

Dietary Supplementation with Anti-Inflammatory Omega-3 Fatty Acids for Cardiovascular Protection: Help or Hoax?

Y. Robert Li¹⁻⁵, Zhenquan Jia¹⁻³, and Hong Zhu⁶

¹Department of Pharmacology, Campbell University Medical School, Buies Creek, NC 27506, USA;

²Department of Pharmaceutical Sciences, Campbell University College of Pharmacy and Health Sciences,

Buies Creek, NC 27506, USA; ³Department of Biology, University of North Carolina College of Arts and

Sciences, Greensboro, NC 27412, USA; ⁴Virginia Tech–Wake Forest University School of Biomedical

Engineering and Sciences, Blacksburg, VA 24061, USA; ⁵Department of Biomedical Sciences and

Pathobiology, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, USA; ⁶Department

of Physiology and Pathophysiology, Campbell University Medical School, Buies Creek, NC 27506, USA

Correspondence: yli@campbell.edu (Y.R.L.)

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ABSTRACT | Dietary supplementation with omega-3 fatty acids, also known as n-3 fatty acids, has been widely considered cardiovascular protective in the general human population. This widely acclaimed status of omega-3 fatty acids as cardiovascular protective molecules has, however, been questioned by findings from multiple rigorously designed randomized controlled trials, recently reported in the New England Journal of Medicine. Although the anti-inflammatory and other beneficial effects of omega-3 fatty acids are substantiated by research in experimental models as well as findings from observational epidemiological studies, dietary supplementation with omega-3 fatty acids at the typical dosage of 1 g daily does not appear to be an effective strategy for either primary or secondary prevention of cardiovascular disease in humans.

KEYWORDS | Antiinflammation; Antioxidant; Cardiotoxicity; Cardiovascular disease; Doxorubicin; n-3 Fatty acids; Omega-3 fatty acids

ABBREVIATIONS | ALA, α -linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GPR120, G protein-coupled receptor 120; NEJM, New England Journal of Medicine; RCT, randomized controlled trial; US FDA, United States Food and Drug Administration

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1. OVERVIEW

Substantial research in experimental models has led to the identification of omega-3 fatty acids (also called n-3 fatty acids) as potential beneficial molecules that may alleviate inflammatory and oxidative stress, thereby protecting against various forms of degenerative disorders, especially cardiovascular disease in humans. This notion is supported by findings from numerous observational epidemiological studies and some early randomized controlled trials (RCTs), leading to the wide-spread claim of n-3 fatty acids as cardiovascular protective molecules. However, multiple rigorously designed RCTs recently reported in the New England Journal of Medicine (NEJM), the most prestigious medical journal in the world, failed to show a beneficial effect for omega-3 fatty acids in either primary or secondary prevention of cardiovascular disease. Neither did the RCTs reveal a protective effect of omega-3 fatty acid in diabetes and cancer. Despite the disappointing results, pharmaceutical preparations providing large dosages of omega-3 fatty acids are effective treatment for severe hypertriglyceridemia and may reduce ischemic events, including cardiovascular death, in such patients. Hence, the widely acclaimed status of omega-3 fatty acids as cardiovascular protective molecules might need to be scrutinized. In this Research Highlights article, we first briefly review the basic chemistry and biology, as well as the US FDA-approved clinical use of omega-3 fatty acid, and then describe the key findings of the RCTs on omega-3 fatty in cardiovascular protection reported in the NEJM over the past few years, especially in 2018.

2. BASIC CHEMISTRY AND BIOLOGY

2.1. Basic Chemistry

Omega-3 fatty acids, also written as ω -3 fatty acids, constitute a series of essential unsaturated fatty acids that have a final carbon-carbon double bond in the n-3 position (also known as the ω position), that is, the

third bond from the methyl end of the fatty acid. As such, omega-3 fatty acids are commonly referred to as n-3 fatty acids [1–3]. Nutritionally important omega-3 fatty acids include the plant-derived α -linolenic acid (ALA) and the marine animal-derived eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), all of which are polyunsaturated [4, 5] (structures shown in **Figure 1**).

2.2. Basic Biology

Findings from various experimental models including animals and cultured cells show that omega-3 fatty acids are anti-inflammatory molecules [5]. In animal models, omega-3 fatty acids protect against various forms of cardiovascular injury including myocardial ischemia-reperfusion injury [6, 7] and doxorubicin-induced cardiotoxicity [8, 9]. Evidence also suggests an antioxidant property for omega-3 fatty acid likely via activating Nrf2 signaling, an essential mechanism of upregulation of antioxidative gene expression [10]. Notably, Nrf2 also is an anti-inflammatory regulator [11]. Hence, it is not surprising that Nrf2-activating antioxidative molecules are usually anti-inflammatory. In addition to Nrf2 signaling, the G protein-coupled receptor 120 (GPR120) has been shown to function as an omega-3 fatty acid receptor/sensor to mediate the anti-inflammatory and insulin-sensitizing effects of omega-3 fatty acids [12–14] (**Figure 2**).

3. THE US FDA-APPROVED CLINICAL USE

Besides the anti-inflammatory and antioxidative properties of omega-3 fatty acids, reduction of triglycerides in individuals with severe hypertriglyceridemia by large dosages of these fatty acids is well established. Indeed, the US FDA has approved three pharmaceutical preparations of large dosages of omega-3 fatty acids, namely, Lovaza, Vascepa, and Epanova, for treating severe hypertriglyceridemia (≥ 500 mg/dl) [15]. At the recommended dosage of 4 g daily, these omega-3 fatty acid-based drugs can re-

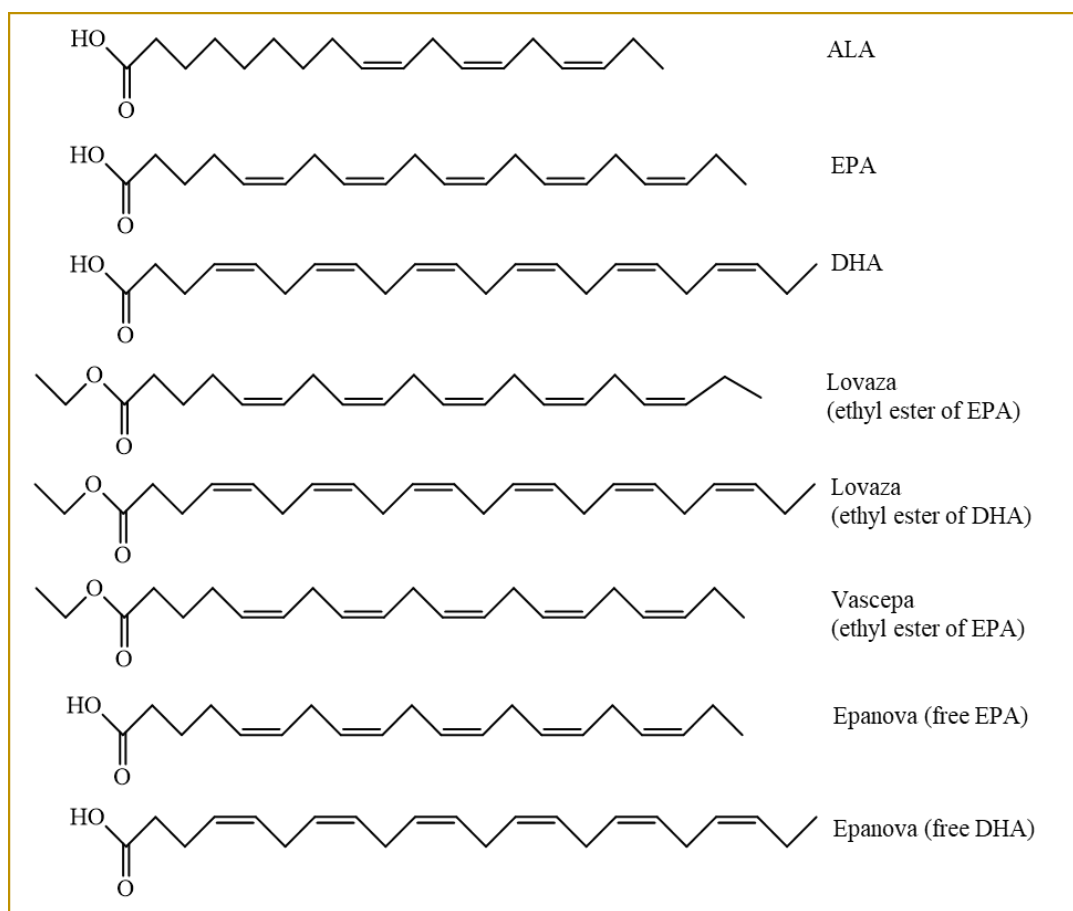


FIGURE 1. Chemical structures of omega-3 fatty acids. The three main forms of omega-3 fatty acids are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Lovaza is a mixture of esters of EPA and DHA, whereas Vascepa is an ester of EPA. Different from Lovaza and Vascepa, Epanova is a mixture of free EPA and DHA (adapted from [15] with permission).

duce blood triglyceride levels by ~20–50% [15]. The mechanisms by which omega-3 fatty acids at high dosages reduce triglycerides remain elusive. It has been suggested that the triglyceride-lowering effect of omega-3 fatty acids may result from the inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase (DGAT, an important enzyme in triglyceride biosynthesis) and activation of lipoprotein lipase (an important enzyme in triglyceride hydrolysis), as well as increased oxidation of fatty acids (fatty acids as building blocks for triglyceride synthesis) [15]. Whether GPR120 is involved in the triglyceride-lowering effect, however, remains unknown.

4. OBSERVATIONAL STUDIES VERSUS RCTS

4.1. Observational Epidemiological Studies

Dietary intake of fatty fish or fish oil supplements rich in omega-3 fatty acids is associated with a reduced risk of cardiovascular events and cardiovascular mortality. This notion has been demonstrated in numerous observational epidemiological studies [16–18]. However, observational epidemiological studies cannot establish a causal relationship between intake of omega-3 fatty acids and reduction of cardiovascular events/death.

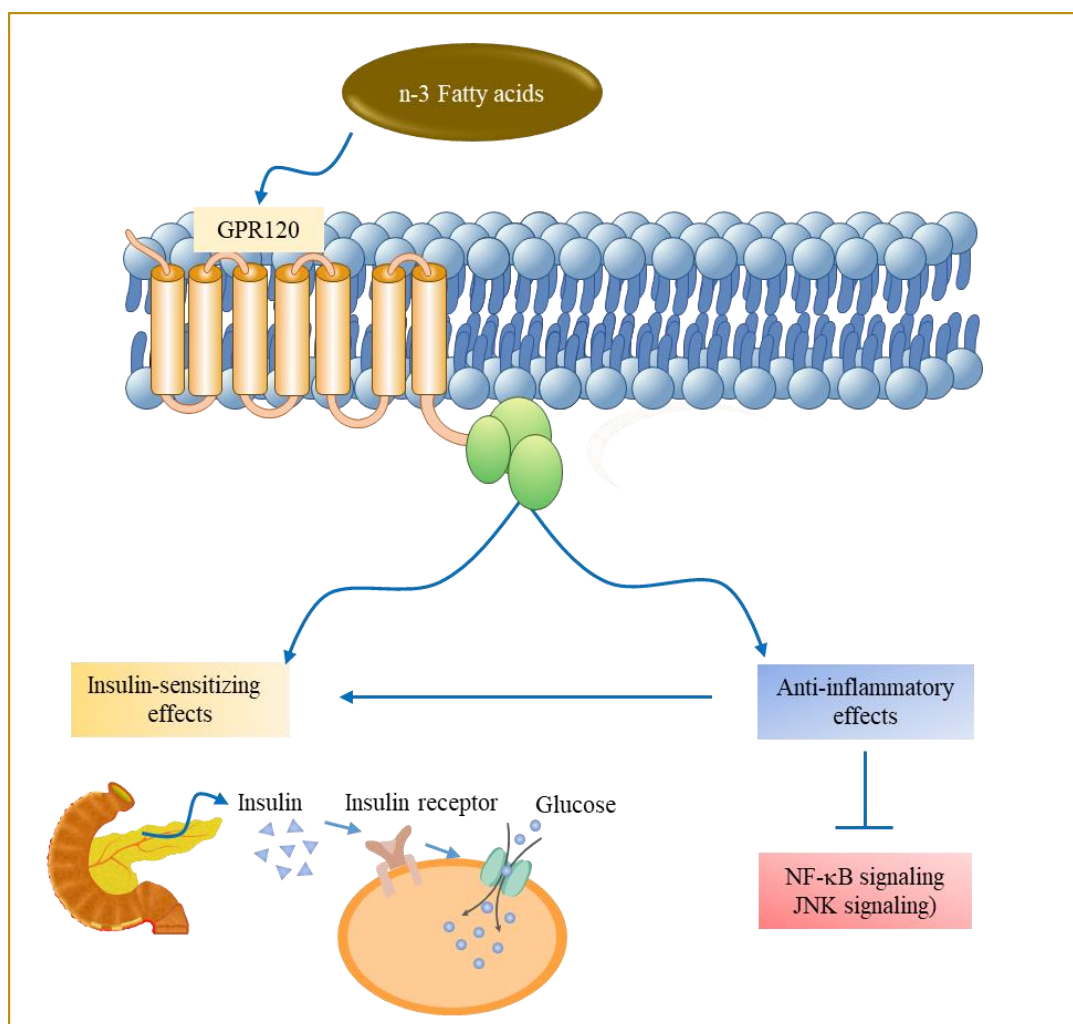


FIGURE 2. G protein-coupled receptor (GPR) 120 as a potential receptor/sensor for omega-3 fatty acids. Human genetic and animal gene-knockout studies suggest a crucial role for GPR120 in regulating insulin sensitivity and metabolism and in anti-inflammation. Activation of this receptor by omega-3 fatty acids has been demonstrated to mediate the insulin-sensitizing (e.g., increased glucose uptake) and anti-inflammatory effects of these dietary fatty acids in experimental models (adapted from [15] with permission).

4.2. RCTs

The cardiovascular benefits of omega-3 fatty acids have been scrutinized in many RCTs, a gold-standard of methodology for demonstrating a causal relationship. The results from such studies have, however, yielded conflicting results. For example, in an early RCT (Lancet, 2008) involving 6,975 patients with chronic heart failure on standard therapy,

supplementation with omega-3 fatty acids (1 g daily) for a median of 3.9 years led to a small, but statistically significant 8–9% reduction in mortality and admission to hospital for cardiovascular reasons [19]. On the other hand, a multicenter RCT (NEJM, 2010) on 4,837 patients who had had a myocardial infarction, concluded that low-dose supplementation with “EPA + DHA” (400 mg daily) or ALA (2 g daily) did not significantly reduce the rate of major cardio-

vascular events among patients who had had a myocardial infarction and who were receiving state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy [20].

In a subsequent RCT (NEJM, 2012) involving a total of 12,536 individuals without cardiovascular disease, but had impaired fasting glucose, impaired glucose tolerance, or diabetes, daily supplementation with 1 g of omega-3 fatty acids did not reduce the rate of cardiovascular events in these people during a 40-month follow-up [21]. This conclusion was further supported by findings from a recent RCT (NEJM, 2018) involving 15,480 patients with diabetes but without evidence of atherosclerotic cardiovascular disease [22]. Likewise, an RCT (NEJM, 2013), involving 12,513 individuals with multiple cardiovascular risk factors or atherosclerotic vascular disease who had not had a myocardial infarction, showed no benefit for treatment with omega-3 fatty acids (1 g daily for a median of 5 years) in reducing cardiovascular mortality and morbidity [23].

A more recent RCT (NEJM, 2018) on a total of 25,871 participants from the general population reported that during a median follow-up of 5.3 years, supplementation with omega-3 fatty acids (1 g daily) did not result in a lower incidence of major cardiovascular events or cancer than placebo [24]. Taken together, all the findings of the RCTs reported in the NEJM over the past few years do not support a beneficial effect for supplementation with omega-3 fatty acid in either primary or secondary prevention of cardiovascular disease. This conclusion is also in line with that reached in two recent systemic reviews and meta-analyses [25, 26] of 10 RCTs with 77,917 participants and 79 RCTs with 112,059 participants, respectively.

5. DO DOSAGES MATTER?

Multiple reasons may account for the null effects of supplementation with omega-3 fatty acids in cardiovascular protection demonstrated in the recent rigorously designed RCTs and meta-analyses. One commonly argued reason, particularly for the failure of omega-3 fatty acids in the secondary prevention of cardiovascular disease, was that the patients involved in the trials had already received effective therapies, such as statins, which are also potent anti-inflammatory drugs. In the presence of such a back-

ground anti-inflammatory therapy, the additional beneficial effect of omega-3 fatty acids might become negligible, especially when the dosages of omega-3 fatty acids were low. Indeed, as noted above, most RCTs employed a dosage of 1 g daily, which might not high enough to cause an incremental effect on cardiovascular pathophysiology. In this context, as mentioned earlier, large dosage regimens (4 g daily) of omega-3 fatty acid-based pharmaceutical preparations are effective for treating severe hypertriglyceridemia (≥ 500 mg/dl), a risk factor of cardiovascular disease [27]. Encouragingly, in a recent RCT (NEJM, 2018) involving 8,179 patients with a fasting triglyceride level of 135–499 mg/dl and a low-density lipoprotein cholesterol level of 41–100 mg/dl, treatment with a pharmaceutical preparation of omega-3 fatty acids, namely, Vascepa (a highly purified EPA ethyl ester with improved bioavailability; **Figure 1**) at 2 g twice daily (a total of 4 g daily) for a median of 4.9 years led to a significant 25% reduction in cardiovascular events and mortality as compared with placebo [28]. It should be noted that the patients involved in the trial received statin therapy as well. The trial concluded that among patients with elevated triglyceride levels despite the use of statins, the risk of ischemic events, including cardiovascular death, was significantly lower among those who received 2 g of icosapent ethyl twice daily than among those who received placebo [28]. The cardiovascular protective potential of high doses of omega-3 fatty acids with improved pharmacokinetic profiles in other patient populations as well as the general population warrants investigation in rigorously designed RCTs.

6. CONCLUSION

In conclusion, dietary supplementation with low doses of omega-3 fatty acids (1 g daily) does not appear to offer a significant benefit in primary and secondary prevention of cardiovascular disease. Large doses (4 g daily) of pharmaceutical preparations of omega-3 fatty acids, however, represent an effective therapy for reducing both blood triglyceride levels and improving cardiovascular outcomes in patients with hypertriglyceridemia despite the use of statins. Future studies should focus on using high doses of omega-3 fatty acids, particularly those preparations with improved pharmacokinetic properties in the in-

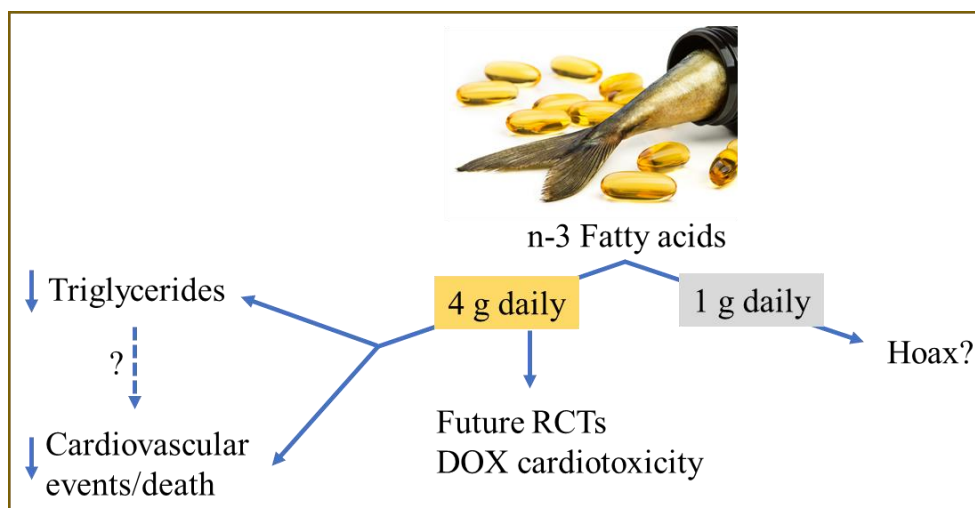


FIGURE 3. Help or hoax up to dosages? Dietary supplementation with low dosages of omega-3 fatty acids (1 g daily) for cardiovascular protection seems to be a hoax, whereas intake of large dosages (4 g daily) appears to be helpful in reducing cardiovascular morbidity and mortality in individuals with elevated blood triglycerides. Future RCTs should focus on testing the efficacy of large dosages of omega-3 fatty acids in protecting against other forms of cardiovascular disorders, including cardiomyopathy/heart failure caused by doxorubicin (DOX) and other cancer chemotherapeutic drugs.

tervention of cardiovascular disorders, including drug-induced cardiotoxicity, an increasingly important issue in clinical oncology [29] (Figure 3).

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