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Review

Omega-3 fatty acids: biological mechanisms, clinical benefits, and translational implications in nutrition and human health

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Abstract

Omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), play a central role in maintaining cardiovascular, metabolic, neurological, and immune health. Sufficient omega-3 status has been consistently linked to a lower incidence of major cardiovascular events, alongside improvements in endothelial function and blood pressure regulation. Importantly, clinical outcomes appear to vary according to dosage and formulation, with purified EPA generally showing more robust and reproducible effects than combined EPA/DHA preparations.

In the context of brain health, omega-3s are essential for preserving neuronal structure and function, mitigating age-related cognitive decline, and decreasing the likelihood of mood disorders and neurodegenerative conditions, particularly during the early phases of disease and among individuals genetically predisposed, such as carriers of the apolipoprotein E ε4 (ApoE4) allele. Their capacity to generate specialized pro-resolving mediators (SPMs) bioactive lipid compounds derived from omega-3 fatty acids that actively regulate and resolve inflammation also underpins significant anti-inflammatory and metabolic benefits, reinforcing their relevance in chronic inflammatory and metabolic disorders.

Despite the breadth of these protective effects, population-wide intake of omega-3 fatty acids remains below recommended levels. At the same time, the disproportionate consumption of omega-6 relative to omega-3 fatty acids persists as a critical nutritional imbalance, emphasizing the urgent need for more effective and sustainable dietary strategies.

Keywords:

Omega-3, cardioprotection, neuroprotection, inflammation, metabolism, supplementation.

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1. Introduction

Omega-3 fatty acids, particularly EPA and DHA, exert broad and well-documented beneficial effects on cardiovascular, metabolic, neurological, and inflammatory health. Adequate omega-3 status is associated with a reduced risk of major cardiovascular events, as well as improvements in vascular function and blood pressure, with effects that appear to be dose- and formulation-dependent. Notably, purified EPA has demonstrated more consistent efficacy than combined EPA/DHA formulations [1-4]. In the neurological domain, omega-3s contribute to the preservation of brain integrity, attenuate cognitive decline, and lower the risk of depression and dementia, especially in early stages and among carriers of the ApoE4 allele [5-9]. Moreover, their anti-inflammatory and metabolic actions—partly mediated by specialized pro-resolving lipid mediators—support their therapeutic potential in chronic inflammatory and metabolic disorders [10-12]. Despite these well-established benefits, global omega-3 intake remains insufficient, and the persistent imbalance in the omega-6/omega-3 ratio continues to represent a major public health concern, underscoring the need for targeted and sustainable nutritional strategies [13-15].

Omega-3 polyunsaturated fatty acids constitute a family of bioactive lipids essential for optimal bodily function. EPA and DHA, primarily of marine or microalgal origin, as well as ALA of plant origin, play a role in cell membrane structure, intracellular signaling, and the regulation of key inflammatory, metabolic, and neurobiological processes [11, 16, 17]. However, the endogenous conversion of ALA to EPA and DHA is limited in humans, making direct dietary intake of long-chain omega-3 fatty acids particularly important [14, 18].

Over the past few decades, a growing imbalance in the omega-6/omega-3 ratio, characteristic of Western diets, has been associated with an increased risk of cardiovascular, metabolic, inflammatory, and neuropsychiatric diseases [14, 15, 19]. Conversely, high circulating levels of omega-3 fatty acids are consistently associated with a reduced risk of coronary heart disease, ischemic stroke, and cardiovascular mortality, reinforcing their vascular protective role [20-23].

Beyond the cardiovascular system, omega-3 fatty acids have major effects on the brain and mental health. DHA is a fundamental structural component of brain tissue, and sufficient omega-3 intake is associated with improved brain integrity, enhanced cognitive performance, and a reduced risk of cognitive decline, dementia, and Alzheimer's disease, with increased efficacy in prevention and early stages [5, 7, 8, 9, 24]. In parallel, omega-3 fatty acids are emerging as key modulators of neuroinflammation and neuronal plasticity, offering therapeutic prospects for depression, anxiety disorders, and other neuropsychiatric conditions [6, 25, 26].

Despite the abundance of favorable data, clinical outcomes remain heterogeneous and highly dependent on dose, formulation (purified EPA versus EPA/DHA blends), clinical context, and baseline nutritional status [3, 4, 23, 27]. Furthermore, the global prevalence of omega-3 deficiency, combined with challenges related to the sustainability of sources, supplement quality, and regulatory compliance, necessitates an integrative approach combining nutrition, technology, and public health [13, 28-31]. In this context, this review aims to synthesize current data on the effects of omega-3 fatty acids, their mechanisms of action, and future prospects for optimized and personalized use.

2. Omega-3 and cardiovascular health

Long-chain omega-3 fatty acids have a well-documented cardioprotective potential. High circulating levels are inversely associated with the risk of coronary heart disease, myocardial infarction, and ischemic stroke [20, 22]. Omega-3 supplementation reduces the risk of major cardiovascular events, with optimal efficacy observed at moderate doses around 1 g/day for primary prevention [2], while higher doses may be beneficial in high-risk patients or those with hypertriglyceridemia [21].

Cardiovascular benefits appear to be highly dependent on the formulation. Purified EPA demonstrates more consistent vasculoprotective effects than EPA/DHA mixtures, particularly on endothelial function and vascular inflammation [3, 4]. Omega-3 fatty acids also contribute to blood pressure regulation, with a combined intake of 2 to 3 g/day of EPA + DHA associated with a significant reduction in blood pressure, particularly in populations at high cardiovascular risk [1, 32]. In terms of safety, omega-3 supplementation is generally well tolerated, with a clinically low risk of bleeding, limited to high doses of purified EPA [33, 34].

3. Metabolic and hepatic effects

Omega-3 fatty acids exert pleiotropic metabolic effects via interconnected molecular mechanisms, including modulation of gene expression, enhancement of insulin sensitivity, and reduction of low-grade chronic inflammation [11, 17]. They improve adipose tissue function, reduce local and systemic inflammation, and exert a protective effect against obesity and high-fat diet-induced liver disease, unlike omega-6 fatty acids [19, 35].

In patients with NAFLD, omega-3 fatty acids improve hepatic lipid metabolism and potentiate the reduction in liver fat associated with weight loss [36]. Benefits are also reported in polycystic ovary syndrome, independent of significant weight loss [37].

4. Omega-3, inflammation, and the gut-immunity axis

The anti-inflammatory properties of omega-3 fatty acids largely rely on their conversion into specialized pro-resolutive lipid mediators, such as resolvins, protectins, and maresins. Resolvin D2 and its omega-3 precursors significantly attenuate experimental intestinal inflammation, identifying this pathway as a promising therapeutic target in chronic inflammatory bowel diseases [10].

EPA appears to be the main component associated with a reduction in the risk of IBD, via specific metabolic mechanisms and genetic mediation involving the FADS2 gene [12]. Omega-3 fatty acids also contribute to the integrity of the intestinal barrier, although their effect remains less pronounced than that of short-chain fatty acids [38]. These properties support their potential in autoimmune diseases, particularly in synergy with vitamin D [39].

5. Brain, cognition, and mental health

DHA is a major structural component of the brain, particularly abundant in neuronal membranes. In middle-aged and older adults, high levels of omega-3 fatty acids are associated with improved brain structure, superior cognitive performance, and a slowing of cognitive decline [5, 24, 40]. These effects are particularly pronounced in the early stages of cognitive decline and in carriers of the ApoE4 allele [8, 9].

From a psychiatric perspective, omega-3 fatty acids exert protective effects against stress-induced depressive and anxiety symptoms through anti-inflammatory, metabolic, and neuroendocrine mechanisms [6, 25, 26]. They could represent a complementary approach in major depression, postpartum depression, and other neuropsychiatric disorders, although long-term clinical trials are needed [41].

6. Peripheral clinical applications: vision, skin, muscle, and bone

Omega-3 fatty acids effectively reduce the symptoms of dry eye, particularly when administered at high doses and over a long period, with a high EPA content [42]. They also exert a dose-dependent protective effect against diabetic retinopathy [43] and may reduce the risk of myopia, especially with early intake [44, 45].

In dermatology, correcting omega-3 deficiency improves the severity of acne [46] and pediatric atopic dermatitis, particularly in combination with GLA [47]. Omega-3s improve muscle strength and function in older adults, supporting their role in preventing sarcopenia, even without a significant increase in muscle mass [48]. Their potential in maintaining bone health and healthy aging is also recognized, although clinical limitations remain [49]. Table 1 summarizes the recommended doses and the results observed according to the cited studies. Table 2 details how omega-3 fatty acids act at the cellular and genetic levels.

Table 1. Summary of dosages and clinical efficacy by pathology

Health Sector	Pathology / condition	Recommended dose	Key result	Ref.
Cardiovascular	High blood pressure	2 g to 3 g/day	Optimal blood pressure reduction (J-curve)	[1, 32]
Cardiovascular	Myocardial infarction (prevention)	0.8 g to 1.2 g/day	Significant reduction in the risk of MACE (Major Adverse Cardiovascular Events)	[2, 21]
Cardiovascular	Heart failure	High dose (>2 g)	Improved ventricular function (>1 year)	[56, 57]
Neurology	Cognitive decline / Alzheimer's disease	0.1 g DHA/day (min)	8-10% reduction in the risk of decline	[7, 9]
Psychiatry	Major depression	Target index > 8%	Microglial modulation and improved blood-brain barrier function	[6, 23]
Metabolism	Obesity / NAFLD (Non-Alcoholic Fatty Liver Disease)	3.6 g/day	Decreased GGT (gamma-glutamyl transpeptidase) and reduced visceral fat	[36, 58]
Ophthalmology	Dry eyes	High dose EPA	Improved tear film (Schirmer test)	[42]
Gynecology	Dysmenorrhea	0.3 g to 1.8 g/day	Notable reduction in menstrual pain	[59]
Pregnancy	Premature birth prevention	0.6 g to 1 g/day	To be started before the 20th week	[60]

Table 2. Molecular Mechanisms of Action

Level of action	Biological mechanism	Physiological effect	Ref.
Genetics	Epigenetic regulation	Suppression of NF-κB pathways (anti-inflammatory)	[11]
Cellular	Resolvin (RvD2) synthesis	Active resolution of inflammation (IBD, colitis)	[10, 12]
Mitochondrial	Respiratory enhancement	Increased cellular energy efficiency	[17]
Membrane	Fluidity and plasticity	Improved synaptic communication	[8]
Microbiota	Bacterial modulation	Increased Akkermansia and intestinal integrity	[11, 38]

7. Sources, sustainability, and technological innovations

The majority of the world's population has insufficient omega-3 status and an unbalanced omega-6/omega-3 ratio, representing a major public health challenge [13, 14, 18, 50]. Microalgae synthesize omega-3s via distinct biosynthetic pathways and constitute the primary source of DHA in marine food chains [30]. Microbial-derived omega-3s thus represent a sustainable and effective alternative to traditional marine sources [29].

Furthermore, technological innovations such as encapsulation, protein-thymol nanocarriers, and the use of natural antioxidants from red algae improve the oxidative stability, bioavailability, and therapeutic efficacy of omega-3-enriched formulations [31, 51, 52]. Table 3 distinguishes the specific characteristics of the different forms of omega-3 available on the market.

Table 3. Comparison of Formulations and Sources

Source / form	Major component	Specific advantages	Limitations	Ref.
Purified EPA	100% EPA	Superior for stabilizing atherosclerotic plaques	Less direct impact on brain structure	[3, 4]
EPA/DHA blend	Variable ratio	Pleiotropic action (heart + brain)	Sometimes mixed results in cardiology	[23]
Flaxseed oil	ALA (Plant)	Antioxidant and osteoprotective properties	Limited conversion to EPA/DHA in humans	[61]
Microalgae	DHA/EPA	Sustainable, fish-free, high purity	Production cost sometimes higher	[29, 30]
Enriched eggs	DHA/ALA	An accessible alternative for non-fish eaters	Lower intake per unit than supplements	[62]

8. Limitations, controversies and perspectives

Despite their numerous benefits, omega-3 fatty acids have not demonstrated clinical efficacy in all indications, particularly in peripheral arterial disease at low doses or certain chronic pain conditions in the elderly [27, 53]. Furthermore, a significant proportion of dietary supplements contain health claims that do not comply with European regulations, impacting consumer confidence [54].

Current data support personalized approaches that integrate baseline omega-3 status, genetic factors, the clinical context, and the formulation used [23, 55]. Standardization of measurement methods, particularly through the omega-3 index, also appears essential [18].

9. Conclusion

Omega-3 fatty acids represent a major multi-target nutritional approach with documented effects on cardiovascular, metabolic, brain, and inflammatory health. However, their clinical efficacy is highly dependent on the dose, formulation, timing of intervention, and individual profile. Faced with the global omega-3 deficit and the challenges of sustainability and quality, integrative, technologically optimized and evidence-based nutritional strategies are essential to fully exploit their therapeutic potential.

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