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Review Article

Omega-3 Fatty Acids in Cardiovascular Diseases: A Comprehensive Overview

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ABSTRACT

Cardiovascular disease (CVD) increases worldwide with varying etiological factors. The considerable change in daily life or adoption of a modern lifestyle, including changing eating habits from conventional to modern high-energy foods, results in CVD. In addition to several factors, dietary modification is recommended to reduce CVD prevalence. Omega-3 fatty acids (ω-3 FAs) derived from various sources are beneficial for preventing CVD. This comprehensive review was undertaken to determine the dietary sources of ω-3 FAs and their impacts on the health of cardiovascular patients. Using keywords such as cardiovascular diseases, ω-3 FAs, and modern lifestyle, the literature was searched from PubMed, Scopus, and Google Scholar, and the most recent relevant findings were discussed and cited in this article. The results show how dietary sources of ω-3 FAs positively impact human health regarding cardio protection. Furthermore, the data also provided pieces of evidence that the mechanism(s) by which Omega-3 fatty acids decrease CVD incidence help design new therapeutic strategies against the onset or treatment of CVD. In addition, dietary behavior, its importance, and the role that ω-3 FAs play in CVD in Gulf countries, mainly Saudi Arabia, are also discussed. The outcomes of this study concluded that much research has been done on the positive role of ω-3 FAs in lowering CVD incidence. Nevertheless, there is a need for device-specific recommendations of ω-3 FAs supplementation according to the region, as risk factors involved in the onset of CVD vary from region to region.

INTRODUCTION

The World Health Organization (WHO) reported that CVD is responsible for causing 31% of deaths worldwide every year (Balta et al., 2021). Similar findings were also reported in another study where they stated that CVD is responsible for causing 17.3 million deaths each year, of which 25% of deaths occurred in developing countries (Sokoła-Wysoczańska et al., 2018). The mortality rate due to CVD is found to vary with geographic regions. Over the past two centuries, it has been recorded in European countries that there has been a ten-fold increase in CVD cases compared to cancer cases (a two-fold increase) (Trebatická et al., 2017). This increase in deaths due to cardiac diseases is associated with several risk factors, such as hypertension, blood pressure anomalies, endothelial dysfunction, impaired glucose metabolism, unhealthy diet, Diabetes Mellitus (DM), abdominal obesity, psychosocial stress, and smoking (Balta et al., 2021;

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Gupta et al., 2016). A balanced and healthy diet may have positive cardioprotective effects, improving and maintaining human health. In the mid-nineteenth (19th)-century, our predecessors consumed various natural foods, mainly wild plants, vegetables, fruits, berries, fish, lean meat, and a few kinds of cereal. Although human dietary behavior has changed, grains have become one of the most affordable parts of the diet due to innovations, advancements, or revolutions in industry and agriculture (Simopoulos, 2002a). It resulted in increased consumption of omega-6 (ω-6) fatty acids (FAs) and decreased consumption of omega-3 (ω-3) FAs at the same time. This change in dietary behavior, such as reducing the consumption of ω-3 FAs and increasing carbohydrate intake, results in hypertension, insulin resistance, coronary heart disease, and obesity (Simopoulos, 2002a). For example, modification in food intake of ω-6 to ω-3 from 1:1 to 15-20:1 leads to molecular and physiological changes such as increased expression of pro-inflammatory mediators and alteration of various receptor signals. Therefore, it contributes to the significant role in events of pathophysiological alterations responsible for producing CVD, DM, and sometimes psychological disorders. In humans, various factors, mainly eating behavior and variation in food intake, significantly affect the level of essential fatty acids (EFAs), which are the principal contributing factors to CVD. The FAs are essential building blocks for cellular structures, tissues, and organs. They also play a vital role in synthesizing several important biologically active substances and properly functioning different metabolic processes (Sokoła-Wysoczańska et al., 2018). The muscular tissues of the heart obtain myocardial energy from FAs for the proper functioning of its muscles, as they are the repository of adenosine triphosphate (ATP). Besides this, β-oxidation of FAs is also one of the significant contributors to myocardial energy (Stamenkovic et al., 2019). Previous studies indicated the importance of FA metabolites in cardiac medicine; hence, they have been extensively studied. Still, some questions remained unanswered, such as their biological mechanism of action and how ω-3 prevents cardiovascular diseases. Furthermore, biomarkers for ω-3 FAs in the reduction of CVD are also discussed in this review. Therefore, the structure and biosynthesis of ω-3 FAs are discussed in this narrative review as their mechanism for preventing CVD. The dietary behavior of Mediterranean people and the possibility of heart disease are also reviewed here.

Structure of omega-3 fatty acids and their sources

Omega-3 fatty acids are essential polyunsaturated fatty acids crucial in maintaining human health, particularly cardiovascular well-being (Sherratt et al., 2023). Structurally, omega-3 fatty acids are characterized by the location of their double bonds, which are situated three carbon atoms away from the terminal methyl group of the molecule. This unique arrangement confers distinct biological properties that have been extensively studied for their health benefits (Simonetto et al., 2019). There are three main types of omega-3 fatty acids: alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (Krupa et al., 2023). ALA is classified as an essential fatty acid, meaning the human body cannot synthesize it, and must be obtained through dietary sources. Flaxseeds, chia seeds, walnuts, and hemp seeds are rich sources of ALA. Once consumed, ALA can undergo limited conversion to EPA and DHA in the body, albeit at a relatively low rate (Krupa et al., 2023). EPA and DHA, on the other hand, are primarily found in marine sources. Fatty fish such as salmon, mackerel, sardines, and anchovies are excellent sources of these long-chain omega-3 fatty acids. These marine sources are not only rich in EPA and DHA but also provide them in forms that are readily absorbable and bioavailable to the human body (Sherratt et al., 2023; Krupa et al., 2023; Simonetto et al., 2019). The structural composition of EPA and DHA is significant for their physiological functions. EPA is characterized by a chain of 20 carbon atoms with five double bonds, while DHA has a 22-carbon chain with six double bonds. This distinctive structure imparts fluidity and flexibility to cell membranes, contributing to their optimal function. In cardiovascular health, EPA and DHA exhibit multiple mechanisms of action that collectively benefit the cardiovascular system (Sherratt et al., 2023; Krupa et al., 2023; Simonetto et al., 2019). Publish reports have shown that omega-3 fatty acids, particularly EPA and DHA, have anti-inflammatory effects (Calder et al., 2017; Calder et al., 2010). Inflammation is a critical, crucial contributor to the development and progression of cardiovascular diseases.

Omega-3 fatty acid's mechanism in cardio-protection

The ω-3 FAs are a group of polyunsaturated FAs (PUFA) (Weylandt et al., 2012). Long-chain ω-3 FAs are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) with 20 and 22 carbons, respectively. Seafood is a rich source of EPA and DHA. However, EPA and DHA can also be synthesized in small amounts in the body by using the alpha-linolenic acid (ALA) and ω-3 FAs found in plants such as canola, walnuts, and flaxseed (Mozaffarian &Wu, 2011). A constant and adequate supply of FAs from various sources is essential to properly functioning the cardiovascular (CV) system. It is mentioned earlier that marine/seafood is the predominant source of DHA and EPA; fish oils have the highest concentration of these two FAs (Calder, 2015). The mechanism by which these FAs exhibit cardio-protective effects as effective modulators for preventing CV risk factors is essential (Innes &Calder, 2020). A regular supply of FAs will help the CV system function properly. Providing a steady supply of FAs will be helpful not only in the supply of oxygen (O_2) and nutrients to cells, tissues, and organs but also in clearing the body's metabolic waste products. Cardiac arrhythmia (CA), high blood pressure (BP), increased blood triglyceride (TG), decreased level of high-density lipoprotein (HDL), variability in heart rate, and inflammation are the major risk factors involved in CVD (Innes &Calder, 2020; Mozaffarian &Wu, 2011). Given the literature review, it is reasonable to conclude that ω-3 FAs have anti-inflammatory properties since they alter the signaling mechanism of toll-like receptor-4 (TLR4) by

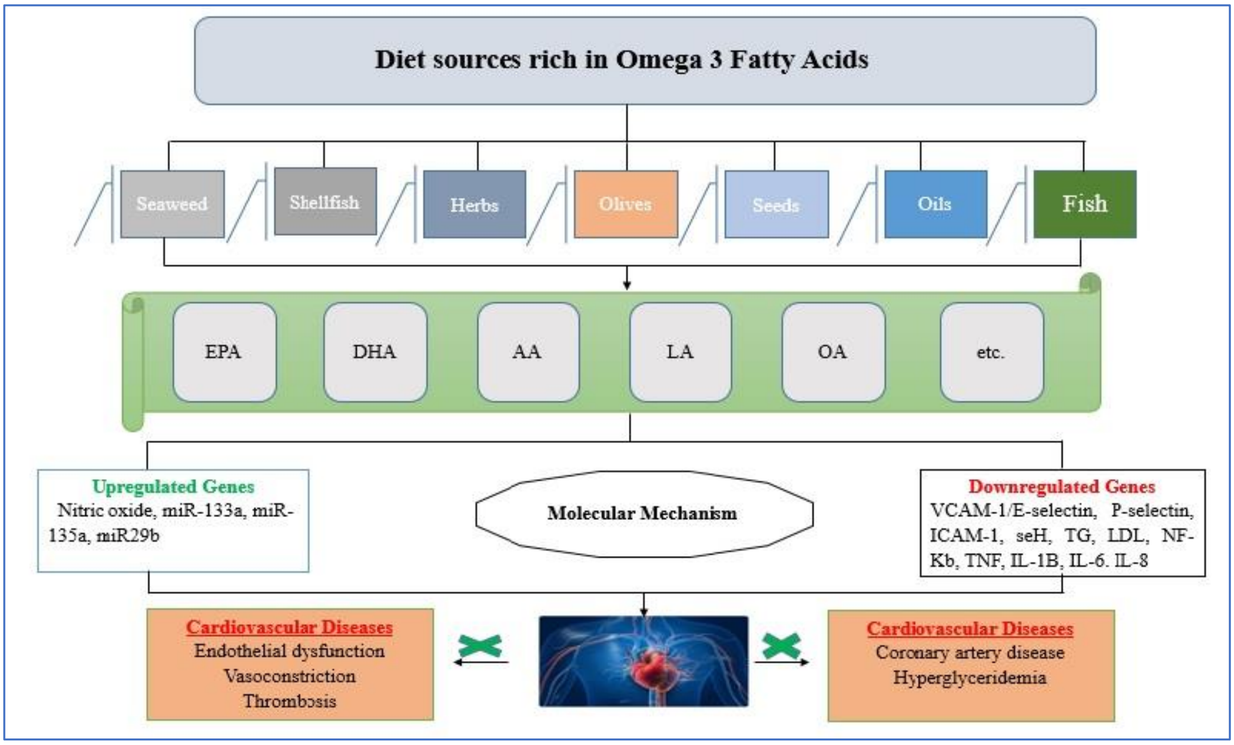

Figure 1: *Dietary sources of beneficial Omega 3 (ω-3) fatty acids and their impact on CVDs. The most common dietary sources are seaweed, shellfish, herbs, olives, seeds, oils, and fish. They provide ω-3 fatty acids, including polyunsaturated fatty acids {Eicosatetraenoic acid (EPA), Docosahexaenoic acid (DHA), Arachidonic acid (AA), Linoleic acid (LA)} and monounsaturated fatty acids (Oleic acid (OA), etc). Daily intake of ω-3 fatty acids prevents the onset of CVD by downregulating (VCAM-1/E-selectin, P-selectin, ICAM-1, seH, TG, LDL, NF-Kb, TNF, IL-1B, IL-6, and IL-8) and upregulating (NO, miR-133a, miR-135a, miR29b) genes.*

suppressing the dimerization in cellular- membranes, resulting in the downregulation of toll-like receptor-4 (TLR4). Similarly, ω-3 FAs (PUFA) modulate sodium (Na^+) and calcium (Ca^+) ion channels (Mozaffarian &Wu, 2011). Previous studies showed that PUFA influences electrophysiology by alleviating atrial and ventricular cardiomyocyte excitability and controlling cytosolic calcium fluctuations (Mozaffarian &Wu, 2011). Additionally, ω-3 FAs also mitigate meta-inflammation, CVD, and DM2 in obese humans (Rogero & Calder, 2018; Yagi et al., 2017). It is reported that ω-3 FAs, particularly the PUFA, inhibit several inflammatory mediators such as prostaglandins (E2), leukotrienes (B4), and thromboxane (B2) that are found to be associated with CV risk factors. Furthermore, they also regulate the activity of T-helper 1 cells, reduce the expression of the human adhesive molecule (P-selection, E-selection, VCAM-1, and ICAM-1), and decrease the expression of pro-inflammatory cytokines (IL-1β, TNF-α, IL-8, and IL-6) (Rogero & Calder, 2018; Verveniotis et al., 2018; Yagi et al., 2017) (Figure 1).

Daily intake of Omega-3 fatty acids and their association with CVD

According to dietary guidelines, daily intake (300-600 mg) of ω-3 FAs gives primary protection against CV events. However, a 900-1200 mg dose range is recommended for secondary prevention. Additionally, ω-3 FAs (3000-4000 mg) are necessary to reduce the elevated levels of TG in the blood (Jain et al., 2015; Verveniotis et al., 2018). These FAs lower (25%-30%) the TG in the blood by maintaining and improving lipoprotein metabolism (Verveniotis et al., 2018). In addition, daily intake of EPA and DHA with a concentration of 4g/day is considered a safe and effective therapeutic option for reducing TG index and helps prevent atherosclerotic CVD risk (Jain et al., 2015; Skulas-Ray et al., 2019). It is also reported that high doses of ω-3 FAs effectively lower blood pressure (Jain et al., 2015). Moreover, a meta-analysis of previous studies revealed that fish consumption or supplementation of fish oil decreases mortality due to coronary heart diseases and mitigates the probability of death due to myocardial infarction or sudden cardiac arrest in humans (Rogero, 2018). It was mentioned earlier that ω-3 FAs could effectively combat inflammatory diseases. Some studies reported that these FAs could regulate the mechanism of several inflammatory mediators, particularly nuclear factor kappa B (NF-kB) in human peripheral blood mononuclear cells (PBMC) (Allam-Ndoul et al., 2016; Bouwens et al., 2009). This can help reduce pro-inflammatory proteins such as IL-1 β, TNF- α, IL-6, and the activity of COX-2 (Sigal, 2006). Likewise, Miller and his colleagues (2019) reported that statin-treated patients with high-sensitivity C-reactive protein (hs-CRP) have an increased risk of CVD with TG 200 to 499 mg/dl. They reported that consuming icosapent-ethyl 4g/day instead of 2g/day significantly reduces the TG, inflammatory, and other atherogenic parameters in statin-treated patients with increased hs-CRP (Miller et al., 2019).

Table 1: *Omega-3 fatty acids derived from Various natural sources*

Sr. No	Plant sources	References
1	Flax Seed *(Linum usitatissimum)*	Parikh et al., 2019
2	Hemp *(Cannabis sativa)*	Baker et al., 2020
3	Black Currant *(Ribes nigrum)*	Baker et al., 2020
4	Mushrooms species	Sande et al., 2019
5	Corn Gromwell *Buglossoides arvensis*	Baker et al., 2020
	Marine sources	
6	Tunicate *Halocynthia aurantium*	Monmai et al., 2018
7	Australian Sardine *Sardinopssagax*	Ahmad et al., 2019
8	Atlantic Salmon *Salmo salar*	Ahmad et al., 2019
9	Eastern King Prawn *Penaeus plebejus*	Ahmad et al., 2019
10	Brown Seaweed *Fucus vesicuosus*	Barta et al., 2021
11	Squid *Sepioteuthis australis*	Ahmad et al., 2019

The ω-3 FAs also inhibit several major signaling pathways in cardiomyocytes, e.g., protein kinase A, protein kinase C and Ca+-dependent protein kinase II (Mirnikjoo et al., 2001). Hence, they reduce oxidative stress by directly inhibiting the Na^+ and Ca^+ channels in the sarcoplasmic reticulum of myocytes. Therefore, it is safer to say that ω-3 FAs directly or indirectly prevent ischemia-induced ventricular fibrillation and arrhythmias (Mirnikjoo et al., 2001). The plasma membrane has rafts and caveolae (lipid micro-domain structures) with signaling proteins such as H-Ras and endothelial nitric oxide (eNOS). In 2004, a study on mouse colon epithelial cells revealed that ω-3 FAs suppress the H-Ras distribution by modifying the membrane (Ma et al., 2004). In addition, these FAs also help in vasorelaxation by activating eNOS in a Ca^{2+}-independent manner (Omura et al., 2001). Moreover, it is also documented that supplementation of ω-3 FAs helps mitigate the pro-thrombolytic effect (Simopoulos, 2002b). Apart from the positive effects of ω-3 FAs on human health, these FAs also have a positive role in bronchial disorders and intraocular neovascularization (Schunck et al., 2018). Furthermore, Bernasconi and his co-researchers conducted a meta-analysis and meta-regression of interventional trials and determined the effect of ω-3 FAs dosage on CVD. They reported that supplementation of EPA and DHA in daily life is an effective strategy for CVD prevention (Bernasconi et al., 2021). According to a study conducted in 2013, ω-3 FAs have antioxidant activity, particularly in the Caucasian population (Rudkowska et al., 2013). This antitoxic effect might be due to the activation of nuclear erythroid factor-2 in PBMC, which enhances the synthesis of antioxidant enzymes such as glutathione peroxidase one and superoxide dismutase 2 (Rudkowska et al., 2013). Supplementation of ω-3 FAs (2.7g/d) for three months in humans can reduce oxidative stress by inhibiting the 5-lipoxygenase activity. However, daily intake of ω-3 FAs (1.2g) for three months can inhibit the phospholipase-A2 activity (Smesny et al., 2014).In 2018, Harris and his team tried to determine the extent to which ω-3 FAs status is related to the risk of death from CVD. They used red blood cell levels of EPA and DHA as biomarkers to measure the baseline in humans. Based on their findings, they concluded that a higher index of ω-3 FAs helps in the reduction of CVD and its associated risk (Harris et al., 2018). Recently, a similar study was also conducted in which they investigated the association of ω-3 PUFA within the erythrocyte membrane and CVD in humans. They analyzed plasma biomarkers such as glucose, lipids, C-reactive protein, and erythrocyte membrane FAs. They reported that ω-3 PUFA in erythrocyte membranes are independent predictors of low-risk CVD (Gonçalinho et al., 2021). It is well-known that serum TG level is a significant risk factor for CVD since it causes fibrinolysis impairment, pro-inflammatory cytokines release, and several coagulation factors (Reiner, 2017). A review of a randomized trial published in 2013 reported that daily intake of ω-3 FAs (4g) significantly reduces the TG level in serum and, hence, can be considered a therapeutic option for patients with high serum TG levels (Kimmig &

Karalis, 2013). However, the effect of these FAs on high-density lipoprotein (HDL) and low-density lipoprotein (LDL) is debatable. In addition, the review published in 2017 reported that the effect of ω-3 FAs on HDL and LDL concentration is small (Balk & Lichtenstein, 2017). Furthermore, researchers in 2018 tried to find the association of ω-3 FAs consumption with CVD. They did a meta-analysis of 10 trials involving 77917 human participants supplementing marine-derived ω-3 FAs for more than four years. From meta-analysis, they reported that ω-3 FAs did not have a significant association with CVD (Aung et al., 2018). In 2014, Bonds and his colleagues determined the effect of supplementation of long-chain ω-3 FAs in elderly CVD patients. They reported that dietary supplementation of long-chain ω-3 FAs and vitamins and minerals did not reduce CVD risk in elderly patients (Bonds et al., 2014). Recently, researchers have determined the association of atrial fibrillation (AF) onset in patients taking a high dose of ω-3 FAs derived from fish oil. They did a meta-analysis and reported that consumers already at higher cardiovascular risk have a chance of AF development upon consuming fish oil at a high dosage (Doshi et al., 2021).

Dietary sources of Omega-3 fatty acids

Humans can get ω-3 FAs from natural sources such as plants, marine, and yak butter. The details of these resources are given in Table 1.

Omega 3 fatty acids derived from plant sources

Generally, ω-3 FAs are found in fish, green leafy vegetables, lean meat, tunicates, and seeds (Hernáez et al., 2019; Monmai et al., 2018; Shulgina et al., 2019; Valdez et al., 2019). Humans can get ω-3 FAs from hemp, walnut, flax, and algae (Komarnytsky et al., 2021). Human patients with severe heart problems or with increased CV risk showed promising HDL functionality enhancement by consuming foodstuffs with a large proportion of nuts, virgin olive oil, and legumes for more than one year (Hernáez et al., 2019). The bioavailability of plant-based ω-3 FAs is essential for PUFA and is considered effective in reducing human CVDs (Gumus & Gharibzahedi, 2021). Due to this factor, it was reported that an emulsion of flaxseed, fish, and algal oil in the yogurt matrix elevates the bioavailability of ω-3 FAs. According to a review published in 2018, flaxseed has several cardioprotective properties (Parikh et al., 2018). They discussed that flaxseed is a rich source of ω-3 ALA contents that inhibit the soluble epoxide hydrolase (seH), resulting in significant antihypertensive effects (Parikh et al., 2018). The activation of seH results in the release of inflammatory and cytotoxic oxylipins like dihydroxy octadecenoic acids. This plant also showed anti-proliferative and anti-inflammatory properties as it suppresses the activity of Proliferating Cell Nuclear Antigen (PCNA), interleukin 6 (IL-6), and VCAM-1 (Parikh et al., 2018). In addition, flaxseed is reported to help in the restoration of CV function by improving the growth of new blood vessels (neovascularization) through a compound known as secoisolariciresinol diglucoside (SDG) (Parikh et al., 2018). SDG bears good antioxidant properties and showed a remarkable reduction in the manifestation of arrhythmias in myocardial infarct mice when fed with milled flaxseed (10%) and supplemented with flax oil (4.4%) enriched with ALA or flax SDG (0.44%). Furthermore, histology revealed that dietary treatment significantly lowers the possibilities of infarction, dilation of the left ventricle (dilated cardiomyopathy), and alleviation of myocardial fibrosis compared to the control group of rats (Parikh et al., 2019). An in vivo study on male Sprague Dawley rats recently deciphers the novel molecular mechanism of endogenously encoded microRNA (miRNAs) involved in CVD and health. It was reported that several microRNAs (miR-1, miR-29b, miR-133a, and miR-135a) play a vital role in CV pathophysiological processes such as cardiac apoptosis and fibrosis in case of myocardial infarction. An increased expression of miR-1 in cardiomyocytes was observed during arrhythmias. On the other hand, the upregulation of miR-133 was associated with the modulation of apoptosis. The miR-29b and miR-135a regulated cardiac fibrosis (Parikh et al., 2020). An *in vivo* study on mice reported that ω-3 FAs protect cardiomyocytes after myocardial infarction and cause downregulation of pro-apoptotic miRNAs and upregulation of nine anti-apoptotic miRNAs (Ma et al., 2018). Another revealed that using flaxseed oil in diet modulates the expression of miRNAs associated with cardio-protective outcomes. In addition, the administration of flaxseed in the diet also protects against spontaneous cardiac infarction, lowers the cholesterol level, and enhances the systolic and diastolic function in the rat model (Parikh et al., 2021). Stearidonic acid (SDA) is a ω-3 FA abundantly present in the oil extracted from *Echium plantagineum* (Paterson's curse), *Cannabis sativa* (Hemp), *Ribes nigrum* (Blackcurrant), and *Buglossoides arvensis* (bastard alkanet). An experimental trial was recently conducted on human endothelial cells pre-treated with plant SDA (50 µM). This reduced the synthesis and expression of ICAM-1 (Baker et al., 2020).

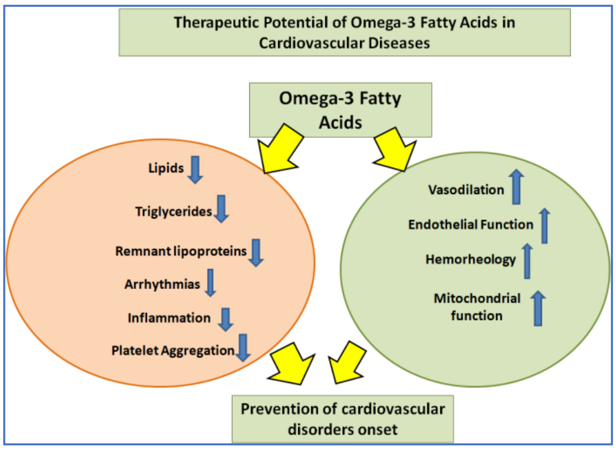

Figure 2: *Overview of the therapeutic potential of Omega 3 (ω-3) fatty acids and their impact on preventing CVDs. Down head arrows in blue represent reduction, whereas up head arrows in blue represent increased parameters. Arrows in blue showed the therapeutic potential of ω-3 FAs.*

Omega-3 fatty acids derived from marine sources

The marine inhabitants are a rich source of ω-3 FAs, with anti-inflammatory properties in alleviating CV risks. It has been shown that ω-3 FAs reduce TG concentration and regulate cholesterol levels by increasing the HDL and decreasing the LDL (Balk and Lichtenstein, 2017). Several previous studies also reported that ω-3 FAs, particularly PUFAs, improve endothelial function, influence arterial stiffness, and hence ameliorate arterial compliance (Casanova et al., 2017; Pizzini et al., 2018; Verveniotis et al., 2018). Apart from these positive effects, it is also reported that fish oil helps reduce hypercholesterolemia (Marcelino et al., 2019). It is well-known that using marine-derived ω-3 FAs helps reduce TG levels and ultimately lowers the risk of CV morbidity and mortality (Mason, 2019). This statement is supported by a clinical trial in which ω-3 FAs were given to human patients with a high TG level (200 and 500mg/dL). A significant decrease in high-sensitivity C-reactive protein (hs-CRP) and oxidized LDL was observed in those patients in the control group (Mason, 2019). It is also reported that supplementation of EPA induced the downregulation of genes, notably Hypoxia Inducible Factor (HIF)-1 and cAMP Response Element Binding (CREB) Protein 1, resulting in the occurrence of CVD (Mason, 2019). Recently, researchers conducted randomized control trials assessing the effects of ω-3 FAs (derived from marine sources) supplementation on CVD occurrence. They reported that patients with CVD should use ω-3 FAs derived from marine sources in their diet (O'Keefe et al., 2019). *Halocynthia aurantium* is another rich marine source of ω-3 FAs, especially EPA, DHA, and eicosatrienoic acid (ETA) (Monmai et al., 2018). They conducted an *in vitro* study and reported that these FAs increase prostaglandin E2 (PGE2) and NO production and enhance anti-inflammatory and immune responses (Monmai et al., 2018). In addition, it is also reported in another *in vitro* study conducted on RAW264.7 cells that ω-3 FAs significantly suppress the synthesis of various inflammatory mediators, including iNOS, COX-2, TNF-α, IL-1, and IL-6. IL-6 is an important cytokine involved in generating C-reactive protein (CRP), a well-known biological marker for accessing the likelihood of imminent CVD (Marcelino et al., 2019). Australian seafood is also rich in ω-3 FAs and showed similar effects in *in vitro* studies, like suppressing TNF- α production in RAW 264.7 macrophages (Ahmad et al., 2019). *Sepioteuthis australis* and *Octopus tetricus* displayed the highest ω-3 FAs contents and remarkable anti-inflammatory activity (Ahmad et al., 2019). Similarly, *the Euphausia superba* (Krill) from the Antarctic Ocean received global attention due to its high contents of ω-3 FAs (EPA and DHA) and nutraceutical potential (Ahmad et al., 2019; Colletti et al., 2021). Recently, researchers reported that Krill oil more efficiently normalizes hyperlipidemia than fish oil (Ahmad et al., 2019). Furthermore, several studies showed that krill oil could alleviate CVD due to various phytochemicals manifesting anti-inflammatory, anti-diabetic, and anti-obesity properties (Ahmad et al., 2019; Colletti et al., 2021).

Dietary behavior of Gulf countries and cardiovascular diseases

Since limited information is available regarding the association of the dietary behavior of Gulf countries, notably the Kingdom of Saudi Arabia, with CVD; therefore, we tried to summarize the available literature on the association of dietary behavior with CVD in Gulf countries. The Gulf Cooperation Council (GCC) countries, including the Kingdom of Saudi Arabia, have undergone significant economic development that has resulted in the adaptation of modern lifestyles by the population of Gulf countries (Aljefree &Ahmed, 2015a). Adopting a contemporary lifestyle means transitioning their daily patterns and dietary intake habits. The change in dietary behavior has diverted the Saudi people from their traditional diet to the Western diet (high-energy processed food). Thus, the incidence of CVD and associated risk factors has increased among the Gulf population (Aljefree &Ahmed, 2015a; Musaiger, 2004). According to a national survey, the prevalence of CVD in the Saudi population was reportedly 5.5% (Al-Nozha et al., 2004). Statistical data collected over the past four decades in Saudi Arabia indicates a significant increase in deaths due to CVD-related conditions (Kumosani et al., 2011). Saudi Arabia's Ministry of Health 2018 ranked CVD as the 2nd most common cause of death (6,372 out of 44,783) (Aljefree et al., 2021). Most studies regarding nutritional risk factors and CVD were conducted in the developed world. In Saudi Arabia, limited research investigating the relationship between dietary behavior and CVD risk is available (Alissa &Alama, 2015; Aljefree &Ahmed, 2015b). Recently, a study on humans determined the association between nutrient intake and CVD in Saudi Arabia. They reported that a high intake of total energy and sodium is associated with an increased risk of CVD. Likewise, deficient intake of ω-3 FAs, vitamin A, zinc, and vitamin C is associated with an increased risk of CVD. Researchers recommended that having a balanced diet with ω-3 FAs could prevent and control CVD in Saudi Arabia (Aljefree et al., 2021). In 2015, a study was conducted in which they investigated CV risk and distribution of ω-3 FAs in the Saudi population compared to the US population. They collected human blood samples (n=2,614) from Saudi Arabia and n=1,097 from the US and analyzed them for EPA and DHA using mass spectroscopy. They reported that the Saudi population has a significantly lower blood level of ω-3 FAs than the US population. This difference may contribute to CVD in the Saudi population (Superko et al., 2015). In addition, GCC countries face an epidemic of obesity, DM, and CVD (Alghamdi et al., 2020). In 2014, a study reported that the prevalence of type-2 DM in the Saudi population was 25.4% (Al-Rubeaan et al., 2014). Likewise, another study reported that obesity in GCC countries was 13-50% (Alhyas et al., 2011). This dramatic rise in obesity and diabetes poses a severe threat to the Saudi population because it increases the risk of CVD if left untreated. Since it is established that the daily use of ω-3 FAs derived from natural sources or as a supplement reduces the risk of CVD, ω-3 FAs demand is rising in this region. It is anticipated that the ω-3 market will boost over the forecast period. The overall view of the therapeutic potential of **ω-3** FAs has been summarized in Figure 2.

CONCLUSION

Omega-3 fatty acids, including eicosapentaenoic acid and docosahexaenoic acid, are found in fatty fish such as salmon, mackerel, and sardines, as well as in specific plant sources like flaxseeds and walnuts. They have been associated with various potential cardiovascular benefits, but the research landscape could have evolved since then. Here are some prospects and considerations regarding using omega-3 fatty acids in cardiovascular patients:

(A), *Reduction of Triglycerides:* Omega-3 fatty acids have been shown to help reduce elevated triglyceride levels, a risk factor for cardiovascular disease. Prescription omega-3 medications, such as icosapent ethyl, have been approved for this purpose and may continue to be researched for their effectiveness in reducing cardiovascular events.

(B), *Anti-Inflammatory Effects:* Omega-3 fatty acids possess anti-inflammatory properties that could benefit individuals with chronic inflammatory conditions, including atherosclerosis. Ongoing research might explore how these anti-inflammatory effects impact overall cardiovascular health.

(C), *Arrhythmia Management:* Some studies have suggested that omega-3 fatty acids might reduce the risk of certain arrhythmias (irregular heart rhythms). Further investigation could delve into the mechanisms underlying this potential benefit.

(D), *Heart Failure:* Omega-3 fatty acids might be useful in managing heart failure. Future research may provide more insights into whether they can improve symptoms, quality of life, and outcomes for heart failure patients.

(E), *Combination Therapies:* Researchers might explore the potential synergistic effects of omega-3 fatty acids when combined with other cardiovascular medications or lifestyle interventions. This could include investigating whether omega-3s enhance the effectiveness of statins, blood pressure medications, or exercise regimens.

(F), *Personalized Medicine:* The future of cardiovascular care might involve personalized approaches, considering an individual's genetic makeup, metabolic profile, and specific cardiovascular risk factors. Omega-3 fatty acids could be tailored to individuals more likely to benefit based on their genetic predispositions.

(G), *Dosing and Formulation:* Research could focus on optimizing the dosing and formulation of omega-3 supplements or medications to achieve the best balance of benefits and potential risks. This could involve exploring different ratios of EPA to DHA and examining the most effective delivery methods.

(H), *Long-Term Effects*: Continued research could provide more insights into the long-term effects of omega-3 fatty acid supplementation on cardiovascular health. This is especially important given the growing interest in dietary supplements and their potential impact on chronic disease prevention. It is important to note that while omega-3 fatty acids hold promise for cardiovascular health, not all studies have consistently shown significant benefits. As research progresses, healthcare providers must stay updated on the latest evidence-based recommendations to make informed decisions about incorporating omega-3 fatty acids into treating and preventing cardiovascular disease. If you are looking for the most current information, we recommend consulting recent medical literature or seeking advice from a qualified healthcare professional.

AUTHOR CONTRIBUTION

WAA, HTA, ZR, AQ, ASA, and RA contributed to the concept designing and manuscript drafting: SAA, acquisition, analysis, and interpretation of the data; RA, MAA, AAA, RA, SAA, RSA, acquisition, analysis, and interpretation of the data; NAA, MAJ, MAK, TAA, SAA, MSA, AA, and MSAH manuscript drafting; All authors read and approved the final manuscript.

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Not Applicable.

Participants Consent

Not Applicable.

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Conflict of Interest

All authors have declared that no other relationships or activities could appear to have influenced the submitted work.

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