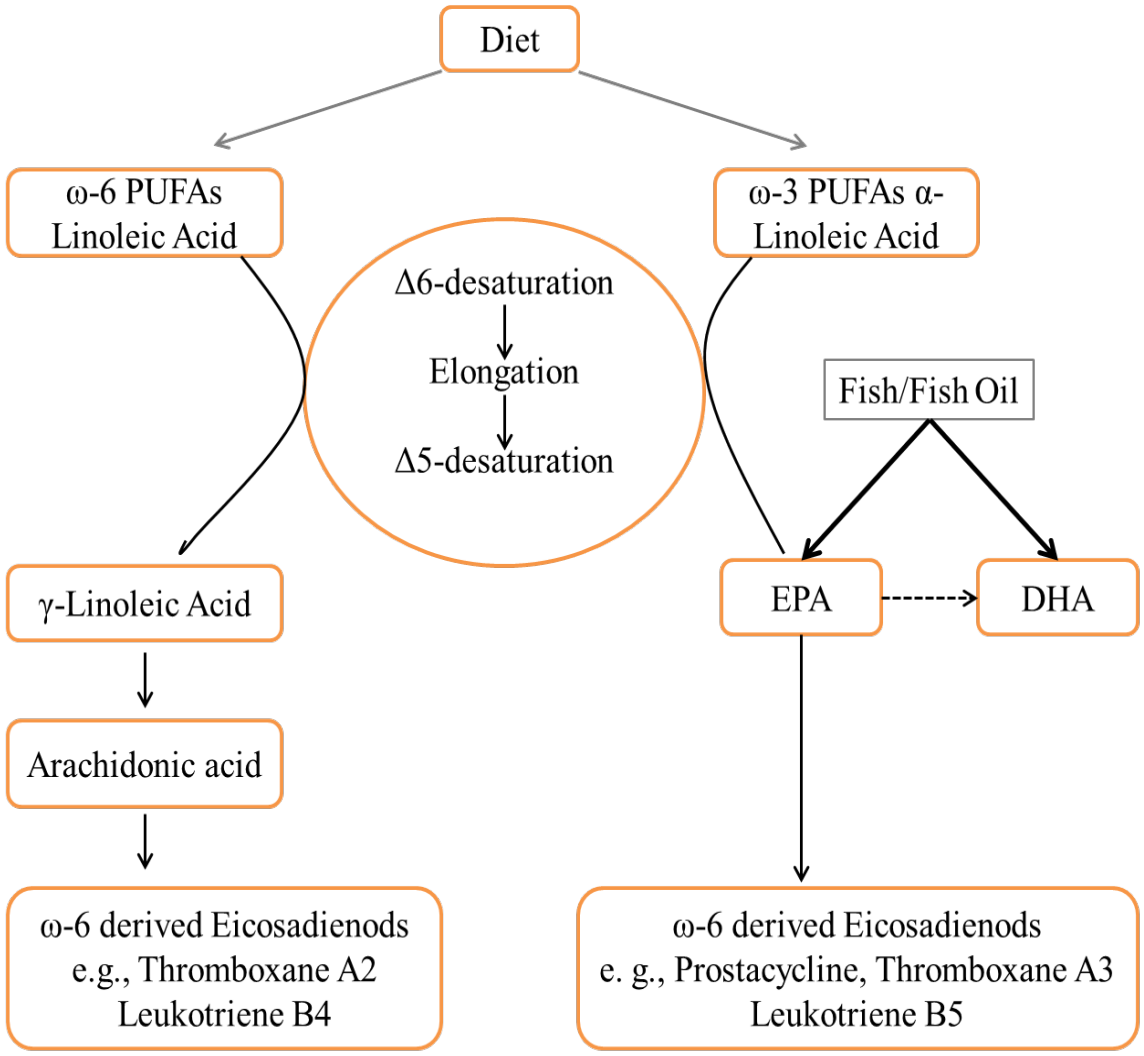

Figure 2: Desaturation and elongation pathway of the omega-3 and -6 PUFAs

1.5. Omega-3 Fatty Acid Effects on Molecular and Cellular Levels:

Lipid composition of the cell membrane affects a number of biological activities. Animal studies have shown that adding omega-3 fatty acids to the cell membrane can alter the way the cell works by interacting with and regulating the membrane proteins and channels and altering the physiochemical properties of the cell membrane. Omega-3 fatty acids may be able to alter membrane protein signalling when incorporated into membranes. Omega-3 fatty acid absorption into cell membranes also altered the H-Ras signalling protein and decreased protein kinase in animal tests. Signalling from C-theta(Mozaffarian & Wu, 2011). There are several ways that omega-3 fatty acids' anti-inflammatory actions are mediated. Omega-3 fatty acids may prevent inflammation caused by lipopolysaccharide and decrease interleukin-2 production, according to certain animal studies. The rapid control of transcription may have an immediate impact on inflammatory pathways. Additionally, omega-3 fatty acids prevent acute phase reactants(Adkins & Kelley, 2010). The impact of omega-3 fatty acids on inflammation has been disputed by a number of studies. In a rat model of the disease, therapy with EPA and DHA was insufficient to lessen the hepatic inflammatory response induced by spinal cord damage or laminectomy. The study found that whereas EPA had no anti-inflammatory properties, DHA had some(Weylandt et al., 2012). Omega-3 fatty acids may also improve endothelial function by promoting the production of nitric oxide from endothelial cells(Massaro et al., 2008).

It is also believed that omega-3 fatty acids have anti-thrombotic properties at very high concentrations, which may prolong the time that blood clots(Cohen et al., 2011). This may be explained by omega-3 fatty acids' ability to inhibit platelets. Arachidonic acid may be replenished in cell membranes and its levels in tissues can be reduced by EPA and DHA.

EPA-derived eicosanoids had less of a vasoconstrictive and platelet aggregating effect than arachidonic acid-derived eicosanoids(Harris et al., 2008). The thromboxane A3 produced by the metabolism of omega-3 fatty acids is less potent than thromboxane A2 at activating platelets and causing vasoconstriction. Arachidonic acid, on the other hand, is converted into thromboxane A2 by a metabolic process(Cohen et al., 2011).

However, investigations on humans do not consistently demonstrate an impact on coagulation factors and platelet aggregation, at least not at doses of omega-3 fatty acids that are commonly advised(Mozaffarian & Wu, 2011). Omega-3 fatty acids may directly affect heart rate because of their capacity to inhibit myocyte voltage-gated sodium channels and prolong the relative refractory period. Larger voltages will therefore be required to depolarize the cell membrane, lowering heart rate(Massaro et al., 2008).

2. CVD Risk Factors and the Effects:

It is well-known that omega-3 fatty acids reduce blood triglyceride levels in part by slowing the liver's generation of very low-density lipoprotein and in part by boosting fatty acid destruction and accelerating the removal of triglycerides from plasma(Jacobson et al., 2012). The effects of randomised controlled research on lipoproteins have resulted in a variety of results. Comparatively few research using EPA than those using DHA generally demonstrated an increase in low-density lipoprotein. High-density lipoprotein levels are often increased in patients who get DHA supplements, although the response to EPA supplementation has been inconsistent.

2.2. Heart disease, fatty seafood, and the Mediterranean diet:

According to extensive a population-based research, eating fish is strongly associated with reduced incidences of ischemic heart disease and heart failure, as well as lower heart rate and systemic vascular resistance(Mozaffarian et al., 2005)(Mozaffarian et al., 2006). Dietary guidelines from the American Heart Association state that you should have fish at least twice a week, preferably oily fish like salmon, herring, and mackerel(Yashodhara et al., 2009). Fish and other seafood are prominent components of the Mediterranean diet. This diet also includes a moderate amount of poultry, a small amount of red meat, processed milk, and dairy products, as well as plenty of fruits, vegetables, nuts, and grains(“Primary Prevention of Cardiovascular Disease with a Mediterranean Diet,” 2013). A Mediterranean diet may assist to minimise CVD risk factors, according to several research. The risk of significant cardiovascular events, such as myocardial infarction (MI), stroke, and mortality from cardiovascular causes, can be reduced by adding extra virgin olive oil or almonds to the Mediterranean diet. According to a new primary preventive randomised study including over 7000 people at high risk of vascular events, this is particularly true(“Primary Prevention of Cardiovascular Disease with a Mediterranean Diet,” 2013).

2.3. Supplements with omega-3:

The majority of omega-3 supplements may be purchased without a prescription, however some, like icosapent ethyl (Vascepa®) and EPA and DHA ethyl esters (Lovaza®), do. Over the last 20 years, a number of randomised trials have looked at the

efficacy of omega-3 supplements in treating various cardiovascular issues, with variable degrees of success. Some studies have looked at the impact of omega-3 supplementation in reducing cardiovascular events and mortality in patients with a history of MI or chronic heart failure(Galan et al., 2011)(Marchioli, 1999)(NCT00127452, 2005)(Rauch et al., 2010)(GISSI-HF investigators, 2008).

2.4. Amino-3 fatty acid's part in cardiovascular disease

2.4.1. Role of Omega-3 fatty acid in coronary heart disease:

Elevated TG levels can result from a genetic or metabolic defect that lengthens the plasma residence period of potentially atherogenic chylomicron and/or VLDL remnants. Hypertriglyceridemia linked with increases in VLDL can be brought on by increased intravascular lipolysis of VLDL-TG, overproduction of VLDL particles by the liver, delayed clearance of minute (remnant) VLDL particles from the plasma, and/or reduced intravascular lipolysis of VLDL-TG. TG, which is produced from plasma-extracted long-chain free fatty acids, recycled fatty acids, and/or de novo synthesis from acetyl coenzyme A (CoA), is used to make VLDL particles in the liver from apo B, cholesterol, cholesteryl ester, phospholipids, and TG. Omega-3 fatty acids found in fish oil lower fasting and postprandial plasma TG concentrations without significantly affecting fat absorption(Harris, 1989). Clinical investigations typically demonstrate that the TG-lowering effects of EPA and DHA are comparable(Park & Harris, 2003). EPA and DHA proportions in phospholipids increased two to three fold over baseline levels after four months of therapy with 3.4 g/day of EPA and DHA(Harris et al., 1997). These results provide compelling evidence that these fatty acids can reduce hepatic VLDLTG synthesis and release while simultaneously improving TG clearance from chylomicrons and VLDL particles. Other fatty acids, such oleate, are preferentially absorbed into triacylglycerol, whereas EPA (and DHA) are preferentially redirected into phospholipid synthesis routes(Miller et al., 1993).

2.4.2. Role of Omega-3 fatty acid in cerebral blood flow

The necrosis of the brain tissue brought on by ischemia is referred to as a cerebral infarction. The cerebral blood flow (CBF) rate in a healthy person is 50 10 mL/100 g/min. Brain waves and the cerebral cortex evoked potential entirely vanish when CBF falls to 15 mL/100 g/min, yet cerebral cells continue to function. Additionally, when CBF falls even lower, to 8–10 mL/100 g/min, the ion pumps in neuronal membrane start to malfunction, causing sodium inflow and potassium efflux, which leads to the death of brain cells and cerebral infarction. Traditional definitions of TIA included bouts of neurologic impairment brought on by localized cerebral ischemia that resolve entirely in 24 hours(Mijalski & Silver, 2015). In 2009, the American Heart Association updated the terminology, switching it from a time-based definition to a tissue-based definition(Kaur et al., 2014). Currently, the diagnosis of TIA primarily depends on the results of CT or MRI scansWhen an ischemic stroke damages brain cells, it is referred to as cerebral ischemia/reperfusion (I/R) injury, and the ischemic injury even worsens once hemoperfusion is restored. N-3 PUFAs can reduce the size of cerebral infarction by dietary supplementation in part by altering the activity of antioxidant enzymes and in part by acting directly as an antioxidant(Shirle et al., 2014). By improving the antioxidative ability, decreasing the induction of chaperon molecules, stabilizing membrane integrity, and decreasing lipid peroxidation, n-3 PUFA supplementation and chronic administration can alleviate the symptoms of cerebral I/R(D. Y. Yang et al., 2007). DHA can raise the expression of Nrf2 and HO-1 in glial cell cultures, but it is insufficient to promote their expression in living organisms. Actually, DHA therapy after an ischemic stroke can only act as a catalyst for Nrf2 and HO-1 promotion(Y. C. Yang et al., 2013). Ischemic stroke will result in complicated cellular reactions that include the activation of glial cells and the recruitment of inflammatory cells in terms of inflammation(Zúñiga et al., 2011). By increasing the expression of chemo attractant receptors, EPA and DHA can have neuroprotective benefits by preventing the activation of macrophages and microglia as well as the migration of neutrophils and monocytes. The production of ant apoptotic proteins like Bcl-xL and Bcl-2, which block the inflammatory response mediated by microglial cells, can also be increased by DHA(Duling, 1973).

2.4.3. Role of Omega-3 fatty acid in Peripheral artery disorder:

The illness known as peripheral artery disease (PAD) has a big influence on our society's health. Population-based studies indicate that more than 12% of individuals over 65 and more than 20% of those over 75 are thought to be affected by PAD(Criqui et al., 1985). According to a more recent research, over one-third of primary care patients over the age of 70 had PAD(Hirsch et al., 2001). In general, the public lacks adequate understanding of PAD, with significant knowledge gaps about the disease's description, risk factors, symptoms, and risks of amputation or fatality(Hirsch et al., 2007). The International Reduction of Atherothrombosis for Continued Health (REACH) Registry found that

hospitalisation and drug costs for treating PAD were higher than those for treating either coronary artery disease (CAD) or cerebrovascular disease (CVD)(Mahoney et al., 2008). There is a tremendous need for affordable therapy to prevent and cure PAD.

The HMG-CoA reductase and ACE enzymes are assumed to be naturally inhibited by n-3 FAs, which are also believed to work as anti-arrhythmic, anti-hypertensive, anti-atherosclerotic, anti-inflammatory, cytoprotective, and cardio protective agents(Das, 2008).

2.4.4. Role of Omega-3 fatty acid in aortic disorder:

The most frequent reason for interventional therapy of the heart valves is aortic valve stenosis (AVS)(Nkomo et al., 2006), impacting 10% or more of those over the age of 80(Eveborn et al., 2013). Aortic valve leaflets that are fibro calcific and have a smaller valve aperture are symptoms of AVS(Bäck et al., 2013). Significant cardiac outflow blockage arises when AVS is bad enough. Aortic valve replacement is the only currently accessible and efficient therapeutic option for AVS because there is no pharmaceutical therapy for the condition. The left ventricle's blood can flow towards the aorta when the aortic valve opens and shuts in a synchronized motion(Bäck et al., 2013). AVS has been associated with inflammation, which is shown systemically by elevated levels of C-reactive protein (CRP), according to several research(Galante et al., 2001)(Aikawa et al., 2007). More proof of the critical role that inflammation plays in AVS is provided by animal models of aortic valve disease that exhibit increased lipoprotein infiltration combined with endothelial damage, inflammatory cell infiltration, and calcification of the aortic valve(Weiss et al., 2013). phagocytes and other cells that are inflammatory upregulate ECM-degrading enzymes and pro-inflammatory cytokines(Aikawa et al., 2007)

2.4.5. Role of Omega-3 in arrhythmia

Laboratory research on isolated newborn rat cardiac myocytes and experimental studies on canine models have both been used to investigate the purported anti-arrhythmic characteristics of n-3 PUFAs, particularly EPA and DHA. For instance, in exercising conscious dogs with prior surgically-induced, large myocardial infarctions, ischaemia-induced sudden cardiac death was reduced by preventing ventricular fibrillation by intravenously infusing an emulsion of fish oils and free fatty acids just before coronary artery obstruction (with an inflatable cuff placed around the left circumflex artery). The administration of pure free EPA, DHA, and -LNA in separate intravenous doses had similar outcomes(McLennan, 2001)(Billman et al., 1997)(Billman et al., 1999).

In fact, the mechanism(s) underlying the antiarrhythmic effects of n-3 PUFAs were subsequently investigated in isolated spontaneously contracting cultured neonatal rat cardiac myocytes. These myocytes were induced to fibrillate by adding various toxic agents (such as toxic concentrations of Ca2+, ouabain, and beta-adrenergic agonist) separately to the bathing superfusate. Curiously, low dosage n-3 PUFAs(Leaf, 2002).

Table 1: Omega-3 fatty acids' ability to prevent arrhythmias has been demonstrated

S.No.	Studies	Methods	Finding	References
1.	Animal studies	Pre-fed n-3 PUFAs and programmed electrical stimulation in anaesthetized marmoset monkeys	The sensitivity of healthy or ischemic myocardium to arrhythmias is increased by dietary n-3 PUFAs.	(McLennan et al., 1993)
2.	Animal Studies	One of four experimental food groups was randomly assigned to rats for a 12-week period. By blocking and opening cardiac arteries, arrhythmias were generated.	Diets including canola oil (55% oleic, 8% ALNA), as well as fish oil, significantly increased the risk of VF, mortality, and arrhythmia scores when compared to other diets; however, high amounts of LA reduce ALNA's efficacy.	(McLennan & Dallimore, 1995)
3.	Animal Studies	Two significant dietary n-3 PUFAs found in fish oil were administered intravenously in a model of sudden cardiac mortality brought on by coronary blockage in an active dog.	Purified n-3 PUFAs can avert VF brought on by ischaemia.	(Billman et al., 1999)
4.	Isolated Working Heart Model	For 16 weeks, 60 mature male rats were given a low-fat standard diet, an isoenergetic saturated fat diet, or a fish oil diet. Washing porcine erythrocytes were utilised to	When isolated hearts were exposed to various stimulus, dietary fish oil reduced the onset and increased the extent of arrhythmias.	(Pepe & McLennan, 1996)

		perfuse the separated hearts.		
5.	Human studies	The use of fish oil or sunflower seed oil as a placebo was randomly assigned to 68 outpatients with frequent VPCs (minimum of 2000 VPCs over 24 hours) on Holter.	Nearly 50% of people using fish oil supplements experience a decrease in VPCs as a result of the moderate dose of fish oil's anti-arrhythmic action.	(Sellmayer et al., 1995)
6.	Isolated Animal Cardiac Myocytes	Rat neonatal cardiac myocytes were tested for their capacity to stop tachyarrhythmias brought on by a beta-adrenergic agonist.	Mono-unsaturated and saturated fatty acids, but not fish oil in particular, were unable to effectively stop and prevent arrhythmias without impairing the ability of cells to contract.	(Kang & Leaf, 1995)
7.	Case-control study	493 controls and 334 instances of primary cardiac arrest	As n-3 PUFAs from seafood are consumed regularly, the risk of primary cardiac arrest is reduced by 50% as compared to those who do not.	(Siscovick et al., 1995)

2.4.6. Role of omega-3 fatty acid in Myocardial Infarction

Patients with a recent acute MI were evaluated with an EPA/DHA prescription formulation (1.8 g/d) in the OMega-3 fatty acids in Elderly with Myocardial Infarction (OMEMI) experiment. Even though median EPA levels (87%) rose, the EPA/DHA therapy did not lower the main outcome of CV events. In outcome studies utilising n3-FAs, a minimum or threshold level of EPA could be necessary for a substantial decrease in CV risk. Even when compared to the JELIS trial's baseline levels (89.6 vs. 97 g/mL, respectively), the overall median on-treatment EPA levels were low in strength and were 40% lower than in reduce-it participants. Further research is necessary, but it's possible that the chemical form of the fatty acids in each formulation has a role in variations in absorption, distribution, and ultimately clinical effects (Kapoor et al., 2021)(Kalstad et al., 2021)(Myhre et al., 2021).

Conclusion:

This comprehensive study offers a solid understanding of the significance of Omega-3 fatty acids for the cardiovascular system. Omega-3 fatty acids may be useful tools in the prevention and management of cardiovascular illnesses, according to the research that has been given. Healthcare practitioners, academics, and everyone interested in improving cardiovascular health should consider the implications of these results.

A diet and way of living that encourages regular consumption of Omega-3 fatty acids, together with wise supplementation when necessary, can enhance heart health and general wellbeing. There are several methods via which omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are advantageous for cardiovascular health. These include lipid-lowering capabilities, anti-inflammatory benefits, and antiarrhythmic actions. These processes are essential for reducing the risk factors for cardiovascular illnesses. Numerous investigations, including epidemiological and randomized controlled trials, have repeatedly shown that Omega-3 fatty acids have a positive effect on a variety of cardiovascular risk factors. They have been proven to lessen endothelial dysfunction, hypertension, and hyperlipidemia, all of which are key contributors to the development of cardiovascular illnesses. Psoriatic arthritis is a major issue since it is one of much comorbidity that is linked to psoriasis. In order to stop future joint deterioration and enhance the patient's overall quality of life, early detection and treatment are crucial. In this context, regular monitoring and cooperation between dermatologists and rheumatologists are crucial.

References

1. Adkins, Y., & Kelley, D. S. (2010). Mechanisms underlying the cardioprotective effects of omega-3 polyunsaturated fatty acids. In Journal of Nutritional Biochemistry. https://doi.org/10.1016/j.jnutbio.2009.12.004
2. Aikawa, E., Nahrendorf, M., Sosnovik, D., Lok, V. M., Jaffer, F. A., Aikawa, M., & Weissleder, R. (2007). Multimodality molecular imaging identifies proteolytic and osteogenic activities in early aortic valve disease. Circulation. https:// doi.org/ 10.1161/ CIRCULATIONAHA.106.654913
3. Albert, C. M., Campos, H., Stampfer, M. J., Ridker, P. M., Manson, J. E., Willett, W. C., & Ma, J. (2002). Blood Levels of Long-Chain n–3 Fatty Acids and the Risk of Sudden Death. New England Journal of Medicine. https://doi.org/10.1056/nejmoa012918
4. Anand, R. G., Alkadri, M., Lavie, C. J., & Milani, R. V. (2008). The role of fish oil in arrhythmia prevention. In Journal of Cardiopulmonary Rehabilitation and

Prevention. https:// doi.org/ 10.1097/ 01.HCR. 0000314202.09676.f0
5. Bäck, M., Gasser, T. C., Michel, J. B., & Caligiuri, G. (2013). Biomechanical factors in the biology of aortic wall and aortic valve diseases. In Cardiovascular Research. https:// doi.org/10.1093/cvr/cvt040
6. Balk, E. M., Lichtenstein, A. H., Chung, M., Kupelnick, B., Chew, P., & Lau, J. (2006). Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: A systematic review. In Atherosclerosis. https://doi.org/10.1016/j.atherosclerosis.2006.02.012
7. Billman, G. E., Kang, J. X., & Leaf, A. (1997). Prevention of ischemia-induced cardiac sudden death by n-3 polyunsaturated fatty acids in dogs. Lipids. https://doi.org/10.1007/s11745-997-0149-2
8. Billman, G. E., Kang, J. X., & Leaf, A. (1999). Prevention of sudden cardiac death by dietary pure ω-3 polyunsaturated fatty acids in dogs. Circulation. https://doi.org/10.1161/01.CIR.99.18.2452
9. Brown, K., & Arthur, J. (2001). Selenium, selenoproteins and human health: a review. Public Health Nutrition. https:// doi.org/ 10.1079/phn2001143
10. Burgess, S., Freitag, D. F., Khan, H., Gorman, D. N., & Thompson, S. G. (2014). Using multivariable Mendelian randomization to disentangle the causal effects of lipid fractions. PLoS ONE. https:// doi.org/ 10.1371/ journal. pone.0108891
11. Burr, M. L., Gilbert, J. F., Holliday, R. M., Elwood, P. C., Fehily, A. M., Rogers, S., Sweetnam, P. M., & Deadman, N. M. (1989). EFFECTS OF CHANGES IN FAT, FISH, AND FIBRE INTAKES ON DEATH AND MYOCARDIAL REINFARCTION: DIET AND REINFARCTION TRIAL (DART). The Lancet. https:// doi.org/10.1016/S0140-6736 (89)90828-3
12. Cohen, M. G., Rossi, J. S., Garbarino, J., Bowling, R., Motsinger-Reif, A. A., Schuler, C., Dupont, A. G., & Gabriel, D. (2011). Insights into the inhibition of platelet activation by omega-3 polyunsaturated fatty acids: Beyond aspirin and clopidogrel. Thrombosis Research. https:// doi.org/ 10.1016/j.thromres.2011.04.023
13. Criqui, M. H., Fronek, A., Barrett-Connor, E., Klauber, M. R., Gabriel, S., & Goodman, D. (1985). The prevalence of peripheral arterial disease in a defined population. Circulation. https://doi.org/10.1161/01.CIR.71.3.510
14. Das, U. N. (2008). Essential fatty acids and their metabolites could function as endogenous HMG-CoA reductase and ACE enzyme inhibitors, anti-arrhythmic, anti-hypertensive, anti-atherosclerotic, anti-inflammatory, cytoprotective, and cardioprotective molecules. Lipids in Health and Disease. https://doi.org/10.1186/1476-511X-7-37
15. De Backer, G., Ambrosioni, E., Borch-Johnsen, K., Brotons, C., Cifkova, R., Dallongeville, J., Ebrahim, S., Faergeman, O., Graham, I., Mancia, G., Cats, V. M., Orth-Gomér, K., Perk, J., Pyörälä, K., Rodicio, J. L., Sans, S., Sansoy, V., Sechtem, U., Silber, S., … Wood, D. (2004). European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of eight societies and by invit. Atherosclerosis. https:// doi.org/ 10.1097/ 01.hjr.0000120621.99766.ef
16. Duling, B. R. (1973). The preparation and use of the hamster cheek pouch for studies of the microcirculation. Microvascular Research. https://doi.org/10.1016/0026-2862(73)90059-9
17. Eveborn, G. W., Schirmer, H., Heggelund, G., Lunde, P., & Rasmussen, K. (2013). The evolving epidemiology of valvular aortic stenosis. the Tromsø Study. Heart. https://doi.org/10.1136/heartjnl-2012-302265
18. Ference, B. A., Kastelein, J. J. P., Ray, K. K., Ginsberg, H. N., Chapman, M. J., Packard, C. J., Laufs, U., Oliver-Williams, C., Wood, A. M., Butterworth, A. S., Di Angelantonio, E., Danesh, J., Nicholls, S. J., Bhatt, D. L., Sabatine, M. S., & Catapano, A. L. (2019). Association of Triglyceride-Lowering LPL Variants and LDL-C-Lowering LDLR Variants with Risk of Coronary Heart Disease. JAMA - Journal of the American Medical Association. https://doi.org/10.1001/jama.2018.20045
19. Flores-Mateo, G., Navas-Acien, A., Pastor-Barriuso, R., & Guallar, E. (2006). Selenium and coronary heart disease: A meta-analysis. American Journal of Clinical Nutrition. https://doi.org/10.1093/ajcn/84.4.762
20. Friedman, A. N., Yu, Z., Denski, C., Tamez, H., Wenger, J., Thadhani, R., Li, Y., & Watkins, B. (2013). Fatty acids and other risk factors for sudden cardiac death in patients starting hemodialysis. American Journal of Nephrology. https:// doi.org/ 10.1159/ 000351764
21. Galan, P., Kesse-Guyot, E., Czernichow, S., Briancon, S., Blacher, J., & Hercberg, S. (2011). Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: A randomised placebo controlled trial. BMJ. https://doi.org/10.1136/bmj.c6273
22. Galante, A., Pietroiusti, A., Vellini, M., Piccolo, P., Possati, G., De Bonis, M., Grillo, R. L., Fontana, C., & Favalli, C. (2001). C-reactive protein is increased in patients with

degenerative aortic valvular stenosis. Journal of the American College of Cardiology. https://doi.org/10.1016/S0735-1097(01)01484-X
23. Ganda, O. P., Bhatt, D. L., Mason, R. P., Miller, M., & Boden, W. E. (2018). Unmet Need for Adjunctive Dyslipidemia Therapy in Hypertriglyceridemia Management. In Journal of the American College of Cardiology. https://doi.org/10.1016/j.jacc.2018.04.061
24. GISSI-HF investigators. (2008). Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. The Lancet. https:// doi.org/ 10.1016/ S0140-6736(08)61239-8
25. Harris, W. S. (1989). Fish oils and plasma lipid and lipoprotein metabolism in humans: A critical review. In Journal of Lipid Research. https://doi.org/10.1016/s0022-2275(20)38310-3
26. Harris, W. S. (2005). Extending the cardiovascular benefits of omega-3 fatty acids. In Current Atherosclerosis Reports. https:// doi.org/10.1007/s11883-005-0050-0
27. Harris, W. S., Ginsberg, H. N., Arunakul, N., Shachter, N. S., Windsor, S. L., Adams, M., Berglund, L., & Osmundsen, K. (1997). Safety and efficacy of Omacor in severe hypertriglyceridemia. Journal of Cardiovascular Risk. https://doi.org/10.1097/00043798-199710000-00011
28. Harris, W. S., Miller, M., Tighe, A. P., Davidson, M. H., & Schaefer, E. J. (2008). Omega-3 fatty acids and coronary heart disease risk: Clinical and mechanistic perspectives. In Atherosclerosis. https:// doi.org/ 10.1016/ j.atherosclerosis.2007.11.008
29. Hirsch, A. T., Criqui, M. H., Treat-Jacobson, D., Regensteiner, J. G., Creager, M. A., Olin, J. W., Krook, S. H., Hunninghake, D. B., Comerota, A. J., Walsh, M. E., McDermott, M. M., & Hiatt, W. R. (2001). Peripheral arterial disease detection, awareness, and treatment in primary care. Journal of the American Medical Association. https:// doi.org/ 10.1001/ jama.286.11.1317
30. Hirsch, A. T., Murphy, T. P., Lovell, M. B., Twillman, G., Treat-Jacobson, D., Harwood, E. M., Mohler, E. R., Creager, M. A., Hobson, R. W., Robertson, R. M., Howard, W. J., Schroeder, P., & Criqui, M. H. (2007). Gaps in public knowledge of peripheral arterial disease: The first national PAD public awareness survey. Circulation. https://doi.org/10.1161/CIRCULATIONAHA.107.725101
31. Howard, W. J. (2007). AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease; 2006 Update: Endorsed by the National Heart, Lung, and Blood Institute [AHA/ACC Guideline]. Yearbook of Endocrinology. https://doi.org/10.1016/s0084-3741(08)70051-9
32. Hu, F. B., Bronner, L., Willett, W. C., Stampfer, M. J., Rexrode, K. M., Albert, C. M., Hunter, D., & Manson, J. E. (2002). Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. JAMA. https://doi.org/10.1001/jama.287.14.1815
33. Iso, H., Rexrode, K. M., Stampfer, M. J., Manson, J. A. E., Colditz, G. A., Speizer, F. E., Hennekens, C. H., & Willett, W. C. (2001). Intake of fish and omega-3 fatty acids and risk of stroke in women. JAMA. https://doi.org/10.1001/jama.285.3.304
34. Jacobson, T. A., Glickstein, S. B., Rowe, J. D., & Soni, P. N. (2012). Effects of eicosapentaenoic acid and docosahexaenoic acid on low-density lipoprotein cholesterol and other lipids: A review. In Journal of Clinical Lipidology. https:// doi.org/ 10.1016/ j.jacl.2011.10.018
35. Kalstad, A. A., Myhre, P. L., Laake, K., Tveit, S. H., Schmidt, rik B., Smith, P., Nilsen, D. W. T., Tveit, A., Fagerland, M. W., Solheim, S., Seljeflot, I., & Arnesen, H. (2021). Effects of n-3 Fatty Acid Supplements in Elderly Patients after Myocardial Infarction: A Randomized, Controlled Trial. Circulation. https://doi.org/10.1161/CIRCULATIONAHA.120.052209
36. Kang, J. X., & Leaf, A. (1995). Prevention and termination of β-adrenergic agonist-induced arrhythmias by free polyunsaturated fatty acids in neonatal rat cardiac myocytes. Biochemical and Biophysical Research Communications. https://doi.org/10.1006/bbrc.1995.1385
37. Kapoor, K., Alfaddagh, A., Stone, N. J., & Blumenthal, R. S. (2021). Update on the omega-3 fatty acid trial landscape: A narrative review with implications for primary prevention. In Journal of Clinical Lipidology. https://doi.org/10.1016/j.jacl.2021.06.004
38. Kaptoge, S., Pennells, L., De Bacquer, D., Cooney, M. T., Kavousi, M., Stevens, G., Riley, L. M., Savin, S., Khan, T., Altay, S., Amouyel, P., Assmann, G., Bell, S., Ben-Shlomo, Y., Berkman, L., Beulens, J. W., Björkelund, C., Blaha, M., Blazer, D. G., … Di Angelantonio, E. (2019). World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. The Lancet Global Health. https://doi.org/10.1016/S2214-109X (19) 303 18-3
39. Kaur, N., Chugh, V., & Gupta, A. K. (2014). Essential fatty acids as functional components

of foods- a review. In Journal of Food Science and Technology. https:// doi.org/ 10.1007/ s13197-012-0677-0
40. Kones, R., Howell, S., & Rumana, U. (2018). N-3 polyunsaturated fatty acids and cardiovascular disease: Principles, practices, pitfalls, and promises - A contemporary review. In Medical Principles and Practice. https://doi.org/10.1159/000485837
41. Kris-Etherton, P. M., Harris, W. S., & Appel, L. J. (2003). Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. In Arteriosclerosis, thrombosis, and vascular biology. https:// doi.org/ 10.1161/ 01.atv.0000038493.65177.94
42. Lavie, C. J., O'Keefe, J. H., Milani, R. V., Ventura, H. O., & Mehra, M. R. (2009). New data on the clinical impact of exercise training, fish oils, and statins in heart failure. In Physician and Sportsmedicine. https://doi.org/10.3810/psm.2009.06.1706
43. Leaf, A. (2002). Prevention of fatal cardiac arrhythmias by polyunsaturated fatty acids. Nutrition and Health. https:// doi.org/ 10.1177/026010600201600112
44. Libby, P. (2015). Triglycerides on the rise: Should we swap seats on the seesaw? European Heart Journal. https:// doi.org/ 10.1093eurheartj/ehu500
45. Lo, E. K. K., Felicianna, Xu, J. H., Zhan, Q., Zeng, Z., & El-Nezami, H. (2022). The Emerging Role of Branched-Chain Amino Acids in Liver Diseases. In Biomedicines. https://doi.org/10.3390/biomedicines10061444
46. Madsen, T., Schmidt, E. B., & Christensen, J. H. (2007). The Effect of n-3 Fatty Acids on C-Reactive Protein Levels in Patients With Chronic Renal Failure. Journal of Renal Nutrition. https:// doi.org/ 10.1053/ j.jrn.2007.03.003
47. Mahoney, E. M., Wang, K., Cohen, D. J., Hirsch, A. T., Alberts, M. J., Eagle, K., Mosse, F., Jackson, J. D., Steg, P. G., & Bhatt, D. L. (2008). One-year costs in patients with a history of or at risk for atherothrombosis in the United States. Circulation: Cardiovascular Quality and Outcomes. https:// doi.org/ 10.1161/CIRCOUTCOMES.108.775247
48. Marchioli, R. (1999). Dietary supplementation with N-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: Results of the GISSI-Prevenzione trial. Lancet. https://doi.org/10.1016/S0140-6736(99)07072-5
49. Mason, R. P., & Eckel, R. H. (2021). Mechanistic Insights from REDUCE-IT STRENGTHen the Case Against Triglyceride Lowering as a Strategy for Cardiovascular Disease Risk Reduction. In American Journal of Medicine. https:// doi.org/ 10.1016/ j.amjmed.2021.03.014
50. Mason, R. P., Sherratt, S. C. R., & Eckel, R. H. (2022). Rationale for different formulations of omega-3 fatty acids leading to differences in residual cardiovascular risk reduction. Metabolism: Clinical and Experimental. https://doi.org/10.1016/j.metabol.2022.155161
51. Massaro, M., Scoditti, E., Carluccio, M. A., & De Caterina, R. (2008). Basic mechanisms behind the effects of n-3 fatty acids on cardiovascular disease. Prostaglandins Leukotrienes and Essential Fatty Acids. https://doi.org/10.1016/j.plefa.2008.09.009
52. McLennan, P. L. (2001). Myocardial membrane fatty acids and the antiarrhythmic actions of dietary fish oil in animal models. Lipids. https://doi.org/10.1007/s11745-001-0692-x
53. McLennan, P. L., Bridle, T. M., Abeywardena, M. Y., & Charnock, J. S. (1993). Comparative efficacy of n-3 and n-6 polyunsaturated fatty acids in modulating ventricular fibrillation threshold in marmoset monkeys. American Journal of Clinical Nutrition. https://doi.org/10.1093/ajcn/58.5.666
54. McLennan, P. L., & Dallimore, J. A. (1995). Dietary canola oil modifies myocardial fatty acids and inhibits cardiac arrhythmias in rats. Journal of Nutrition. https:// doi.org/ 10.1093/ jn/125.4.1003
55. Mijalski, C., & Silver, B. (2015). TIA Management: Should TIA Patients be Admitted? Should TIA Patients Get Combination Antiplatelet Therapy? In The Neurohospitalist. https://doi.org/10.1177/1941874415580598
56. Miller, M., Motevalli, M., Westphal, D., & Kwiterovich, P. O. (1993). Incorporation of oleic acid and eicosapentaenoic acid into glycerolipids of cultured normal human fibroblasts. Lipids. https:// doi.org/ 10.1007/ BF02536351
57. Mozaffarian, D. (2009). Fish, mercury, selenium and cardiovascular risk: Current evidence and unanswered questions. In International Journal of Environmental Research and Public Health. https:// doi.org/ 10.3390/ijerph6061894
58. Mozaffarian, D., Bryson, C. L., Lemaitre, R. N., Burke, G. L., & Siscovick, D. S. (2005). Fish intake and risk of incident heart failure. Journal of the American College of Cardiology. https:// doi.org/ 10.1016/ j.jacc.2005.03.038
59. Mozaffarian, D., Prineas, R. J., Stein, P. K., & Siscovick, D. S. (2006). Dietary Fish and n-3 Fatty Acid Intake and Cardiac Electrocardiographic Parameters in Humans. Journal of the American College of Cardiology. https:// doi.org/ 10.1016/ j.jacc.

2006.03.048
60. Mozaffarian, D., & Wu, J. H. Y. (2011). Omega-3 fatty acids and cardiovascular disease: Effects on risk factors, molecular pathways, and clinical events. In Journal of the American College of Cardiology. https://doi.org/10.1016/j.jacc.2011.06.063
61. Myhre, P., Smith, E. B., Kalstad, A. A., Tveit, S., Laake, K., Smith, P., Nilsen, D. W. T., Tveit, A., Solheim, S., Arnesen, H., & Seljeflot, I. (2021). Changes in EPA and DHA during supplementation with omega-3 fatty acids and incident cardiovascular events: secondary analysis from the OMEMI trial. European Heart Journal. https:// doi.org/ 10.1093/eurheartj/ehab724.2429
62. NCT00127452. (2005). Alpha Omega Trial: study of Omega-3 Fatty Acids and Coronary Mortality. Https:// Clinicaltrials. Gov/ Show/ NCT00127452.
63. Nkomo, V. T., Gardin, J. M., Skelton, T. N., Gottdiener, J. S., Scott, C. G., & Enriquez-Sarano, M. (2006). Burden of valvular heart diseases: a population-based study. Lancet. https://doi.org/10.1016/S0140-6736(06)69208-8
64. Ouellet, V., Weisnagel, S. J., Marois, J., Bergeron, J., Julien, P., Gougeon, R., Tchernof, A., Holub, B. J., & Jacques, H. (2008). Dietary cod protein reduces plasma C-reactive protein in insulin-resistant men and women. Journal of Nutrition. https:// doi.org/ 10.3945/jn.108.092346
65. Park, Y., & Harris, W. S. (2003). Omega-3 fatty acid supplementation accelerates chylomicron triglyceride clearance. Journal of Lipid Research. https:// doi.org/ 10.1194/jlr.M200282-JLR200
66. Pepe, S., & McLennan, P. L. (1996). Dietary fish oil confers direct antiarrhythmic properties on the myocardium of rats. Journal of Nutrition. https://doi.org/10.1093/jn/126.1.34
67. Primary prevention of cardiovascular disease with a mediterranean diet. (2013). In Zeitschrift fur Gefassmedizin. https://doi.org/10.1056/nejmoa1200303
68. Rauch, B., Schiele, R., Schneider, S., Diller, F., Victor, N., Gohlke, H., Gottwik, M., Steinbeck, G., Del Castillo, U., Sack, R., Worth, H., Katus, H., Spitzer, W., Sabin, G., & Senges, J. (2010). OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. Circulation. https://doi.org/10.1161/CIRCULATIONAHA.110.948562
69. Saito, Y., Yokoyama, M., Origasa, H., Matsuzaki, M., Matsuzawa, Y., Ishikawa, Y., Oikawa, S., Sasaki, J., Hishida, H., Itakura, H., Kita, T., Kitabatake, A., Nakaya, N., Sakata, T., Shimada, K., & Shirato, K. (2008). Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: Sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis. https://doi.org/10.1016/j.atherosclerosis.2008.06.003
70. Sellmayer, A., Witzgall, H., Lorenz, R. L., & Weber, P. C. (1995). Effects of dietary fish oil on ventricular premature complexes. The American Journal of Cardiology. https://doi.org/10.1016/S0002-9149(99)80276-8
71. Sherratt, S. C. R., Libby, P., Bhatt, D. L., & Mason, R. P. (2022). A biological rationale for the disparate effects of omega-3 fatty acids on cardiovascular disease outcomes. In Prostaglandins Leukotrienes and Essential Fatty Acids. https:// doi. org/ 10. 1016/ j.plefa. 2022.102450
72. Shirle, R., Ord, E. N. J., & Work, L. M. (2014). Oxidative stress and the use of antioxidants in stroke. In Antioxidants. https://doi.org/10.3390/antiox3030472
73. Simopoulos, A. P. (1991). Omega-3 fatty acids in health and disease and in growth and development. In American Journal of Clinical Nutrition. https:// doi.org/ 10.1093/ ajcn/ 54.3.438
74. Simopoulos, A. P. (2003). Essential fatty acids in health and chronic diseases. In Forum of nutrition.
75. Siscovick, D. S., Raghunathan, T. E., King, I., Weinmann, S., Wicklund, K. G., Albright, J., Bovbjerg, V., Arbogast, P., Smith, H., Kushi, L. H., Cobb, L. A., Copass, M. K., Psaty, B. M., Lemaitre, R., Retzlaff, B., Childs, M., & Knopp, R. H. (1995). Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. JAMA. https:// doi.org/ 10.1001/jama.274.17.1363
76. Mandal S, Vishvakarma P. Nanoemulgel: A Smarter Topical Lipidic Emulsion-based Nanocarrier. Indian J of Pharmaceutical Education and Research. 2023;57(3s):s481-s498.
77. Mandal S, Jaiswal DV, Shiva K. A review on marketed Carica papaya leaf extract (CPLE) supplements for the treatment of dengue fever with thrombocytopenia and its drawback. International Journal of Pharmaceutical Research. 2020 Jul;12(3).
78. Pal N, Mandal S, Shiva K, Kumar B. Pharmacognostical, Phytochemical and Pharmacological Evaluation of Mallotus philippensis. Journal of Drug Delivery and Therapeutics. 2022 Sep 20;12(5):175-81.

79. Singh A, Mandal S. Ajwain (Trachyspermum ammi Linn): A review on Tremendous Herbal Plant with Various Pharmacological Activity. International Journal of Recent Advances in Multidisciplinary Topics. 2021 Jun 9;2(6):36-8.
80. Mandal S, Jaiswal V, Sagar MK, Kumar S. Formulation and evaluation of carica papaya nanoemulsion for treatment of dengue and thrombocytopenia. Plant Arch. 2021;21:1345-54.
81. Mandal S, Shiva K, Kumar KP, Goel S, Patel RK, Sharma S, Chaudhary R, Bhati A, Pal N, Dixit AK. Ocular drug delivery system (ODDS): Exploration the challenges and approaches to improve ODDS. Journal of Pharmaceutical and Biological Sciences. 2021 Jul 1;9(2):88-94.
82. Shiva K, Mandal S, Kumar S. Formulation and evaluation of topical antifungal gel of fluconazole using aloe vera gel. Int J Sci Res Develop. 2021;1:187-93.
83. Ali S, Farooqui NA, Ahmad S, Salman M, Mandal S. Catharanthus roseus (sadabahar): a brief study on medicinal plant having different pharmacological activities. Plant Archives. 2021;21(2):556-9.
84. Mandal S, Vishvakarma P, Verma M, Alam MS, Agrawal A, Mishra A. Solanum Nigrum Linn: An Analysis Of The Medicinal Properties Of The Plant. Journal of Pharmaceutical Negative Results. 2023 Jan 1:1595-600.
85. Vishvakarma P, Mandal S, Pandey J, Bhatt AK, Banerjee VB, Gupta JK. An Analysis Of The Most Recent Trends In Flavoring Herbal Medicines In Today's Market. Journal of Pharmaceutical Negative Results. 2022 Dec 31:9189-98.
86. Mandal S, Vishvakarma P, Mandal S. Future Aspects And Applications Of Nanoemulgel Formulation For Topical Lipophilic Drug Delivery. European Journal of Molecular & Clinical Medicine.;10(01):2023.
87. Chawla A, Mandal S, Vishvakarma P, Nile NP, Lokhande VN, Kakad VK, Chawla A. Ultra-Performance Liquid Chromatography (Uplc).
88. Mandal S, Raju D, Namdeo P, Patel A, Bhatt AK, Gupta JK, Haneef M, Vishvakarma P, Sharma UK. Development, characterization, and evaluation of rosa alba l extract-loaded phytosomes.
89. Mandal S, Goel S, Saxena M, Gupta P, Kumari J, Kumar P, Kumar M, Kumar R, Shiva K. Screening of catharanthus roseus stem extract for anti-ulcer potential in wistar rat.
90. Shiva K, Kaushik A, Irshad M, Sharma G, Mandal S. Evaluation and preparation: herbal gel containing thuja occidentalis and curcuma longa extracts.
91. Vishvakarma P, Kumari R, Vanmathi SM, Korni RD, Bhattacharya V, Jesudasan RE, Mandal S. Oral Delivery of Peptide and Protein Therapeutics: Challenges And Strategies. Journal of Experimental Zoology India. 2023 Jul 1;26(2).
92. Ventura, H. O., Milani, R. V., Lavie, C. J., Smart, F. W., Stapleton, D. D., Toups, T. S., & Price, H. L. (1993). Cyclosporine-induced hypertension: Efficacy of ω-3 fatty acids in patients after cardiac transplantation. Circulation.
93. Weiss, R. M., Miller, J. D., & Heistad, D. D. (2013). Fibrocalcific aortic valve disease: Opportunity to understand disease mechanisms using mouse models. Circulation Research. https://doi.org/10.1161/CIRCRESAHA.113.300153
94. Weylandt, K. H., Chiu, C. Y., Gomolka, B., Waechter, S. F., & Wiedenmann, B. (2012). Omega-3 fatty acids and their lipid mediators: Towards an understanding of resolvin and protectin formation. Omega-3 fatty acids and their resolvin/protectin mediators. In Prostaglandins and Other Lipid Mediators. https://doi.org/10.1016/j.prostaglandins.2012.01.005
95. Yang, D. Y., Pan, H. C., Yen, Y. J., Wang, C. C., Chuang, Y. H., Chen, S. Y., Lin, S. Y., Liao, S. L., Raung, S. L., Wu, C. W., Chou, M. C., Chiang, A. N., & Chen, C. J. (2007). Detrimental effects of post-treatment with fatty acids on brain injury in ischemic rats. NeuroToxicology. https://doi.org/10.1016/j.neuro.2007.08.003
96. Yang, Y. C., Lii, C. K., Wei, Y. L., Li, C. C., Lu, C. Y., Liu, K. L., & Chen, H. W. (2013). Docosahexaenoic acid inhibition of inflammation is partially via cross-talk between Nrf2/heme oxygenase 1 and IKK/NF-κB pathways. Journal of Nutritional Biochemistry. https://doi.org/10.1016/j.jnutbio.2012.05.003
97. Yashodhara, B. M., Umakanth, S., Pappachan, J. M., Bhat, S. K., Kamath, R., & Choo, B. H. (2009). Omega-3 fatty acids: A comprehensive review of their role in health and disease. In Postgraduate Medical Journal. https:// doi.org/ 10.1136/pgmj.2008.073338
98. Yokoyama, M., Origasa, H., Matsuzaki, M., Matsuzawa, Y., Saito, Y., Ishikawa, Y., Oikawa, S., Sasaki, J., Hishida, H., Itakura, H., Kita, T., Kitabatake, A., Nakaya, N., Sakata, T., Shimada, K., & Shirato, K. (2007). Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. https:// doi.org/ 10.1016/S0140-6736(07)60527-3

99. Zhang, P. Y. (2015). Role of ω-3 Fatty Acids in Cardiovascular Disease. Cell Biochemistry and Biophysics. https:// doi.org/ 10.1007/ s12013-015-0554-3
100. Zhao, G., Etherton, T. D., Martin, K. R., Gillies, P. J., West, S. G., & Kris-Etherton, P. M. (2007). Dietary α-linolenic acid inhibits proinflammatory cytokine production by peripheral blood mononuclear cells in hypercholesterolemic subjects. American Journal of Clinical Nutrition. https:// doi.org/ 10.1093/ajcn/85.2.385
101. Zúñiga, J., Cancino, M., Medina, F., Varela, P., Vargas, R., Tapia, G., Videla, L. A., & Fernández, V. (2011). N-3 PUFA supplementation triggers PPAR-α activation and PPAR-α/NF-κB interaction: Anti-inflammatory implications in liver ischemia-reperfusion injury. PLoS ONE. https://doi.org/10.1371/journal.pone.0028502.