Nassar *et al.*
The Egyptian Journal of Internal Medicine (2023) 35:81
https://doi.org/10.1186/s43162-023-00265-6

The Egyptian Journal of Internal Medicine

REVIEW

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The multidimensional benefits of eicosapentaenoic acid: from heart health to inflammatory control

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Abstract

Eicosapentaenoic acid (EPA) is an omega-3 fatty acid found in fatty fish and fish oil supplements. Over the past few decades, research has suggested that EPA has various potential health benefits, particularly for heart health.

EPA has been associated with reduced inflammation, improved cholesterol levels, and reduced blood pressure, all of which can contribute to a lower risk of heart disease. Additionally, EPA has been found to reduce the risk of blood clots, which can lead to heart attacks and strokes. This comprehensive review article aims to summarize the current state of knowledge regarding the potential health benefits of EPA. We focus on its effects on cardiovascular health, inflammation, atherosclerotic plaques, blood clots, diabetes, obesity, and cancer. Finally, we provide an overview of the recommended daily dose of EPA for optimal health benefits.

This review highlights the importance of EPA in promoting overall health and well-being and provides insights into its potential therapeutic applications.

Keywords Eicosapentaenoic acid, Cardiovascular health, Inflammation, Cholesterol, Blood clots, Vascepa, Omega-3 fatty acid, Fish oil

Background

Eicosapentaenoic acid (EPA) is an omega-3 fatty acid that can be found in fatty fish and nutritional supplements. EPA has several health benefits, including anti-inflammatory properties and a reduced risk of heart disease. EPA may treat depression and anxiety [1, 2]. Eicosanoids, which are derived from EPA, play a multitude of indispensable physiological functions within the body. Eicosanoids regulate immune response, blood pressure, and inflammation. Fatty acid degradation produces them. These molecules act locally, respond to various stimuli, and are not stored in the body. EPA from dietary supplements is better absorbed when taken with a moderate-fat meal. EPA absorption may be affected by diet fats, age, health, and supplement formulation [3]. As per a study conducted in 1978, the indigenous people of Alaska, who are recognized as Eskimos, demonstrated reduced risk and fewer deaths related to cardiovascular and cerebrovascular disorders because they were consuming an elevated amount of n-3 PUFAs (DHA and EPA) sourced from fish that resided within polar marine environments. Subsequent to that time, scholars researched for their potential in treating various human diseases [4, 5].

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Dietary source and importance

EPA content is in various fish oils, uncooked fish, and beef. Menhaden oil has the highest EPA content, with 13.18, salmon 13.3, herring 6.28, and sardine 10.15. The EPA content of various types of raw fish varies, with salmon having a value of 0.89, sardine 0.51, cod 0.02, trout 0.15, and herring 1.09. Beef has the lowest EPA content, while New Zealand liver and kidney have 0.11 and 0.15, respectively [6, 7]. Santos et al. (2020) found EPA in flaxseeds and chia seeds but not as much as in fatty fish [8]. Alpha-linolenic acid (ALA), an omega-3 fatty acid found in plants, is not a direct source of EPA, and the human body is poor at converting it [9]. Jehi et al. (2022) found that older adults who consumed walnuts, which are high in ALA, did not improve their omega-3 index, suggesting the need for EPA/DHA [10]. Wan et al. (2022) examined dietary fats and fatty liver in adolescents and young adults. They found that a high intake of EPA in early adolescence was linked to a higher risk of fatty liver, though this link may not be causal, and other factors may also play a role [11].

Endothelium dysfunction

In maintaining homeostasis, endothelial cells secrete vasoactive agents such as nitric oxide, prostacyclin, and various vasoconstrictors, which regulate vasoactivity and vascular tone, cellular growth and adhesion, inflammatory response, and oxidation. Endothelial dysfunction may impair the secretion of endothelial factors crucial in regulating inflammation, platelet aggregation, and vascular smooth muscle cell relaxation. These dysfunctions can contribute to developing various cardiovascular conditions, including atherosclerosis [12]. Furthermore, patients with hypertriglyceridemia exhibit heightened endothelial dysfunction directly related to increased triglyceride-rich lipoproteins (TRLs) in the bloodstream. The metabolism of triglycerides results in small TRL remnants that damage endothelial cells, allowing the expression of pro-inflammatory and pro-apoptotic genes. Lipolysis of TRL increases fatty acids, inducing inflammation, and VLDL remnants deposited in the arterial wall increase reactive oxygen species, endothelial cell permeability, and, ultimately, apoptosis of endothelium [13].

Numerous research studies have shown the efficacy of EPA in treating patients with dyslipidemia, type 2 diabetes, and coronary heart disease by improving endothelial function. For instance, 3 months of EPA administration revived endothelium-dependent vasodilation [14], and diabetic and coronary artery disease patients who received EPA plus statins showed improvements in endothelial function [15]. High serum EPA levels also reduced vascular endothelial dysfunction in Japanese hemodialysis patients due to their anti-inflammatory effects [16]. In a study by Fukumoto et al. (2020), EPA reduced triglyceride levels and enhanced flow-mediated dilation (FMD) in mild hypertriglyceridemia patients. The improvement in FMD was related to the patient's baseline high-density lipoprotein cholesterol level and the shift in the EPA/arachidonic acid ratio [17]. Another research found that EPA and DHA benefit human blood vessels by reducing vascular reactivity by working with potassium channels [18].

Moreover, EPA supplementation increases TRPV4 activity in human endothelial cells, leading to vasodilation, and reduces TRPV4 desensitization, contributing to prolonged vasodilation, which improves vascular disorders [19]. On the other hand, a study investigating the impact of EPA and DHA intake on extended sitting revealed that supplementation was ineffective in preventing the adverse effects of extended sitting on leg endothelial function, probably because of the lower average dose of EPA and DHA prescribed [20].

Finally, targeting free fatty acid receptor 4 (Ffar4) may have implications for treating cardiovascular disease, as Ffar4 is necessary for an adaptive response to pressure overload caused by constriction of the aorta, reduces oxidative stress in heart cells, and induces the production of 18-hydroxy EPA (18-HEPE) in cardiac myocytes. Ffar4 expression decreases in human heart failure [21]. In conclusion, EPA and DHA have been shown to improve endothelial function and offer a potential avenue for improving vascular health.

Eicosapentaenoic acid/arachidonic acid ratios (EPA/AA)

EPA, which is found in fatty fish and seafood, and AA, which is found in various animal-derived foods, are omega-3 and omega-6 fatty acids, respectively. The EPA/AA ratio is considered an indicator of inflammation and cardiovascular disease. A lower risk of chronic disease is linked to a higher EPA to AA ratio. It has been proven that EPA treatment improves hemodialysis patients' EPA/AA ratio and lowers their risk of cardiovascular events and inflammatory markers [22–24]. In correlation with ALP in ACS patients, EPA/AA was found to be a better risk marker than DHA/AA in a study of men with the first episode of ACS who were not taking any lipid-lowering medications [25].

Another meta-analysis suggested that fish oil supplementation can reduce arterial stiffness, as indicated by carotid to femoral-pulse wave velocity (cf-PWV) and brachial to ankle-PWV (ba-PWV), especially in trials with low dosages, short duration, and low DHA/EPA ratio and between participants of young age. However, fish oil supplementation did not significantly affect the augmentation index (AIx) or AIx75 [26].

CVS risk in hemodialysis patients

The effect of EPA on cardiovascular (CVS) consequences in patients undergoing regular hemodialysis (HD) has been discussed in many studies. One of these studies, a prospective, randomized, open-label trial by Nasu et al. in 2013, involved 179 subjects and discovered that taking a daily dose of 1.8 g of EPA for 2 years led to an 80% reduction in cardiovascular death, a 50% decrease in cardiovascular events, and a 51% reduction in cardiovascular death or events [27]. A longitudinal, observational cohort study by Inoue in 2015, which involved 176 subjects, revealed that a daily dose of 0.9 g of EPA reduced all-cause mortality by 58% over a follow-up period of 3 years [28]. Umemoto et al. conducted the third study in 2015, which was a longitudinal, observational study involving 459 subjects who received standard therapy. Over a 3-year follow-up period, the findings showed that the EPA group had a 47% and 59% decrease in all-cause mortality and cardiovascular mortality, respectively [29].

Effect of EPA on cardiovascular risk

The International Society for the Study of Fatty Acids and Lipids and the World Health Organization (WHO, 2000) recommend that adults who want to keep their hearts healthy ingest at least 500 mg daily of EPA and DHA combined. This is the minimum amount that should be consumed [30]. Clinical trials like JELIS and REDUCE-IT, which focused on pure EPA, have indicated cardiovascular advantages. In contrast, the ASCEND, VITAL, STRENGTH, and OMEMI trials evaluated combinations of EPA and DHA and did not showcase similar benefits [31].

Table 1 summarizes findings from three randomized controlled trials (RCTs) that investigated the impact of EPA supplementation on cardiovascular outcomes. These studies varied from a few hundred to tens of thousands of participants. The outcomes of interest were primarily focused on the composite of sudden cardiac death (SCD), fatal or nonfatal myocardial infarction (MI), unstable angina, or revascularization, and all studies incorporated the use of statins in their treatment protocols.

EPA may have several potential benefits for heart health, including the following:

EPA has been associated with various potential health benefits, including reducing the risk of heart disease. One mechanism by which EPA may confer cardiovascular protection is by reducing inflammation, a well-established risk factor for heart disease [36]. EPA is metabolized into compounds that possess anti-inflammatory properties and can help lower body inflammation, which might ultimately lower heart disease risk [37].

Moreover, EPA has also been found to lower blood pressure, another risk factor for heart disease [37]. In addition, EPA has been shown to improve cholesterol levels by increasing HDL cholesterol and decreasing LDL cholesterol, which can contribute to heart disease risk [36]. Studies have also linked EPA consumption with reduced heart attack and heart failure risk. EPA and DHA intake was found to decrease the incidence of heart failure by 18–29%, while randomized controlled trials demonstrated that EPA and DHA therapy at doses ranging from 1 to 4 g per day significantly improved left ventricular ejection fraction (LVEF), a measure of heart function [38].

How can EPA improve coronary artery function?

EPA is believed to improve coronary artery function in several ways, such as reducing inflammation, a risk factor for heart disease. EPA can also help lower blood pressure and improve cholesterol levels, both of which can lower the risk of heart disease. Additionally, EPA may help reduce the risk of blood clots, leading to heart attacks and strokes. Studies have found that individuals with low EPA and DHA plasma levels tend to have a higher rate of plaque progression, while those with higher levels do not. This is thought to be due to the imbalance in the ratio of lipid mediators that promote resolution versus those that promote inflammation [39]. Furthermore, EPA and DHA have been found to modulate membrane phospholipids, which can enhance cardiac mitochondrial activity and power production, providing both vascular and cardiac protective effects [40].

Table 1 Cardiovascular outcomes in RCTs evaluating EPA supplementation

Study	Study size	Daily EPA dose	CVS risk profile	Follow-up time (years)	Outcome (*HR*: 95% *CI*)
Yokoyama et al. (2007) (JELIS) [32]	18,645	1800 mg	Hypercholesterolemia	4.6	*HR*: 0.81 (0.69–0.95)
Nosaka et al. (2017) [33]	241	1800 mg	Recent acute coronary syndrome	1	*HR* 0.42, 95% *CI* 0.21–0.87
Bhatt et al. (2019) (REDUCE-IT) [34]	8179	4000 mg	Established ASCVD or diabetes with additional ASCVD risk	4.9	*HR*: 0.75 (0.68–0.83)

EPA Eicosapentaenoic acid, *CVS* Cardiovascular, *HR* Hazard ratio, *CI* Confidence interval, *ASCVD* Atherosclerotic cardiovascular disease (adopted from Jia et al. [35])

How EPA reduces inflammation

EPA is known to have anti-inflammatory effects and may help to reduce inflammation in the body, which is a normal immune response to injury or infection. However, chronic inflammation is thought to play a role in developing chronic diseases such as heart disease, cancer, and diabetes. EPA is converted into compounds called eicosanoids, which have anti-inflammatory effects. EPA also has antioxidant properties, which may help protect against the harmful effects of free radicals. Studies have shown that high amounts of EPA and DHA can reduce oxidative stress, block or inhibit platelet reactivity, and diminish inflammatory indicators such as C-reactive protein and tumor necrosis factor-alpha [41]. Additionally, EPA may have antimicrobial properties and may help treat certain infections. EPA and DHA can be converted into anti-inflammatory and organ-protecting molecules such as D- and E-series resolving [39].

EPA effect on atherosclerotic plaques

EPA is thought to reduce the risk of atherosclerotic plaques in several ways, such as reducing inflammation, improving cholesterol levels, and reducing the risk of blood clots. Chronic inflammation is a risk factor for the development of atherosclerotic plaques, and EPA is converted into compounds that help to reduce body inflammation, which might help to decrease the susceptibility of heart disease. Additionally, EPA may help increase HDL levels and decrease LDL levels, which may help lower the risk of heart disease. Furthermore, EPA may help reduce the risk of blood clots, leading to heart attack and stroke. Studies have shown that individuals with lower levels of EPA + DHA in their plasma were observed to have a significant plaque progression rate, while patients with higher plasma levels of EPA + DHA were not. This was caused by inequity in the ratio of lipid mediators that promote a resolution to those that promote inflammation [39].

A recent article reviewed the positive effects of EPA on various stages of atherosclerosis, such as preventing blood vessel lining damage and slowing down plaque buildup. EPA has been found to affect several aspects of the onset and progression of atherosclerosis, including inflammation and oxidative stress. It also aids in reducing specific blood fats that contribute to the condition. It is crucial to remember that DHA lacks some of the advantages that EPA possesses [42, 43].

Anti-inflammatory effect

According to current studies, highly purified EPA significantly decreases the risk of atherosclerosis. In a mouse model, EPA decreased plaque formation, bloodstream lipid levels, and inflammation. The scientists used microRNA sequencing to identify miR-1a-3p, which they further investigated. Subsequent studies showed that EPA impacts some of the macrophage's pathways as the Wnt/planar cell polarity-c-Jun N-terminal kinase (Wnt/PCP-JNK) pathway. This indicates that EPA might reduce macrophage inflammatory and oxidative reactions by targeting the miR-1a-3p/sFRP1/Wnt/PCP-JNK pathway. This could explain the cardioprotective properties of EPA and support its clinical use [44].

Antioxidant effect

EPA has the potential to function as an antioxidant, which means it can protect cells from damage caused by oxidative stress. Oxidative stress occurs when the body's cells are exposed to high levels of reactive oxygen species (ROS), which are a byproduct of normal metabolism. These ROS can damage cells and contribute to the development of chronic diseases such as heart disease, cancer, and diabetes. EPA can be converted into compounds called eicosanoids, which have been found to have antioxidant effects. These compounds may help to reduce oxidative stress and protect cells from damage. DHA and other polyunsaturated fatty acids (PUFA) also have antioxidant properties that are activated when they are incorporated into cell membranes. DHA is an essential phospholipid for mitochondrial membrane biogenesis and has multiple effects, including increasing the effectiveness of manganese-dependent superoxide dismutase (Mn-SOD) and decreasing oxidative stress and cytochrome c oxidase activity in the mitochondria [40].

Effect of EPA on blood clots

EPA is believed to reduce the risk of blood clots in several ways. EPA is converted into compounds that help to decrease body inflammation, which may help to decrease the possibility of blood clots. It may also improve cholesterol levels by increasing "good" cholesterol and decreasing "bad" cholesterol, lowering the risk of blood clots. Additionally, EPA may help to reduce the stickiness of platelets, which are blood cells that play a role in blood clotting [45].

Effect of EPA on diabetic patients

EPA may have potential benefits for individuals with diabetes, including reducing inflammation, blood sugar control, blood pressure, and cholesterol levels. However, more research is required to fully comprehend the mechanisms by which EPA may provide these benefits. One theory is that EPA may improve insulin sensitivity and reduce inflammation, which is thought to contribute to poor blood sugar control in people with diabetes. Studies have also shown that endothelial dysfunction was reduced in a type 2 diabetes mouse model when the mice were continuously given EPA for a period [46].

EPA and obesity

EPA may aid in weight loss by reducing inflammation and improving body composition. It has anti-inflammatory effects that may lower the risk of obesity and related conditions such as insulin resistance and type 2 diabetes. Studies have also shown that supplementing with EPA can lower body fat mass and increase lean body mass [47].

The most recent clinical trial meta-analysis concluded that n-3 PUFA supplements did not affect body mass index (BMI) [48]. The study examined how EPA and DHA affect fat cell "browning" in mice and lab-grown fat cells to determine how they affect body fat in adults. The findings revealed that high levels of DHA in the blood were associated with lower body fat levels, and that DHA was more effective than EPA in preventing fat cell growth. The researchers believe that DHA's ability to alter the "browning" of fat cells is the reason for its more significant effect [49].

According to certain investigations, individuals who consume or test positively for elevated amounts of EPA within their diet or bloodstream may be less susceptible to the occurrence of a stroke. For example, one study found that people who consumed more EPA had a lower risk of ischemic stroke, while another study found that people with higher levels of EPA in their blood had a lower risk of both ischemic and hemorrhagic stroke. However, more research is necessary to comprehend the connection between EPA and stroke risk fully.

Effect of EPA on cancer

EPA may reduce cancer risk. Some studies propose that the administration of EPA may aid in mitigating one's likelihood of developing breast, colon, and prostate cancers. EPA and DHA inhibit signaling pathways to reduce the risk of aggressive cancers like pancreatic carcinoma and hepatocellular cancer in hepatitis virus-infected patients. It has been speculated that inflammation can influence malignancy pathogenesis, whereas eicosapentaenoic acid is metabolized into substances with anti-inflammatory properties in the organism [46].

The recommended daily dose of EPA

The American Heart Association suggests taking 500 mg of EPA daily or consuming two servings of fat-rich fish weekly. On the other hand, it may be beneficial for specific persons — notably those with coronary heart disease — to increase their intake of EPA and DHA to a daily consumption of 1 g. This is particularly true if higher doses are utilized since they might prove advantageous in such cases. EPA+DHA combinations have been used in studies such as VITAL, ASCEND, and ORIGIN, but daily intake of 1-g capsules containing 840 mg of EPA+DHA did not significantly improve placebo [41, 50, 51]. Consuming adequate fish as part of a balanced, healthy diet is essential for reducing cardiovascular risk [52].

Conclusion

EPA may be a beneficial dietary supplement for people with heart disease risk factors. EPA may help with cardiovascular disease, diabetes, obesity, cancer, and stroke. Inflammation, cholesterol, blood pressure, blood clots, and coronary artery function are all reduced by EPA. EPA reduces inflammation and improves body composition, both of which aid in weight loss. More research is needed, however, to understand how EPA benefits diabetes and obesity. The optimal daily dose of EPA and DHA for health benefits requires more research.

Abbreviations

18-HEPE	18-Hydroxy eicosapentaenoic acid
AA	Arachidonic acid
ACS	Acute coronary syndrome
AIx	Augmentation index
AIx75	Augmentation index at heart rate 75
ALA	Alpha-linolenic acid
ASCEND	A study of cardiovascular events in diabetes
ASCVD	Atherosclerotic cardiovascular disease
ba-PWV	Brachial to ankle-pulse wave velocity
BMI	Body mass index
cf-PWV	Carotid to femoral-pulse wave velocity
CI	Confidence interval
CVS	Cardiovascular
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
Ffar4	Free fatty acid receptor 4
FMD	Flow-mediated dilation
HD	Hemodialysis
HDL	High-density lipoprotein
HR	Hazard ratio
LDL	Low-density lipoprotein
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
miR-1a-3p	MicroRNA-1a-3p
Mn-SOD	Manganese-dependent superoxide dismutase
NSAIDs	Nonsteroidal anti-inflammatory drugs
ORIGIN	Outcome Reduction with an Initial Glargine Intervention
PUFA	Polyunsaturated fatty acids
RCTs	Randomized controlled trials
ROS	Reactive oxygen species
SCD	Sudden cardiac death
sFRP1	Secreted frizzled-related protein 1
TRLs	Triglyceride-rich lipoproteins
TRPV4	Transient receptor potential vanilloid 4
VITAL	Vitamin D and omega-3 trial
VLDL	Very low-density lipoproteins
WHO	World Health Organization
Wnt/PCP-JNK	Wnt/planar cell polarity-c-Jun N-terminal kinase

Acknowledgements

Not applicable.

Authors' contributions

MN contributed to idea conceptualization, wrote the first draft, and participated in the review. AJ conducted the database search and co-wrote the draft. BI was involved in the database search, co-wrote the draft, and handled proofreading. BB also co-wrote the draft, while HA took charge of reviewing, editing, and submitting the manuscript. All authors read and approved the final manuscript.

Funding
None.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 6 September 2023 Accepted: 28 November 2023
Published online: 12 December 2023

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