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Review Article

Omega-3 Fatty Acids: From Natural Sources to Clinical Applications: An Integrative Review

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Abstract

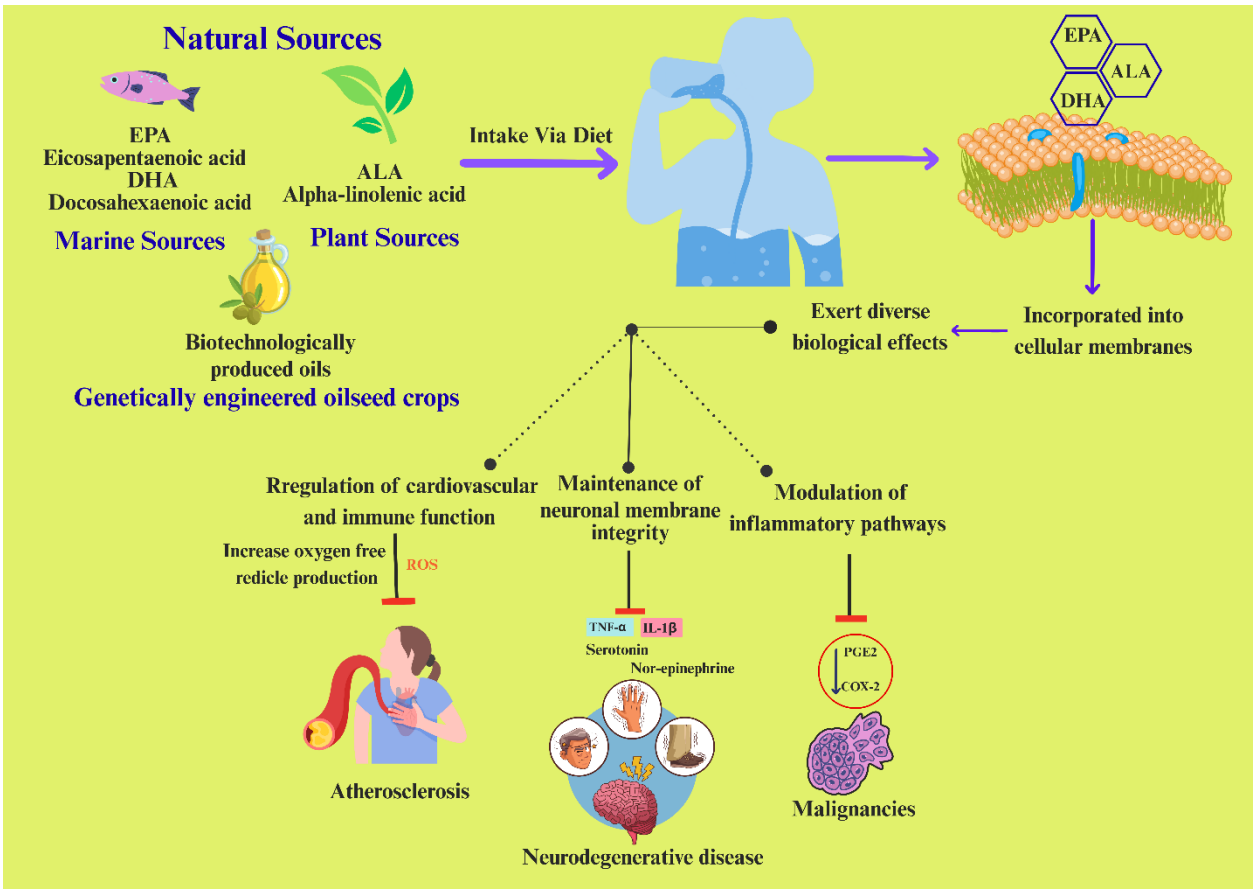
Omega-3 fatty acids, including alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), are essential polyunsaturated fats known for their vital roles in cardiovascular, neurological, and inflammatory health. Growing awareness of their therapeutic benefits, coupled with sustainability concerns, has intensified research into their natural sources, biosynthesis, pharmacokinetics, and clinical applications. This review provides an integrative synthesis of recent advances in omega-3 fatty acid research, encompassing their sources, bioavailability, sustainability, mechanisms of action, and clinical relevance. Plant-based oils, marine fish, krill, and microalgae remain key natural sources, while innovations such as algal oils and genetically engineered crops present sustainable alternatives. The human conversion of ALA to EPA and DHA is inherently limited due to Δ6-desaturase and elongase enzyme constraints, with efficiency affected by genetic, hormonal, and dietary factors. Bioavailability is influenced by molecular form, with triglyceride, ethyl ester, and phospholipid structures displaying varying absorption and metabolic profiles. Mechanistically, omega-3 fatty acids regulate inflammation, maintain neuronal membrane integrity, and improve vascular function, with emerging evidence suggesting potential anti-cancer effects. Collectively, these insights underscore the significant preventive and therapeutic potential of omega-3 fatty acids and highlight the need for optimizing bioavailability, advancing sustainable production, and personalizing clinical applications to support future nutrition and healthcare strategies.

Keywords: Omega-3 fatty acids, Eicosapentaenoic acid, Docosahexaenoic acid , Bioavailability, Sustainable nutrient sources, Clinical nutrition

Highlights:

- ✓ Comparative analysis of plant-derived ALA, marine-based EPA/DHA, and biotechnologically engineered oils, with emphasis on ecological challenges and scalable algal/crop-based alternatives.
- ✓ Limited endogenous conversion of ALA to EPA/DHA and strong genetic, dietary, and physiological influences highlight opportunities for pharmacogenomics-guided dosing strategies.
- ✓ Comprehensive coverage of omega-3 roles in membrane dynamics, signal transduction, epigenetic regulation, inflammation resolution, and metabolic modulation.
- ✓ Strong safety and efficacy profiles support adjunctive use with conventional therapies to enhance treatment outcomes and reduce adverse effects across multiple disease domains.
- ✓ Advances in bioavailability-enhancing formulations and targeted delivery approaches expand therapeutic potential and accessibility.
- ✓ Emerging data on synergistic effects with chemotherapeutic agents to boost anticancer efficacy and reduce treatment-related toxicities.
- ✓ Strategic roadmap linking sustainable production, precision supplementation, and integration into drug discovery, preventive health, and personalized medicine.

Graphical abstract



1. Introduction:

Omega-3 fatty acids are essential polyunsaturated lipids that play a critical role in human physiology, with α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) constituting the most biologically relevant forms .[1] ALA, predominantly derived from plant-based sources such as flaxseed, chia, walnuts, hemp seeds, and selected vegetable oils, serves as the metabolic precursor to EPA and DHA.[2] However, conversion efficiency in humans is inherently low due to rate-limiting steps in the Δ6-desaturase and elongase pathways, underscoring the necessity for direct dietary intake of EPA and DHA .[3]Marine-derived foods, including fatty fish (e.g., salmon, mackerel, sardines), krill oil, and cod liver oil, are rich in preformed EPA and DHA, which are readily incorporated into cellular membranes and exert diverse biological effects.[4] These include modulation of inflammatory pathways, maintenance of neuronal membrane integrity, and regulation of cardiovascular and immune function.[5] Increasing evidence associates optimal omega-3 status with a reduced risk of chronic diseases such as atherosclerosis, neurodegenerative disorders, and certain malignancies. In response to overfishing pressures and environmental degradation, microbial and biotechnological alternatives, particularly microalgae and genetically engineered oilseed crops are emerging as sustainable, contaminant-free omega-3 sources.[6] These innovations, alongside diversification of supply from both terrestrial and marine origins, are critical to meeting global nutritional needs while preserving ecological balance.[7]

This review provides a comprehensive analysis of omega-3 sources, biosynthetic and metabolic pathways, determinants of bioavailability, their pharmacological relevance in health maintenance and disease prevention.

Inclusion Criteria

This review incorporated peer-reviewed original research articles, systematic reviews, and meta-analyses that examined omega-3 fatty acids, specifically α-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid. Eligible studies addressed one or more of the following areas: natural or engineered sources, biosynthetic pathways, bioavailability, sustainable production, molecular mechanisms of action, or clinical and preventive applications. Both human clinical trials and experimental investigations using *in vitro* or *in vivo* models, as well as biotechnology-based production research, were considered. Only publications available in full text, written in English, and presenting clearly defined methodologies with measurable outcomes relevant to the aims of this review were included.

Exclusion Criteria

Studies were excluded, if they did not focus on omega-3 fatty acids or their biological, clinical, or technological dimensions, or if they discussed general dietary fat intake without quantifying or characterizing omega-3 content. Literature that had not undergone peer review, including conference abstracts, editorials, commentaries, and anecdotal accounts, was omitted.

Duplicate publications and preliminary reports that were later replaced by more comprehensive data from the same research group were also excluded. Further, studies lacking adequate methodological description, presenting ambiguous outcome measures, or demonstrating a high risk of bias were removed from consideration. Articles not available in English or without accessible full-text versions were similarly excluded.

2. Biosynthesis and Metabolism:

In humans, the biosynthesis of long-chain omega-3 fatty acids from dietary α-linolenic acid (ALA; 18:3n-3) occurs primarily in the liver, involves a sequence of desaturation and elongation reactions.[8] The process begins with Δ6-desaturase-mediated conversion of ALA to stearidonic acid (SDA; 18:4n-3), followed by elongation to eicosatetraenoic acid (ETA; 20:4n-3) and subsequent Δ5-desaturation to form eicosapentaenoic acid (EPA; 20:5n-3).[9] EPA can then undergo further elongation and desaturation to produce docosapentaenoic acid (DPA; 22:5n-3), which is retro converted to EPA or further metabolized to docosahexaenoic acid (DHA; 22:6n-3) via the Sprecher pathway, involving elongation to 24-carbon intermediates and β-oxidation in peroxisome.[10]This metabolic cascade is intrinsically limited in humans, with conversion efficiency from ALA to EPA estimated at 5-10%, and to DHA often below 1% . Factors influencing this efficiency include genetic polymorphisms in the FADS1 and FADS2 genes encoding fatty acid desaturases, hormonal modulation (notably estrogen, which enhances conversion in females), dietary composition (high n-6 fatty acid intake competitively inhibits enzymatic steps), and overall health status .[11] Once synthesized or ingested, EPA and DHA are esterified into phospholipids, triglycerides, or cholesteryl esters, incorporated into lipoproteins, and transported to tissues . Within cell membranes, they displace arachidonic acid (AA; 20:4n-6), altering the substrate availability for cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, thereby modulating the synthesis of eicosanoids, resolvins, and protectins.[12] These bioactive lipid mediators exert anti-inflammatory, neuroprotective, and cardioprotective effects, linking molecular metabolism directly to clinical outcome.[13]

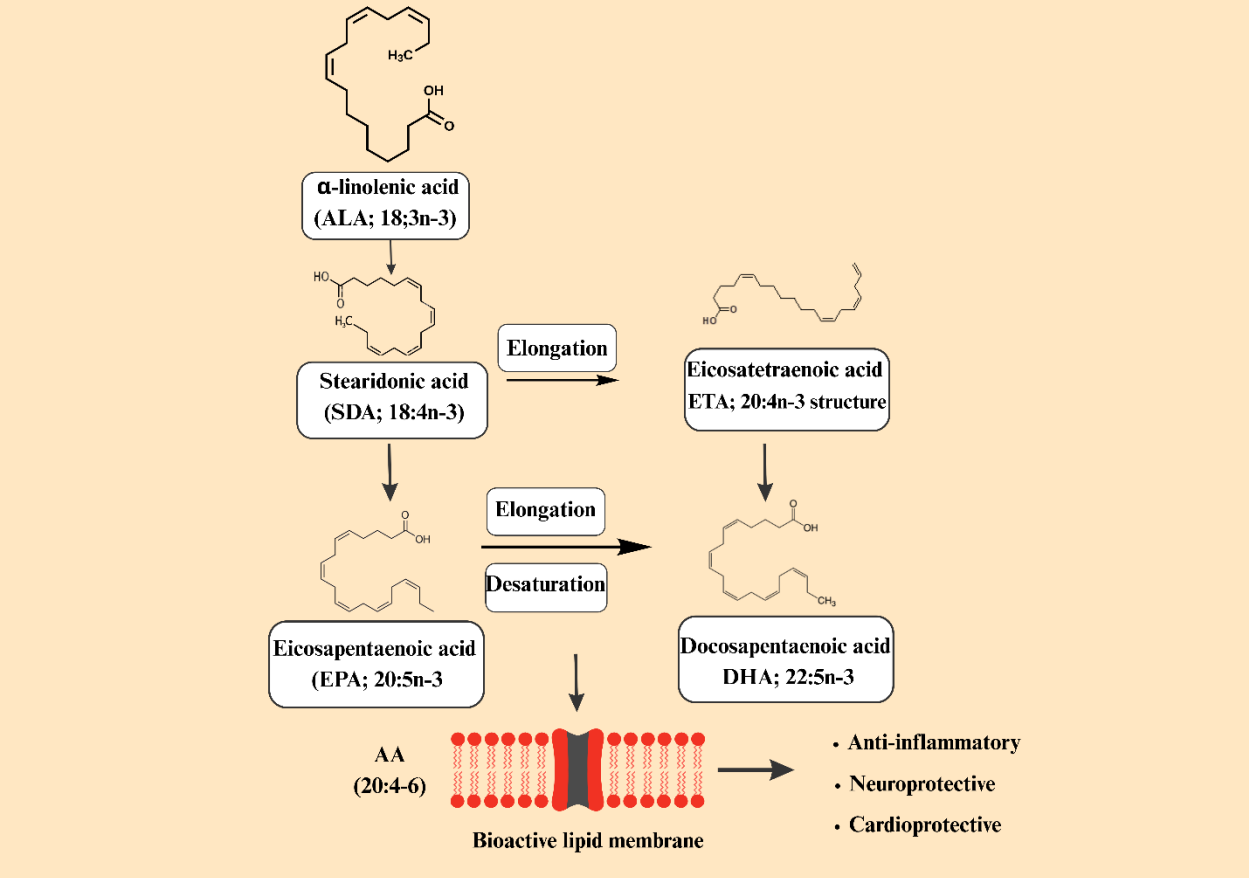


Figure 1: Biosynthesis, metabolism, and physiological roles of long-chain omega-3 fatty acids.

(The schematic illustrates the enzymatic conversion of dietary ALA to EPA and DHA via desaturation, elongation, and the Sprecher pathway.)

Different Sources of Omega-3 Fatty Acids:

3.1. Plant based Omega-3 Fatty Acids:

Plant-based sources of omega-3 fatty acids are primarily rich in ALA, a short-chain omega-3 fatty acid that serves as a precursor to the long-chain fatty acids EPA and DHA, though the conversion in humans is limited. Among the richest sources of ALA are flaxseeds (*Linum usitatissimum*) and their oil, which contain approximately 50-60% ALA by weight.[15] Chia seeds

(*Salvia hispanica*) are another potent source, offering both high ALA content and additional dietary fiber and antioxidants. Walnuts (*Juglans regia*) also contribute a substantial amount of ALA and are commonly included in heart-healthy diets. Other notable sources include hemp seeds, perilla oil, canola oil, and soybeans, which are widely used in vegetarian and vegan diets to meet essential fatty acid requirements.[16] While these plant-based sources are sustainable and suitable for populations avoiding animal products, they do not provide EPA and DHA directly, necessitating either enhanced conversion or supplementation through algal oils. Nonetheless, incorporating ALA-rich foods into the diet has been associated with cardiovascular benefits and anti-inflammatory effects, making them valuable components of plant-based nutritional strategies.[17]

Marine-Based Sources: Fatty fish (salmon, sardines, mackerel)

Fatty fish such as salmon (*Salmo salar*), sardines (*Sardinops spp*.), and mackerel (*Scomber spp*.) are among the richest natural sources of long-chain omega-3 fatty acids, particularly EPA and DHA. These fish accumulate omega-3s through their diet, which includes microalgae and smaller planktonic organisms rich in these essential lipids.[18] Salmon is widely recognized for its high DHA content, which supports brain and eye health, while mackerel and sardines are valued for their high EPA levels, which exhibit potent anti-inflammatory and cardioprotective effects. In addition to their omega-3 content, these fish provide high-quality protein, vitamin D, and selenium, enhancing their nutritional value.[19] Regular consumption of fatty fish has been associated with a reduced risk of coronary heart disease, stroke, and cognitive decline, as evidenced by numerous epidemiological and clinical studies. Moreover, these fish are often recommended in dietary guidelines worldwide due to their superior bioavailability of omega-3s compared to plant-based sources.[20] However, concerns regarding environmental contaminants such as mercury and polychlorinated biphenyls (PCBs) in certain species highlight the need for sustainable sourcing and responsible consumption practices.

Krill oil:

Krill oil, derived from small, shrimp-like marine crustaceans known as Antarctic krill (*Euphausia superba*), is a unique marine source of omega-3 fatty acids, particularly EPA and DHA.[22] Unlike fish oil, where omega-3s are mainly found in the triglyceride form, krill oil delivers a significant portion of EPA and DHA in the phospholipid-bound form, which may enhance intestinal absorption and cellular uptake. This structural advantage has been associated with improved bioavailability and efficacy at lower doses. In addition to omega-3s, krill oil naturally contains astaxanthin, a potent antioxidant that provides oxidative stability and additional health benefits.[23] Emerging clinical and preclinical studies suggest that, krill oil supplementation may help reduce inflammation, improve lipid profiles, and support cardiovascular and joint health. Furthermore, because krill occupy a lower trophic level in the marine food chain, they tend to accumulate fewer environmental toxins such as mercury and heavy metals, making krill oil a relatively clean and sustainable source of omega-3s.[24] However, large-scale harvesting raises ecological concerns, particularly regarding the role of krill as a foundational species in marine ecosystems, necessitating careful regulation and sustainable harvesting practices.

Cod liver oil

Cod liver oil, extracted from the livers of Atlantic cod (*Gadus morhua*), is a traditional and widely used source of omega-3 fatty acids, especially EPA and DHA. Unlike standard fish oils derived from the body tissue of oily fish, cod liver oil is uniquely rich not only in omega-3s but also in fat-soluble vitamins A and D, which contribute to its historical use in preventing rickets and supporting immune function.[25] The presence of these vitamins alongside EPA and DHA enhances its appeal as a multifunctional nutritional supplement. EPA and DHA in cod liver oil contribute to cardiovascular protection, cognitive support, and anti-inflammatory effects, similar to other marine-based sources.[26] However, because it is sourced from the liver, cod liver oil can contain higher levels of environmental toxins and fat-soluble vitamins, making dosage control critical to avoid hypervitaminosis A or D. Despite these concerns, cod liver oil remains a cost-effective and accessible source of omega-3s, particularly in regions with limited access to fresh fatty fish. Its long-standing use and clinical relevance underscore its continued importance in nutritional science and public health.

3.2.4. Microbial and Biotechnological Sources

In recent years, microbial and biotechnological sources of omega-3 fatty acids have gained significant attention as sustainable and scalable alternatives to traditional marine sources. Certain microorganisms, particularly marine microalgae such as *Schizochytrium* and *Crypthecodiniumcohnii*, naturally produce high levels of DHA and are commercially cultivated for omega-3-rich oil production. These algal oils are especially valuable for vegan and vegetarian consumers, as they provide long-chain omega-3s (DHA and sometimes EPA) without relying on animal-derived inputs.[27] In addition to algae, some fungi (e.g., *Mortierellaalpina*) and genetically engineered microorganisms have been developed to biosynthesize omega-3s through fermentation technologies, offering controlled, contaminant-free production.

3.2.5. Genetically Engineered Microorganisms for Omega-3 Biosynthesis via Fermentation Technologies

Advances in synthetic biology and metabolic engineering have enabled the development of genetically engineered microorganisms (GEMs) capable of de novo biosynthesis of long-chain omega-3 polyunsaturated fatty acids (LC-PUFAs) such as EPA and DHA through controlled fermentation processes.[28] Native microbial hosts, typically *Schizochytrium*, *Aurantiochytrium*, or certain diatoms, naturally produce DHA-rich oils via the polyketide synthase-like (PKS) pathway, whereas heterotrophic yeasts (*Yarrowia*

lipolytica), filamentous fungi (*Mortierellaalpina*), and bacterial chassis (*Escherichia coli*, *Corynebacterium glutamicum*) have been engineered to incorporate both the conventional fatty acid desaturation/elongation (FAD/ELO) pathway and the PKS pathway for scalable omega-3 production.[29] At the molecular level, biosynthesis in engineered hosts often begins with the introduction and overexpression of key desaturase and elongase genes, such as Δ6-desaturase, Δ5-desaturase, Δ4-desaturase, Δ12-desaturase, Δ15-desaturase, and C20/22 elongases, sourced from marine microalgae or fungi(Nachtschatt et.al., 2020). The FAD/ELO pathway converts endogenous oleic acid (18:1n-9) or linoleic acid (18:2n-6) into α-linolenic acid (ALA; 18:3n-3), which is sequentially elongated and desaturated to EPA and DHA via the intermediate steps stearidonic acid (SDA; 18:4n-3), eicosatetraenoic acid (ETA; 20:4n-3), and docosapentaenoic acid (DPA; 22:5n-3).[30] In parallel, the PKS pathway operates via multi-domain enzyme complexes comprising ketoacyl synthase (KS), acyl transferase (AT), ketoacyl reductase (KR), dehydratase (DH), and enoyl reductase (ER), that iteratively assemble LC-PUFA chains from malonyl-CoA units without reliance on desaturases. Optimization strategies include codon optimization of heterologous genes, promoter engineering for high transcriptional flux, and CRISPR/Cas-mediated knockout of competitive lipid biosynthetic pathways. Fermentation parameters, such as dissolved oxygen, carbon source feed (e.g., glucose, glycerol), and nitrogen limitation, are tuned to shift metabolic flux toward triacylglycerol (TAG) accumulation enriched with EPA and DHA.[31] In downstream processing, cell disruption is followed by solvent extraction or supercritical CO_2 extraction to yield high-purity omega-3 oils.

Figure 2: Different sources of omega-3 fatty acids: plant-based, marine-based, and microbial/biotechnological-based

4. Comparative Analysis: Omega-3 Fatty acid composition across natural sources:

Omega-3 fatty acids occur in diverse molecular forms across plant, marine, and microbial origins, with characteristic fatty acid profiles that critically influence their nutritional value, bioavailability, and pharmacological potential. Short-chain omega-3s, such as ALA, predominate in plant oils, whereas marine and microbial sources are enriched in LC-PUFAs such as EPA and DHA. These compositional differences underpin their differential physiological effects, directly mediating anti-inflammatory, cardioprotective, and neuroprotective pathways, while ALA must undergo metabolic conversion, an inherently inefficient process in humans.[32]

Table 1. Summary of fatty acid composition of major omega-3 sources and their nutritional implications.

Source Type	Representative Examples	Predominant Omega-3 Form(s)	Typical Composition (% total fatty acids)	Molecular Form	Nutritional/Pharmacological Notes	Ref.
Plant-based oils	Flaxseed, chia seed, perilla seed	ALA (18:3n-3)	ALA: 40-60%; EPA: <1%; DHA: <1%	Triglycerides	High ALA content; supports general omega-3 intake but requires conversion to EPA/DHA for clinical effects.	33
Marine fish oils	Salmon, sardines, mackerel	EPA (20:5n-3), DHA (22:6n-3)	EPA: 15-30%; DHA: 10-20%; ALA: trace	Triglycerides	Direct source of LC-PUFAs; widely studied for cardiovascular and anti-inflammatory benefits.	34
Krill oil	Antarctic krill (*Euphausia superba*)	EPA, DHA	EPA: 20-25%; DHA: 10-15%; ALA: trace	Phospholipids + Triglycerides	Phospholipid-bound EPA/DHA may enhance intestinal absorption and tissue incorporation.	35
Cod liver oil	Atlantic cod (*Gadus morhua*)	EPA, DHA	EPA: 8-12%; DHA: 7-12%; ALA: trace	Triglycerides	Also rich in vitamins A and D; traditional source of omega-3s.	36
Microalgal oils	*Schizochytrium* sp., *Crypthecodiniumcohnii*	DHA (22:6n-3)	DHA: 35-50%; EPA: <5%	Triglycerides	Sustainable, contaminant-free source; widely used in vegan supplements and infant formula.	37
Microalgal oils	*Nannochloropsis* sp.	EPA (20:5n-3)	EPA: 20-30%; DHA: <5%	Triglycerides	Suitable for plant-based EPA supplementation; emerging nutraceutical source.	38
Genetically engineered microorganisms	Engineered *Yarrowialipolytica*, *Mortierellaalpina*	EPA, DHA	EPA and/or DHA profiles tailored via genetic engineering; up to 60% combined LC-PUFAs	Triglycerides	Fermentation-based sustainable production; customizable fatty acid ratios for specific health application	39

5. Sustainability and Environmental Considerations in Pharmacologically Relevant Omega-3 Sources:

The pharmacological utility of omega-3 fatty acids, particularly EPA and DHA, necessitates a stable, contaminant-free, and environmentally sustainable supply chain. Marine-derived sources, including wild-caught fatty fish (*Salmo salar*, *Scomberscombrus*, *Sardinopssagax*), remain the predominant input for pharmaceutical-grade omega-3 formulations but are constrained by ecological pressures such as overfishing, habitat degradation, and bycatch-induced biodiversity loss. While intensive aquaculture reduces direct pressure on wild stocks, it often introduces ancillary concerns, including eutrophication, pathogen proliferation, and continued dependence on wild-caught fishmeal and fish oil.[40] Krill (*Euphausia superba*) oil, valued for its phospholipid-bound EPA and DHA with superior bioavailability, is subject to strict harvesting quotas; however, its removal from the food web may disrupt trophic dynamics critical to marine ecosystem stability. Cod liver oil production is inherently tied to cod (*Gadus morhua*) fisheries, sharing similar overexploitation risks. In contrast, plant-derived α-linolenic acid (ALA) from flaxseed, chia, and walnuts offers a lower ecological footprint but requires metabolic conversion to pharmacologically active LC-PUFAs, limiting its direct therapeutic equivalence. Microbial fermentation technologies using heterotrophic microalgae (e.g., *Schizochytrium*, *Crypthecodinium*) or genetically engineered microorganisms (*Yarrowialipolytica*, *Mortierellaalpina*) provide scalable, high-purity EPA and/or DHA production. These systems bypass marine trophic

chains, reduce bio-accumulated contaminant risk, and enable tailored fatty acid profiles for specific clinical applications, such as cardiovascular disease modulation, anti-inflammatory therapy, and neuroprotection.[41] Given their low land and water use, minimal greenhouse gas emissions, and potential for pharmaceutical-grade standardization, microbial and biotechnological production platforms represent a strategically critical approach to ensuring both therapeutic efficacy and long-term environmental stewardship.

6. Bioavailability of Omega-3 Fatty Acids: Pharmacological and Molecular Mechanistic Considerations

The bioavailability of omega-3 polyunsaturated fatty acids (PUFAs) is determined not only by their dietary source but also by their molecular form, which governs digestion, intestinal uptake, and incorporation into target tissues. In marine-derived triglyceride-bound forms, pancreatic lipase and co-lipase hydrolyze ester bonds to release free fatty acids and mono-acylglycerols, which are subsequently re-esterified within enterocytes and packaged into chylomicrons for lymphatic transport.[42] Ethyl ester forms, common in concentrated pharmaceutical formulations, require additional hydrolysis by carboxyl ester lipase, resulting in comparatively slower and sometimes less complete absorption. Krill oil, enriched in phospholipid-bound EPA and DHA, undergoes digestion via phospholipase A_2, producing lyso-phospholipids and free fatty acids that exhibit high membrane affinity and efficient incorporation into lipoproteins and cellular phospholipid bi-layers. This mechanistic advantage may underlie the observed enhancement in tissue enrichment relative to triglyceride or ethyl ester forms. Plant-derived ALA is absorbed efficiently as triglycerides but must undergo sequential Δ6-desaturation, elongation, and Δ5-desaturation to yield EPA, and subsequently DHA via the peroxisomal β-oxidation-dependent Sprecher pathway. The low catalytic efficiency of these enzymes in humans, combined with competitive inhibition from dietary omega-6 fatty acids, severely limits pharmacologically relevant conversion rat. [43] Microbial and algal oils typically provide EPA and DHA as triglycerides or free fatty acids, exhibiting digestion and absorption kinetics comparable to fish oils, but without the risk of heavy metal or persistent organic pollutant contamination. The presence of dietary emulsifiers, bile salt concentrations, and co-ingestion of dietary fat further modulate micellar solubilization and enterocyte uptake, directly impacting therapeutic plasma levels. For the easy understanding and reader interpretability, we have tried to summarize the content in a tabular form below.[44]

Table 2. Bioavailability and pharmacological considerations of omega-3 fatty acids by source and chemical form.

Source Type	Predominant Omega-3 Form(s)	Molecular Form	Primary Digestive Enzyme(s)	Relative Absorption Efficiency	Pharmacological Notes	Ref.
Marine fish oils (salmon, sardines)	EPA, DHA	Triglycerides	Pancreatic lipase, co-lipase	High	Directly supplies LC-PUFAs for anti-inflammatory, cardioprotective, and neuroprotective effects.	45
Concentrated fish oil supplements	EPA, DHA	Ethyl esters	Carboxyl ester lipase	Moderate–variable	Requires additional hydrolysis; may benefit from co-ingestion with high-fat meals to optimize plasma levels.	46
Krill oil (*Euphausia superba*)	EPA, DHA	Phospholipids	Phospholipase A_2	High–very high	Enhanced membrane incorporation and lipoprotein transport; potential for superior tissue enrichment.	47
Plant-based oils (flaxseed, chia, walnuts)	ALA	Triglycerides	Pancreatic lipase	High (ALA absorption) but low EPA/DHA yield	Limited pharmacological potency due to inefficient Δ6-desaturase and elongase-mediated conversion.	48
Microalgal oils (*Schizochytrium*, *Nannochloropsis*)	DHA or EPA	Triglycerides / Free fatty acids	Pancreatic lipase / direct uptake	High	Sustainable, contaminant-free; suitable for pharmaceutical-grade EPA/DHA formulations.	49
Genetically	EPA, DHA	Triglycerides	Pancreatic	High	Allows tailoring of	50

engineered microorganisms (*Y. lipolytica*, *M. alpina*)			lipase		EPA/DHA ratios for targeted clinical effects (e.g., anti-inflammatory vs. neuroprotective).	

7. Biosynthesis and Metabolism of Omega-3 Fatty Acids

7.1. ALA conversion to EPA and DHA in humans

In humans, alpha-linolenic acid (ALA), an 18-carbon omega-3 fatty acid obtained mainly from plant sources, undergoes a series of enzymatic elongation and desaturation steps to be converted into the long-chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are biologically more active. This conversion begins with the action of Δ6-desaturase, an enzyme that introduces a double bond at the sixth carbon from the carboxyl end of ALA, converting it into stearidonic acid (18:4 n-3).[51] Next, elongase enzymes extend the carbon chain by two carbons, forming eicosatetraenoic acid (20:4 n-3). Subsequently, Δ5-desaturase catalyzes the formation of EPA (20:5 n-3) by introducing another double bond. EPA can then be further elongated and desaturated, ultimately undergoing a complex retro-conversion pathway involving peroxisomal β-oxidation to produce DHA (22:6 n-3). However, this conversion pathway is relatively inefficient in humans, with typical conversion rates reported to be less than 10% for EPA and even lower for DHA, due to competition with omega-6 fatty acids for shared enzymes and individual genetic variations in desaturase activity. Consequently, direct dietary intake of EPA and DHA from marine or microbial sources is often necessary to achieve optimal tissue levels and associated health benefits.[52]

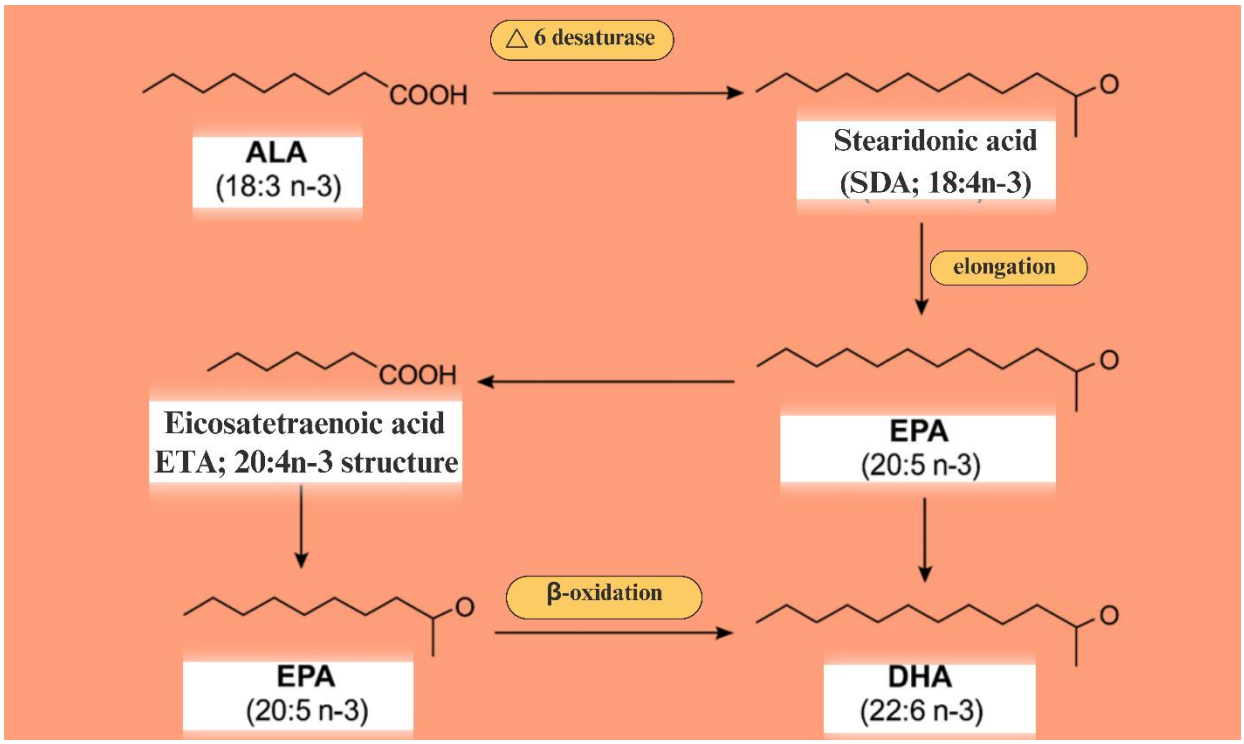


Figure 3: Metabolic conversion pathway of α-linolenic acid (ALA) to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in humans.

7.2. Factors affecting conversion efficiency

The efficiency of converting ALA to its longer-chain metabolites, EPA and DHA, in humans is influenced by multiple physiological, nutritional, and molecular factors. Key enzymes involved in this conversion pathway, such as Δ6-desaturase and Δ5-desaturase, compete with omega-6 fatty acid substrates, particularly LA, for binding and activity, which can significantly reduce omega-3 fatty acid synthesis when omega-6 intake is high. Genetic polymorphisms in genes encoding these desaturases (e.g., FADS1 and FADS2) also modulate enzyme expression and activity, causing interindividual variability in conversion rates. Nutritional status, including adequate levels of cofactors like zinc, magnesium, and vitamins B6 and C, is essential for optimal enzymatic function.[53] Hormonal influences, such as elevated estrogen levels, have been shown to enhance desaturase activity, partly explaining sex differences in conversion efficiency. Additionally, aging and certain metabolic conditions may impair enzyme efficiency, reducing EPA and DHA synthesis. These factors collectively determine the molecular efficiency of ALA metabolism, often limiting endogenous production of EPA and DHA and underscoring the need for direct dietary sources of these critical long-chain omega-3 fatty acids.[54]

7.3. Enzymatic pathways and gene regulation

The biosynthesis of long-chain omega-3 fatty acids, such as EPA and DHA, from ALA in humans involves a complex series of enzymatic reactions governed by tightly regulated gene expression. Key enzymes include Δ6-desaturase and Δ5-desaturase, encoded by the FADS2 and FADS1 genes, respectively, which catalyze critical desaturation steps introducing double bonds into the fatty acid chain.[55] These desaturases work sequentially with elongase enzymes (encoded by ELOVL family genes) that add carbon units to elongate the fatty acid chain. The expression of these genes is influenced by various factors, including dietary fatty acid composition, hormonal signals, and cellular lipid status, through transcriptional regulators such as sterol regulatory element-binding proteins (SREBPs) and peroxisome proliferator-activated receptors (PPARs). For instance, diets high in omega-3 fatty acids can up-regulate desaturase and elongase gene expression to facilitate fatty acid metabolism. Conversely, excess omega-6 fatty acids may competitively inhibit these pathways. Furthermore, genetic polymorphisms in FADS and ELOVL genes can lead to variability in enzyme activity and efficiency of omega-3 fatty acid biosynthesis among individuals and populations. Understanding the enzymatic pathways and regulatory networks is essential for developing targeted nutritional and therapeutic strategies to optimize omega-3 status and associated health outcomes.[56] The biosynthesis of long-chain omega-3 fatty acids, such as EPA and DHA, from ALA in humans involves a complex series of enzymatic reactions governed by tightly regulated gene expression. Key enzymes include Δ6-desaturase and Δ5-desaturase, encoded by the FADS2 and FADS1 genes, respectively, which catalyze critical desaturation steps introducing double bonds into the fatty acid chain. These desaturases work sequentially with elongase enzymes (encoded by ELOVL family genes) that add carbon units to elongate the fatty acid chain. The expression of these genes is influenced by various factors, including dietary fatty acid composition, hormonal signals, and cellular lipid status, through transcriptional regulators such as sterol regulatory element-binding proteins (SREBPs) and peroxisome proliferator-activated receptors (PPARs).[57] For instance, diets high in omega-3 fatty acids can up-regulate desaturase and elongase gene expression to facilitate fatty acid metabolism. Conversely, excess omega-6 fatty acids may competitively inhibit these pathways. Furthermore, genetic polymorphisms in FADS and ELOVL genes can lead to variability in enzyme activity and efficiency of omega-3 fatty acid biosynthesis among individuals and populations. Understanding the enzymatic pathways and regulatory networks is essential for developing targeted nutritional and therapeutic strategies to optimize omega-3 status and associated health outcomes.[58]

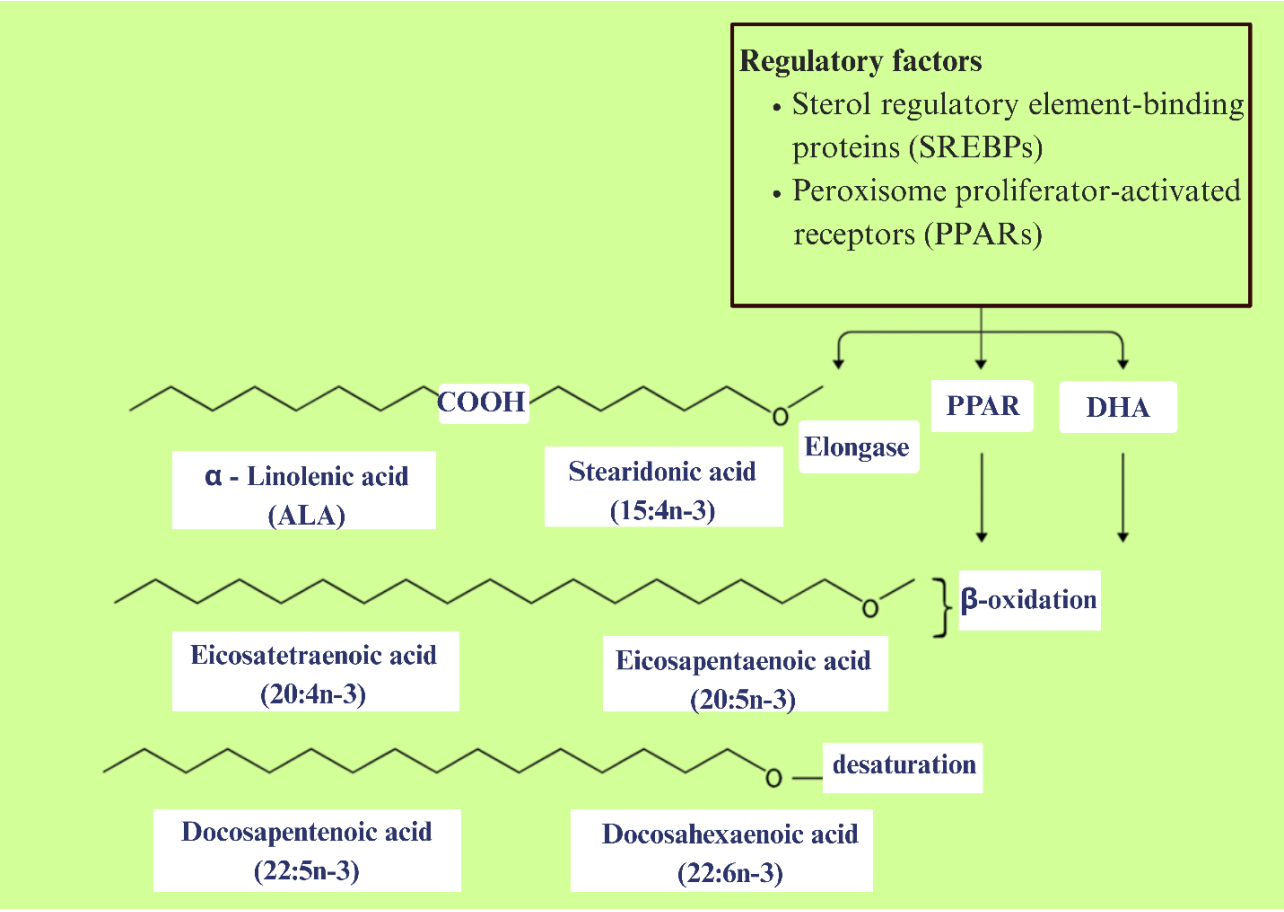


Figure 4: Enzymatic and genetic regulation of long-chain omega-3 fatty acid biosynthesis from α-linolenic acid (ALA) in humans.

7.4. Gender, age, and dietary influences

The metabolism and conversion efficiency of omega-3 fatty acids, particularly the transformation of ALA to EPA and DHA, are significantly influenced by gender, age, and dietary factors. Research indicates that women generally exhibit higher conversion rates of ALA to EPA and DHA than men, likely due to the modulatory effects of estrogen on the activity of key enzymes such as Δ6-desaturase.[59] This hormonal influence may serve an evolutionary purpose to support fetal and infant development during pregnancy and lactation. Age-related declines in enzymatic activity have also been observed, with older adults often showing reduced capacity to synthesize long-chain omega-3s, which may contribute to increased susceptibility to inflammatory and neurodegenerative disease. Nutrient deficiencies (e.g., zinc, magnesium, vitamins B6 and C) and overall diet quality impact enzymatic function and omega-3 bioavailability. These factors collectively highlight the need for personalized dietary strategies, particularly for populations with limited direct intake of preformed EPA and DHA, to ensure adequate omega-3 status for optimal health.[60]

8. Pharmacokinetics of omega-3 fatty acids from different natural sources

The pharmacokinetics of omega-3 fatty acids varies by natural source, chemical form, and molecular carrier, influencing absorption, distribution, metabolism, and excretion (ADME) profiles. Triglyceride-bound EPA/DHA from fish oils undergo pancreatic lipase-mediated hydrolysis to free fatty acids and monoglycerides, followed by micellar solubilization with bile salts for intestinal absorption via passive diffusion and FATP/CD36-mediated transport. Ethyl ester forms require carboxylesterase-mediated hydrolysis, often exhibiting slower and less efficient uptake.[61] Phospholipid-bound omega-3s in krill oil incorporate into mixed micelles more readily, enhancing membrane incorporation. Plant-derived ALA follows similar intestinal uptake but undergoes limited hepatic elongation/desaturation to EPA/DHA. Algal and microbial oils, often in triglyceride or free fatty acid forms, display bioavailability comparable to fish oil, with reduced contaminant burden. Post-absorption, omega-3s integrate into plasma lipoproteins, are transported to tissues, and incorporated into phospholipid membranes, modulating eicosanoid and specialized pro-resolving mediator synthesis.[62]

8.1. Absorption and transport mechanisms of omega-3 fatty acids from different natural sources based on first-order kinetics

The intestinal absorption of omega-3 fatty acids follows first-order kinetics, where the rate of uptake (dC/dt) = ka × Cg, with *ka* representing the absorption rate constant and *Cg* the luminal concentration. Hydrolysis rates vary by chemical form: pancreatic lipase-mediated cleavage of triglycerides (Vmax ≈ 2-3 μmol·min^{-1}·mg^{-1} protein) is typically faster than phospholipase A_2-mediated hydrolysis of phospholipids, while ethyl ester hydrolysis by carboxylesterases is rate-limiting (lower *ka* values). Micellar solubilization efficiency (Sm) is proportional to bile salt concentration and inversely related to critical micelle concentration (CMC).[63] Transport into enterocytes occurs via a mixed model of passive diffusion and saturable carrier-mediated uptake (Michaelis-Menten, V = Vmax × [S] / (Km + [S])) involving CD36 and FATP4. Post-absorption, re-esterified omega-3s are packaged into chylomicrons, entering the lymphatic system with a lag phase (~0.5-1 h) before systemic circulation. Plasma pharmacokinetics display biphasic distribution: an initial distribution half-life (t½α ≈ 0.5–2 h) representing tissue uptake, and an elimination half-life (t½β) of ~2-3 days for EPA and ~4-6 days for DHA, reflecting membrane incorporation and slow turnover. Plant-derived ALA shares similar ka but undergoes hepatic elongation/desaturation with low conversion efficiencies (EPA: 5-10%, DHA: <1%), imposing a metabolic bottleneck.[64]

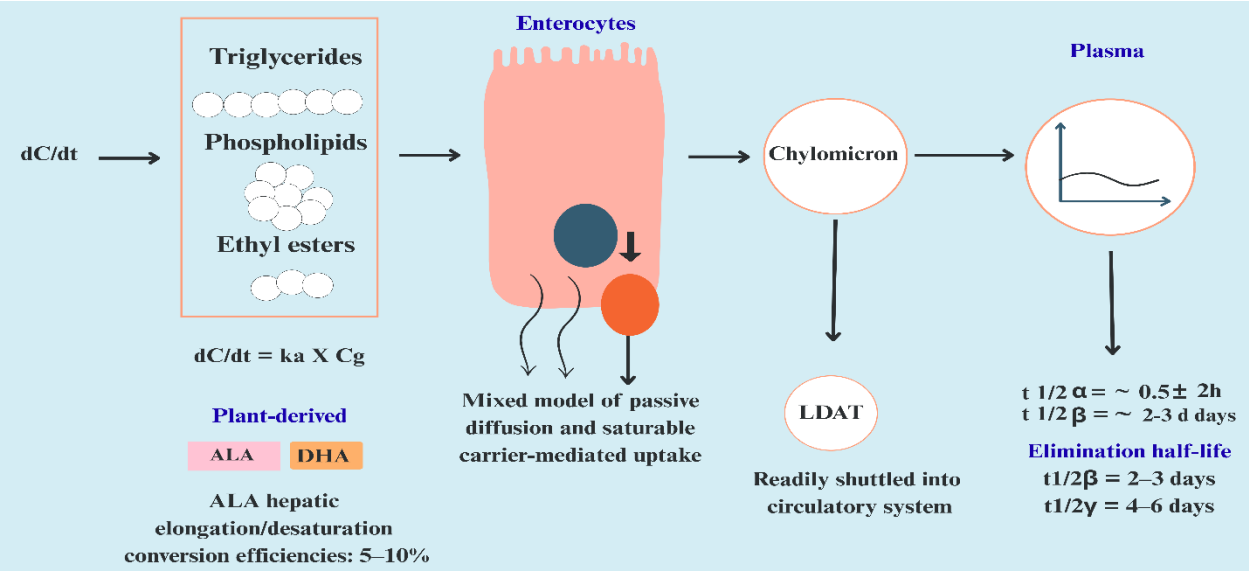


Figure 5: Pharmacokinetic and mechanistic basis of Omega-3 Fatty acid absorption, transport, and distribution Influence of dietary factors and formulations

8.2. Influence of Dietary factors and Formulations:

The absorption and bioavailability of omega-3 fatty acids are significantly influenced by dietary factors and the specific formulations of omega-3 supplements. The presence of dietary fats enhances the emulsification process and stimulates bile secretion, which improves the formation of mixed micelles necessary for efficient intestinal absorption of omega-3s. Consequently, omega-3 supplements taken with a high-fat meal typically demonstrate greater bioavailability compared to those consumed on an empty stomach or with low-fat meals.[65] Additionally, the chemical form of omega-3 fatty acids plays a crucial role; triglyceride-bound omega-3s generally exhibit higher absorption rates than ethyl esters, which require additional enzymatic hydrolysis before uptake. Phospholipid-bound omega-3s, as found in krill oil, may offer superior bioavailability due to enhanced incorporation into cell membranes. Novel delivery systems, such as emulsions, microencapsulation, and liposomal formulations, are being developed to further improve stability, solubility, and targeted release, thereby enhancing absorption efficiency. Furthermore, individual differences, including age, digestive health, and concurrent intake of other nutrients (e.g., antioxidants), can modulate the effectiveness of omega-3 absorption and metabolism. Optimizing dietary conditions and formulation strategies is therefore essential to maximize the therapeutic potential of omega-3 fatty acids.[66]

Table 3: Comparison between ethyl esters, triglycerides, and phospholipid forms

Form	Description	Example Sources	Absorption Mechanism	Notes	Ref.
Ethyl Esters (EE)	Omega-3 fatty acids chemically bound to ethanol molecules; synthetic form often in supplements	Many concentrated fish oil supplements (e.g., Lovaza)	Requires pancreatic lipase and carboxylesterase enzymes to hydrolyze EE into free fatty acids and ethanol before absorption	Lower bioavailability compared to triglycerides; absorption improved when taken with fatty meals	67
Triglycerides (TG)	Natural form where omega-3 fatty acids are esterified to glycerol backbone	Natural fish oils (salmon, mackerel), algal oils	Hydrolyzed by pancreatic lipase into free fatty acids and monoacylglycerols; incorporated into micelles for efficient absorption	Generally higher bioavailability than EE; common in dietary sources	68
Phospholipids (PL)	Omega-3 fatty acids esterified to a glycerol backbone with a phosphate group; major lipid in cell membranes	Krill oil, some microalgal oils	Absorbed both as intact phospholipids and free fatty acids; facilitates direct incorporation into cell membranes	Often exhibits superior bioavailability; enhanced brain and tissue uptake due to membrane affinity	69

9. Pharmacological and Therapeutic Significance of Omega-3 fatty acids

Omega-3 PUFAs, particularly EPA, DHA and ALA, are essential bioactive lipids derived from diverse natural sources and are vital for human health due to the inability to synthesize them de novo. Their pharmacological effects arise from multiple molecular mechanisms: incorporation into phospholipid bilayers to modulate membrane fluidity and receptor conformation; competitive inhibition of arachidonic acid metabolism via COX and LOX pathways, shifting eicosanoid synthesis toward less pro-inflammatory mediators; generation of specialized pro-resolving mediators (SPMs) such as resolvins, protectins, and maresins that actively terminate inflammation; regulation of gene expression through modulation of transcription factors like peroxisome proliferator-activated receptors (PPARs) and nuclear factor-κB (NF-κB); and DHA-specific roles in neuroprotection, synaptogenesis, and brain-derived neurotrophic factor (BDNF) signaling.[70] These mechanisms collectively underpin a wide range of therapeutic effects including cardioprotection through anti-arrhythmic, triglyceride-lowering, and endothelial-enhancing actions; reduction of chronic inflammation in conditions like rheumatoid arthritis, inflammatory bowel disease, and psoriasis; neuroprotection and mood regulation in cognitive decline and depression; and improved metabolic health through enhanced insulin sensitivity and lipid profile modulation, making omega-3 PUFAs a dietary cornerstone for the prevention and management of cardiovascular, inflammatory, and neuropsychiatric disorders.[71]

9.1 Cardiovascular Protection of Omega-3 fatty acids (Molecular mechanism)

Omega-3 fatty acids, especially, EPA and DHA exhibit profound cardioprotective properties mediated through multifaceted molecular pathways. Long-chain omega-3s

exert anti-inflammatory and anti-thrombotic effects via competitive inhibition of arachidonic acid metabolism through COX and LOX enzymes, attenuating the synthesis of pro-inflammatory eicosanoids such as prostaglandin E2 and leukotriene B4, while promoting the biosynthesis of SPMs including resolvins, protectins, and maresins, which orchestrate the resolution phase of inflammation by suppressing neutrophil infiltration, enhancing macrophage efferocytosis, and restoring vascular homeostasis.[72] At the transcriptional level, EPA and DHA modulate NF-κB signaling to down regulate pro-inflammatory cytokine expression (TNF-α, IL-6) and activate PPARα/γ, thereby augmenting fatty acid β-oxidation, inhibiting hepatic very-low-density lipoprotein (VLDL) synthesis, and suppressing de novo lipogenesis, collectively leading to substantial triglyceride reduction and improved lipid profiles. Furthermore, their incorporation into cardiomyocyte membrane phospholipids alters membrane microdomain organization and ion channel kinetics, particularly voltage-gated sodium and L-type calcium channels, resulting in enhanced electrical stability, reduced excitability, and anti-arrhythmic effects that mitigate the risk of sudden cardiac death.[73] While ALA confers modest cardiovascular benefits, its efficacy is constrained by the limited enzymatic conversion to EPA and DHA in human. Bioavailability, molecular form (e.g., triglyceride-bound vs. phospholipid-bound), and source-specific composition critically influence the magnitude of these effects, underscoring the therapeutic priority of bio-available long-chain omega-3s in dietary and pharmacological strategies for the prevention and management of atherosclerosis, arrhythmias, and inflammatory cardiovascular pathologies.

Table 4: Clinical trial evidence of omega-3 fatty acids

Source	Clinical Trial Name/ID	Design & Population	Dosage/Form	Key Outcomes	Trial No.	Ref.
Fish Oil (EPA/DHA)	REDUCE-IT	RCT, high-risk CVD patients	4 g/day EPA ethyl esters	25% reduction in major cardiovascular events	NCT01492361	[74]
Fish Oil (EPA/DHA)	GISSI-Prevenzione	RCT, post-MI patients	1 g/day EPA+DHA triglycerides	Reduced mortality and sudden cardiac death	NCT00140913	[75]
Krill Oil	Krill Oil in Hyperlipidemia	RCT, adults with elevated lipids	1 g/day phospholipid-bound omega-3	Significant reduction in triglycerides and LDL cholesterol	NCT01449718	[76]
Cod Liver Oil	Cardiovascular Benefits Study	RCT, general population	1 g/day EPA+DHA triglycerides	Modest improvement in lipid profile and inflammatory markers	NCT00722715	[77]
Algal Oil	DHA in Pregnancy (DOMInO)	RCT, pregnant women	800 mg/day DHA triglycerides	Improved infant neurodevelopment and reduced preterm birth	NCT00397105	[78]
Algal Oil	Algal DHA Supplementation Study	RCT, healthy adults	1 g/day DHA triglycerides	Increased plasma DHA and improved cognitive function	NCT01400317	[79]
Plant-Based (ALA)	Alpha Omega Trial	RCT, post-MI patients	2 g/day ALA	No significant effect on major cardiovascular events	NCT00127490	[80]

9.2. Neurological and Cognitive Health

PUFAs, particularly, DHA and EPA are indispensable for neurodevelopment, cognitive integrity, and neurological resilience across the lifespan. DHA, a principal structural phospholipid in neuronal membranes, modulates bi-layer fluidity, synaptic vesicle fusion, and receptor topology, thereby optimizing synaptic plasticity, neurotransmission, and neurocircuitry stability. Preformed DHA and EPA from marine-derived sources, fish oil, algal oil, and phospholipid-rich krill oil, exhibit superior cerebral bioavailability, integrating directly into developing neuronal membranes to promote synaptogenesis, neurogenesis, and myelination, particularly during prenatal and early postnatal periods, where maternal DHA intake correlates with enhanced

visual acuity, cognitive performance, and behavioral outcomes.[81] Mechanistically, DHA and EPA competitively inhibit arachidonic acid metabolism via COX and LOX pathways, shifting oxylipin biosynthesis toward specialized pro-resolving mediators (SPMs) such as resolvins, maresins, and neuroprotectin D1, which suppress microglial over activation, facilitate efferocytic clearance of neurotoxic aggregates, and preserve synaptic architecture. These fatty acids attenuate oxidative stress through activation of nuclear factor erythroid 2-related factor 2 (Nrf2), up-regulating endogenous antioxidant enzymes, while modulating neurotrophic pathways by enhancing BDNF expression to sustain neuronal survival and plasticity. Additionally, they regulate transcriptional networks via activation of PPARs and inhibition of NF-κB, thereby down regulating pro-inflammatory cytokines (TNF-α, IL-6) implicated in Alzheimer's disease (AD) and major depressive disorder (MDD). EPA exhibits distinct antidepressant potential through modulation of serotonergic and dopaminergic neurotransmission and reduction of systemic inflammation. Although ALA contributes to overall omega-3 intake, its limited conversion to DHA and EPA underscores the clinical priority of direct long-chain omega-3 intake for optimizing neurodevelopment, mitigating AD pathology, and alleviating mood disorders.[82]

9.3. Cancer Prevention and Therapy:

PUFAs exhibit potent chemo preventive and adjunctive therapeutic effects in malignancies including breast, colorectal, prostate, and pancreatic cancers through multifaceted molecular mechanisms. Upon incorporation into cellular phospholipid bi-layers, EPA and DHA disrupt lipid raft micro domains, thereby altering the spatial organization of membrane-bound receptors and downstream signaling cascades such as PI3K/Akt, MAPK/ERK, and Wnt/β-catenin, resulting in attenuation of proliferative and survival pathways.[83] These fatty acids modulate the tumor microenvironment by competitively inhibiting arachidonic acid metabolism via COX-2 and LOX enzymes, reducing pro-tumorigenic eicosanoids while promoting SPMs such as resolvins and protectins, which suppress chronic inflammation, angiogenesis, and metastatic potential. At the transcriptional level, omega-3s inhibit oncogenic regulators including NF-κB and signal transducer and activator of transcription 3 (STAT3), thereby downregulating inflammatory cytokines (TNF-α, IL-6), cyclin D1, and MYC, while up-regulating tumor suppressor genes and pro-apoptotic proteins such as Bax, caspase-3, and caspase-9, inducing cell cycle arrest and programmed cell death. Furthermore, EPA and DHA sensitize malignant cells to chemotherapeutic agents and radiotherapy by enhancing oxidative stress within tumor cells and impairing DNA damage repair mechanisms, thereby overcoming drug resistance.[84] Although ALA from plant sources exhibits limited anti-proliferative effects, its poor conversion to long-chain derivatives underscores the therapeutic superiority of preformed EPA and DHA, with algal oil offering a sustainable, vegan-compatible alternative of comparable bioactivity in integrated cancer prevention and treatment strategies.[85]

9.4. Synergy with chemotherapeutic agents

Emerging evidence indicates that, PUFAs, notably EPA and DHA, exhibit synergistic interactions with chemotherapeutic agents, enhancing antitumor efficacy through complementary molecular mechanisms. EPA and DHA integrate into tumor cell membranes, altering lipid raft architecture and modulating signaling pathways such as PI3K/Akt, MAPK/ERK, and NF-κB, thereby sensitizing malignant cells to cytotoxic insults. Their competitive inhibition of arachidonic acid metabolism shifts eicosanoid production toward anti-inflammatory and pro-resolving mediators (resolvins, protectins), reducing tumor-promoting inflammation and angiogenesis. Additionally, omega-3s enhance oxidative stress within cancer cells by modulating mitochondrial function and increasing reactive oxygen species (ROS) generation, thereby amplifying apoptosis induced by chemotherapeutic drugs.[86] For example, DHA has been shown to potentiate the efficacy of doxorubicin in breast cancer by promoting lipid peroxidation and caspase activation, while EPA augments 5-fluorouracil-induced cytotoxicity in colorectal carcinoma through suppression of survivin and Bcl-2 expression. This synergism extends to overcoming drug resistance by impairing efflux transporter function and attenuating DNA repair pathways. Collectively, the integration of EPA and DHA into oncological protocols holds promise for lowering effective drug doses, mitigating systemic toxicity, and improving therapeutic outcomes, representing a novel adjunctive strategy in precision cancer therapy.[87]

9.5. Other Benefits:

9.5.1. Beneficial impact of Omega-3 fatty acids on Eye health:

Omega-3, particularly, DHA and EPA, play a pivotal role in ocular physiology, with DHA being a major structural component of photoreceptor outer segment membranes, where it regulates membrane fluidity, photo transduction efficiency, and disc renewal. Emerging evidence highlights their protective effects against retinal degenerative diseases, including age-related macular degeneration (AMD), diabetic retinopathy, and dry eye disease. Mechanistically, DHA and EPA competitively inhibit arachidonic acid metabolism, reducing pro-inflammatory eicosanoids while generating specialized pro-resolving mediators (resolvins, neuroprotectin D1) that suppress microglial activation, mitigate oxidative stress, and preserve retinal pigment epithelial (RPE) cell integrity.[88] DHA's activation of Nrf2 enhances endogenous antioxidant defenses, protecting photoreceptors from light-induced oxidative damage. In dry eye disease, EPA-rich supplementation reduces tear film osmolarity and inflammatory cytokines, improving lacrimal gland function. For example, clinical studies demonstrate that high-DHA supplementation slows progression of early AMD by stabilizing macular pigment density and reducing drusen formation. Furthermore, DHA supports

visual development in infants, with maternal supplementation improving visual acuity outcomes. Collectively, omega-3 fatty acids from marine or algal sources represent a promising nutritional and therapeutic strategy for maintaining retinal health and preventing vision loss across the lifespan. [89]

9.5.2. Therapeutic and nutritional beneficial impact of Omega-3 fatty acids metabolic syndrome and diabetes:

Omega-3 PUFAs represent a valuable adjunct in dietary and therapeutic strategies targeting metabolic dysregulation and vascular complications. They exert significant therapeutic and nutritional benefits in metabolic syndrome and diabetes through multifactorial molecular mechanisms. By incorporating into cell membrane phospholipids, they enhance membrane fluidity and modulate insulin receptor signaling, improving insulin sensitivity in peripheral tissues. EPA and DHA activate PPARα/γ, promoting fatty acid β-oxidation, suppressing hepatic de novo lipogenesis, and reducing very-low-density lipoprotein (VLDL) secretion, thereby lowering plasma triglyceride levels, a hallmark abnormality in metabolic syndrome. In diabetes, omega-3s mitigate oxidative stress by activating the Nrf2 pathway, preserving pancreatic β-cell function and reducing glucotoxicity. Clinical studies, such as that involving high-dose EPA supplementation, have demonstrated improvements in triglyceride profiles and endothelial function in type 2 diabetic patients. Furthermore, omega-3 intake from marine or algal sources contributes to cardio-metabolic protection, reducing atherogenic risk in diabetic populations.[90]

9.5.3. Mechanism involved in Gut microbiota modulation by Omega-3 fatty acids

Long-chain PUFAs, exert a profound influence on the composition and metabolic activity of the gut microbiome via intertwined microbial and host-dependent mechanisms. Upon dietary intake, these fatty acids modify the intestinal lipid milieu, creating a selective environment that favours the proliferation of health-promoting taxa such *as Bifidobacterium, Lactobacillus*, and *Akkermansia*, while suppressing pro-inflammatory, endotoxin-producing Gram-negative species.[91] They enhance epithelial barrier integrity by up-regulating tight junction proteins (occludin, claudin-1) and activating G-protein coupled receptor 120 (GPR120), leading to downstream inhibition of NF-κB and attenuation of mucosal inflammation. In parallel, omega-3s promote microbial fermentation processes that increase short-chain fatty acid (SCFA) production particularly butyrate, supporting colonocyte energy metabolism, immune modulation, and barrier maintenance. Experimental studies, such as those demonstrating fish oil, induced enrichment of *Akkermansiamuciniphila*, link these microbiota shifts to improved metabolic, inflammatory, and insulin-sensitivity profiles.[92]

Table 5: Dosing strategies, therapeutic benefits, and safety of omega-3 fatty acids across different age groups of individuals:

Age Group	Recommended / Therapeutic Dose	Primary Health Objectives	Mechanistic Insights	Example of Clinical Evidence	Safety & Considerations	Ref.
Infants (0–12 months)	0.1–0.5 g/day DHA (via breast milk, fortified formula, or supplementation)	Optimal neurodevelopment, visual acuity, immune maturation	DHA incorporation into photoreceptor membranes; modulation of synaptic plasticity and neurotransmitter release	Maternal DHA supplementation (200–300 mg/day) improved cognitive and visual outcomes in infants	Generally safe; ensure purity of source oils to avoid contaminants	93
Children & Adolescents (1–18 years)	250–500 mg/day EPA + DHA	Cognitive performance, behavioral regulation, visual health	Supports myelination, BDNF-mediated synaptogenesis, and retinal function	Omega-3 intake linked to improved attention and reading skills in ADHD	Rare GI upset; algal oil preferred in plant-based diets	94
Adults (19–64 years)	250–500 mg/day EPA + DHA (general health); 2–4 g/day for hypertriglyceridemia	Cardiovascular prevention, anti-inflammatory support	PPARα activation, reduced VLDL synthesis, SPM production	4 g/day EPA ethyl ester reduced CV events in high-risk patients	Minimal bleeding risk unless on anticoagulants; monitor lipid profiles in high-dose use	95

Pregnant & Lactating Women	300–500 mg/day EPA + DHA, with ≥200 mg DHA	Fetal brain & retinal development, maternal cardiovascular health	DHA enrichment in fetal neural tissue; anti-inflammatory effects in pregnancy	DHA supplementation lowered preterm birth risk	Ensure high-quality, contaminant-free oils; algal DHA ideal for vegan diets	96
Older Adults (65+ years)	500–1000 mg/day EPA + DHA (general); ≥1 g/day for cognitive support	Cognitive preservation, anti-inflammatory benefits, cardiovascular health	NF-κB inhibition, enhanced cerebral blood flow, amyloid-β clearance	DHA/EPA slowed cognitive decline in MCI patients	Safe long-term; may aid joint health; monitor for anticoagulant interactions	97

10. Genetically Engineered Crops and Algae for Omega-3 Fatty Acid Production:

10.1. Camelina sativa (Engineered Oilseed Crop)

Camelina is a fast-growing oilseed crop naturally rich in ALA but lacking EPA and DHA. Through genetic engineering, researchers have successfully introduced multiple genes encoding desaturases and elongases from marine microalgae and fungi into camelina, enabling it to synthesize significant levels of EPA and DHA. For instance, Cargill and BASF have developed genetically modified camelina varieties producing up to 20-40% EPA and DHA in seed oil, approaching fish oil composition. This makes camelina a promising sustainable plant-based source of long-chain omega-3s for food, feed, and nutraceutical applications.[98]

10.2. Canola (*Brassica napus*)

Similar efforts have been made in canola, a globally cultivated oilseed crop. By incorporating genes from microalgae like *Schizochytrium sp*. and other marine organisms, engineered canola oils now contain appreciable EPA and DHA content. This biotechnology has the potential to supplement or replace marine sources for omega-3-rich cooking oils and supplements, with several commercial development pipelines ongoing.[99]

10.3. Soybean (*Glycine max*)

Soybean, a staple oilseed worldwide, has also been genetically engineered to express omega-3 biosynthesis pathway enzymes, increasing EPA and DHA production. While still largely in the research phase, engineered soybean oil with enhanced omega-3 profiles could become a major player in the sustainable omega-3 supply chain.[100]

10.4. Microalgae (*Schizochytrium* and *Nannochloropsis* species)

Microalgae are natural producers of EPA and DHA, and genetic engineering aims to improve their fatty acid yields and productivity. For example, *Schizochytrium sp*. strains have been optimized via metabolic engineering and CRISPR/Cas9 tools to increase DHA content and biomass growth rates under industrial fermentation conditions (Duan et al., 2025). Similarly, *Nannochloropsis* species have been engineered to boost EPA synthesis pathways, making them suitable for large-scale commercial production. These algae-derived oils are used in infant formulas, supplements, and functional foods, offering a vegan-friendly alternative to fish oil.[101]

11. Synthetic Biology Approaches

Beyond direct gene transfer, synthetic biology enables the construction of custom biosynthetic pathways in microbes or plants to optimize omega-3 production. These approaches allow fine-tuning of enzyme expression, substrate channeling, and regulatory elements to maximize yields and stability of EPA/DHA.[102]

11.1. Personalized nutrition and pharmacogenomics

Personalized nutrition and pharmacogenomics are redefining strategies for optimizing omega-3 fatty acid intake to achieve targeted health outcomes. Genetic polymorphisms, particularly in fatty acid desaturase genes (FADS1, FADS2), significantly influence the conversion efficiency of ALA to bioactive long-chain derivatives EPA and DHA, as well as their incorporation into cellular membranes. Variants in genes regulating lipid transport, inflammatory mediators (COX-2, TNF-α), and cardiovascular pathways further modulate individual responsiveness to omega-3 supplementation. Precision nutrition approaches integrate genomic profiling with clinical and lifestyle data to personalize dosing, source selection (marine vs. plant-based), and formulation. For instance, individuals with reduced desaturation activity benefit more from direct EPA/DHA supplementation via fish or algal oils than from ALA-rich sources. Pharmacogenomics insights also refine safety assessments, balancing therapeutic efficacy with risks such as bleeding at high doses. This paradigm shift enables evidence-driven, genotype-tailored omega-3 interventions to optimize cardiovascular, cognitive, and metabolic health.[103]

12. Challenges and Future Perspectives

The escalating global demand for omega-3 fatty acids, underscores pressing sustainability and ecological concerns associated with conventional marine-derived sources such as fish oil and krill oil. Overfishing and habitat disruption threaten fish stock viability, while krill harvesting risks destabilizing Antarctic food webs. Moreover, large-scale fish oil production carries a substantial carbon footprint. Sustainable alternatives, including algal oil cultivation, offer renewable, scalable,

and ecologically benign sources of EPA and DHA, circumventing marine ecosystem exploitation. Advances in biotechnology have enabled the metabolic engineering of oilseed crops (e.g., camelina, canola, soybean) and microalgae through the introduction of desaturase and elongase genes, enabling direct biosynthesis of long-chain omega-3s. CRISPR/Cas9 and synthetic biology approaches further optimize yield, lipid composition, and cultivation efficiency. Plant-derived alpha-linolenic acid (ALA) remains limited by poor conversion to EPA/DHA, but innovations such as microencapsulation, nanoemulsions, co-supplementation with antioxidants, and modulation of desaturation pathways enhance bioavailability. Pro-biotic and pre-biotic co-administration may additionally influence gut microbiota to improve fatty acid metabolism (Conte et al., 2021). While economic, regulatory, and consumer acceptance hurdles persist, these strategies collectively represent a transformative pathway toward sustainable, contaminant-free omega-3 production, aligning global nutritional needs with marine biodiversity preservation and environmental stewardship.[104]

13. Conclusion

Omega-3 fatty acids from diverse sources, including plant-derived ALA, marine-sourced EPA, DHA, and biotechnologically engineered oilsexert multifaceted benefits across cardiovascular, neurological, anti-inflammatory, and metabolic health domains. While marine sources offer superior bioavailability, ecological concerns have accelerated the adoption of algal oils and genetically modified crops as sustainable alternatives. The endogenous conversion of ALA to EPA/DHA is inherently limited and influenced by genetic, dietary, and physiological determinants, underscoring the value of personalized nutrition and pharmacogenomics strategies to optimize outcomes. Robust clinical evidence affirms the safety and therapeutic efficacy of omega-3 supplementation, with global health authorities recommending tailored intakes for specific populations and conditions. Integrative applications include adjunctive use alongside conventional therapies to enhance efficacy and mitigate adverse effects. Advances in sustainable production, targeted formulations, and genotype-specific dosing are poised to expand accessibility and solidify omega-3 fatty acids as pivotal agents in future precision and preventive medicine. Future research on omega-3 fatty acids should prioritize elucidating precise molecular pathways driving their cardioprotective, neuroprotective, anti-inflammatory, and metabolic effects, while advancing pharmacogenomics insights to tailor interventions to genetic and environmental variability. Large-scale, rigorously designed clinical trials must refine population- and disease-specific dosing strategies. Development of advanced delivery systems and bioavailability-enhancing formulations, particularly from sustainable plant-based and biotechnological sources, is essential. Equally critical is scaling environmentally responsible production of engineered crops and microalgae to meet global demand. Integrating omega-3 supplementation into precision nutrition and combinatorial therapeutic frameworks will optimize clinical efficacy and expand their role in next-generation, sustainable healthcare. In this review, the authors have tried to discuss comprehensively, about biochemical, molecular, and clinical dimensions of omega-3 fatty acids, positioning them as versatile bioactive agents with far-reaching implications for future biomedical research and therapeutic innovation. By integrating insights into their mechanistic roles, from modulation of membrane dynamics and signal transduction to epigenetic regulation and inflammation resolution, this work provides a robust scientific framework to guide targeted investigations across diverse disease domains. The detailed evaluation of sustainable sourcing, personalized nutrition strategies, and pharmacogenomics considerations opens avenues for precision-based supplementation, optimizing patient-specific responses. Furthermore, the exploration of omega-3s in synergy with chemotherapeutic agents underscores their potential as adjunct therapies to enhance anticancer efficacy, mitigate treatment-associated toxicities, and improve overall patient outcomes. This review not only consolidates current knowledge but also highlights translational pathways for incorporating omega-3 fatty acids into drug discovery pipelines, integrative treatment protocols, and preventive health strategies. It aims to catalyze multidisciplinary collaborations between nutrition science, molecular biology, oncology, and pharmaceutical research, thereby advancing the clinical and therapeutic utility of omega-3 fatty acids in modern medicine.

List of abbreviations:

ALA -Alpha-Linolenic Acid

ALA-to-EPA/DHA-Conversion of Alpha-Linolenic Acid to EPA and DHA

AMD- Age-related macular degeneration

BDNF -Brain-derived neurotrophic factor

CMC: Critical micelle concentration

COX-2-Cyclooxygenase-2

CRISPR/Cas9-Clustered Regularly Interspaced Short Palindromic Repeats / CRISPR-associated protein 9

DH- Dehydratase

DHA-Docosahexaenoic Acid

DPA- Docosapentaenoic acid

EFSA-European Food Safety Authority

EPA-Eicosapentaenoic Acid

ER- Enoyl reductase

ETA- Eicosatetraenoic acid

FAD/ELO: Fatty acid desaturation/elongation

FADS1/2-Fatty Acid Desaturase 1 and 2

FDA-Food and Drug Administration

GRAS-Generally Recognized as Safe

IL-6-Interleukin-6

KS- Ketoacyl synthase

LCA-Life-Cycle Assessment

LCPUFA-Long Chain Polyunsaturated Fatty Acids

Modification (related to drug delivery)

NF-κB: Nuclear factor-κB

PCBs-Polychlorinated Biphenyls

PEGylation-Polyethylene Glycol

PKS-Polyketide synthase-like

PPARs: Peroxisome proliferator-activated receptors

RCT-Randomized Controlled Trial

ROS: Reactive oxygen species

RPE: Retinal pigment epithelial

LOX- Lipoxygenase

MDD- Major depressive disorder

SCFA: Short-chain fatty acid

SDA- Stearidonic acid

SPMs: Specialized pro-resolving mediators

SREBPs: Sterol regulatory element-binding proteins

STAT3: Signal transducer and activator of transcription 3

TAG- Triacylglycerol

TNF-α-Tumor Necrosis Factor Alpha

VLDL- Very-low-density lipoprotein

WHO-World Health Organization

Ethics approval and consent to participate: This manuscript is a review. Hence, no experiments in animals or humans are included in this study, so ethical approval and consent are not required.

Clinical Trial No: The manuscript is a review article (not a part of Clinical trial), hence no Clinical trial no is applicable.

Consent for publication: This manuscript does not contain any personal data. Hence, no consent is required.

Availability of data and material: Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

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