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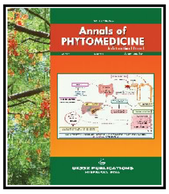

Review Article : Open Access

A comprehensive review of Omega-3 fatty acids: Sources, industrial applications, and health benefits

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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 that play a crucial role in human health. Omega-3 fatty acids are found in both animal and plant sources. Animal sources, particularly fish and algae, are rich in EPA and DHA. On the other hand, plant sources such as flaxseeds, walnuts, and edible seeds primarily contain ALA. It is important to note that while ALA can be converted into EPA and DHA in the body, this conversion is limited. Deficiency of omega-3 fatty acids can lead to several health issues. Symptoms of deficiency can include skin irritation and dryness, sudden joint pain, and mental health problems. It is important to maintain a sufficient intake of omega-3 fatty acids for healthy functioning. Fortification of food with omega-3 fatty acids is an active area of interest for many food and beverage companies. This process involves increasing the content of omega-3 fatty acids in food to improve its nutritional quality and provide health benefits. A variety of food products, ranging from bakery items, eggs, meat, baby meals, cereal bars, chocolates, milk, and milk products, have been enriched with omega-3 fatty acids. Omega-3 fatty acids have found significant industrial applications. Approximately 60% of the omega-3 oils rich in DHA and EPA are used for dietary supplements, 20% for functional foods, 7% for animal feed, 6% for pharmaceuticals, and the rest for infant and clinical nutrition. Biotechnology may contribute towards the industrial production of fatty acids to serve the nutritional demands of DHA and EPA by producing feed enriched with polyunsaturated fatty acids (PUFA), which in turn would increase the content of essential fatty acids in meat, milk, and eggs. Omega-3 fatty acids are vital for human health, and their adequate intake through diet or fortification is essential. The industrial applications of omega-3 fatty acids are vast and growing, underscoring their significance in various sectors. However, more research is needed to fully understand the implications of omega-3 fatty acid deficiency and the optimal levels of intake.

1. Introduction

Omega-3 fatty acids represent a critical category of polyunsaturated fatty acids essential for maintaining human health and well-being. These non-plant sources offer longer-chain and more bioavailable forms of omega-3 fatty acids, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Mori, 2017). Among the most abundant sources of EPA and DHA is fish oil, extracted from fatty fish varieties like salmon, mackerel, sardines, and tuna. These marine origins are valued for their high levels of long-chain omega-3 fatty acids, which the human body readily absorbs and utilizes (Gaffari and Khoshnood, 2021). Extensive research has been dedicated to EPA and DHA, emphasizing their various health advantages, such as reducing inflammation, supporting cardiovascular health, and enhancing brain development and cognitive function (Yashodhara *et al*., 2009). Krill oil, derived from small crustaceans resembling shrimp in Antarctic waters, is another notable source of omega-3 fatty acids. Apart from providing EPA and DHA, krill oil also contains additional bioactive components like astaxanthin, a strong antioxidant, and phospholipids that could potentially improve the bioavailability and absorption of these fatty acids (Bunea *et al*., 2004). Algal oils have recently emerged as a sustainable and vegetarian substitute for fish oils in acquiring DHA. Specific kinds of microalgae, such as *Schizochytrium* sp., are abundant in DHA, offering a feasible choice for individuals adhering to plant-based diets or those with limited access to marine sources (Sijtsma, 2004). The importance of omega-3 fatty acids from non-plant sources lies in their distinct biochemical characteristics and their ability to impact various physiological processes. These fatty acids have gained attention for their potential therapeutic uses in diverse health conditions, encompassing cardiovascular disease, neurological disorders,

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inflammatory ailments, metabolic issues, and eye health. This overview lays the groundwork for a thorough examination of the plant and non-plant origins of omega-3 fatty acids, their bioactive components, health benefits, and potential medicinal uses. Understanding the variety of sources and attributes of these essential fatty acids is essential for promoting optimal health and devising targeted therapeutic strategies.

2. Historical usage of omega-3 fatty acids

The exploration of omega-3 fatty acids has evolved over time, leading to significant discoveries and health implications. Here is a brief historical overview.

2.1 Early observations

In the 1920s, researchers George and Mildred Burr discovered that certain fatty acids were critical for health. They coined the term "essential fatty acids" to describe these vital nutrients.

2.2 Greenland Inuit studies (1970s)

Danish scientists, led by Jorn Dyerberg and H.O. Bang, conducted studies on the indigenous Inuit population in Greenland. The Inuit had a high-fat diet primarily composed of fatty fish and seal meat. Researchers documented the Inuit diet, plasma lipid profiles, and blood fatty acid levels. They "discovered" omega-3 fatty acids (EPA and DHA) in both the Inuit diets and blood. A landmark paper published in the lancet in 1978 proposed that EPA (from seafood) could substitute for arachidonic acid, reducing platelet "stickiness" and potentially preventing thrombosis and atherosclerosis.

2.3 1980s: Omega-3 fatty acids in the spotlight

May 9, 1985: The New England journal of medicine published three pivotal papers, *viz*., epidemiology study titled "the inverse relation between fish consumption and 20-year mortality from coronary heart disease". Clinical medicine study titled "reduction of plasma lipids, lipoproteins, and apoproteins by dietary fish oils in patients with hypertriglyceridemia" and the third one, a basic science study entitled "effect of dietary enrichment with eicosapentaenoic and docosahexaenoic acids on *in vitro* neutrophil and monocyte leukotriene generation and neutrophil function". These articles brought omega-3 fatty acids into the mainstream and emphasized their cardiovascular benefits.

2.4 1989: The DART trial

September 30, 1989: Burr *et al*. (1989) published the "diet and reinfarction trial (DART)" in the lancet. In the study, post-myocardial infarction (MI) patients were assigned to consume oily fish for two years. The result showed that oily fish consumption reduced all-cause mortality by 29%.

2.5 1999: GISSI-Prevenzione trial

August 7, 1999: The lancet published the "GISSI-Prevenzione trial". This ground breaking study used fish oil supplements (Omacor) to reduce the risk of death, cardiovascular death, and sudden cardiac death. The trial demonstrated the efficacy of fish oil supplements in reducing cardiovascular risk.

2.6 2018: REDUCE-IT trial

The REDUCE-IT trial, published in The New England journal of medicine, investigated the use of vascepa, purified EPA (eicosapentaenoic acid) supplement. The results indicated that vascepa significantly reduced cardiovascular events (such as heart attacks and strokes), the necessity for heart stenting procedures, and mortality in high-risk patients.

2.7 2021: STRENGTH trial

The STRENGTH trial, published in JAMA, explored a different formulation of omega-3 fish oil containing both EPA and DHA. Researchers aimed to determine whether this combination would also reduce cardiovascular risk. The study raised questions and highlighted the need for further investigation.

2.8 2020: FDA approval of vascepa

In December 2020, the FDA approved vascepa for reducing cardiovascular events in specific patients with, or at high risk for, cardiovascular disease death. The journey of omega-3 research has been long and impactful, with significant milestones shaping our understanding of these essential fatty acids.

3. Bioactive compounds present in omega-3 fatty acids

Omega-3 fatty acids, also known as omega-3 oils, are a group of polyunsaturated fatty acids (PUFA). Their defining feature is the presence of a double bond, which is three atoms away from the terminal methyl group in their chemical structure.

3.1 Alpha-linolenic acid (ALA)

ALA is an omega-3 PUFA with the chemical formula C18:3n-3 (Figure 1). It contains three double bonds, with the first double bond located three carbon atoms away from the methyl (omega) end of the carbon chain. ALA is primarily found in plant-based sources such as flaxseed, chia seeds, and walnuts (Calvo *et al.,* 2017).

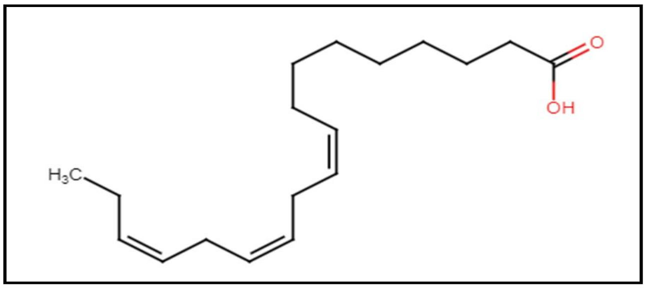

Figure 1: Chemical structure of alpha-linolenic acid.

3.2 Eicosapentaenoic acid (EPA)

EPA is a long-chain omega-3 PUFA with the chemical formula C20:5n-3 (Figure 2). It contains five double bonds and is abundant in marine sources, including fish and algae. EPA plays a crucial role in cardio-vascular health, inflammation regulation, and immune function (Calvo *et al.,* 2017).

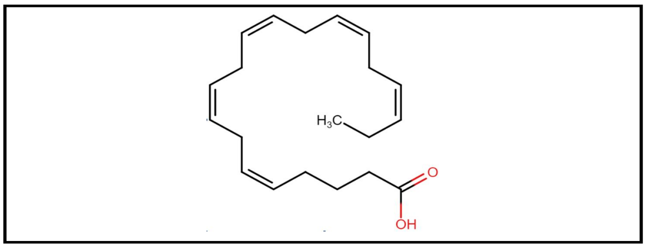

Figure 2: Chemical structure of eicosapentaenoic acid.

3.3 Docosahexaenoic acid (DHA)

DHA is another long-chain omega-3 PUFA with the chemical formula C22:6n-3 (Figure 3). It contains six double bonds and is also found in marine sources. DHA is essential for brain development, cognitive function, and maintaining healthy cell membranes (Tou *et al*., 2011).

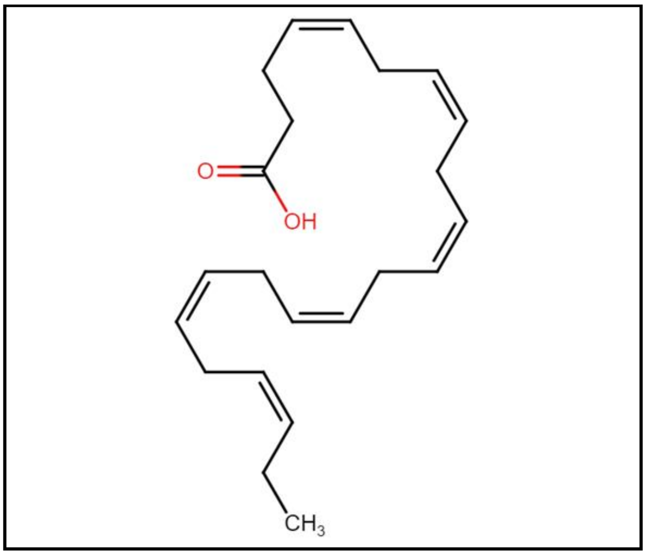

Figure 3: Chemical structure of docosahexaenoic acid.

These fatty acids are easily absorbed and utilized by the human body. EPA, involved in inflammation regulation, blood clotting, and immune function, exhibits favourable effects on cardiovascular health by lowering triglyceride levels, blood pressure, and heart disease risk. EPA may also contribute to brain function and mental health, potentially aiding conditions like depression and cognitive decline (Shirai *et al*., 2006). DHA, a primary structural element of the brain, retina, and sperm cells, is indispensable for proper brain development and function, especially in early life and pregnancy. DHA has been linked to enhanced cognitive function, visual acuity, and reduced risk of age-related macular degeneration (Shirai *et al*., 2006). Krill oil, sourced from small crustaceans akin to shrimp in Antarctic waters, is a rich EPA and DHA source, akin to fish oils. Nonetheless, krill oil also encompasses other bioactive components such as astaxanthin, a robust antioxidant from the carotenoid family. Astaxanthin has been researched for its potential benefits in lowering inflammation, enhancing cardiovascular health, and guarding against oxidative stress (Bunea *et al*., 2004). Krill oil offers omega-3 fatty acids in phospholipid form, potentially elevating their bioavailability and absorption compared to the triglyceride form in fish oils (Bunea *et al*., 2004). Algal oils, derived from specific microalgae varieties like *Schizochytrium* sp., are abundant in DHA. Algal oils present a vegetarian and sustainable substitute for fish oils in acquiring DHA. Algal DHA, structurally identical to fish oil DHA, serves as a supplement for vegetarians and vegans with restricted dietary DHA sources (Sijtsma and De Swaaf, 2004). Algal DHA has demonstrated similar health advantages as fish oil DHA, including bolstering brain and eye health. These non-plant origins of omega-3 fatty acids, particularly EPA, DHA, and affiliated bioactive components, are indispensable for human health and have been extensively examined for their potential advantages in diverse domains such as cardiovascular health, brain function, and inflammation regulation.

4. Sources of omega-3 fatty acids

All the sources vary in their ALA content (Table 1). Fish, especially marine species, are widely recognized as the primary reservoir of omega-3 fatty acids, notably EPA and DHA. The lipid composition of fish is a critical determinant of their nutritional significance and can fluctuate based on factors such as species, environment, diet, and other variables. Both marine and freshwater fish play a role in supplying omega-3 fatty acids. Gaffari and Khoshnood (2021) found that freshwater fish like barbel fillets have the highest monounsaturated fatty acids (MUFA) content at 18.51%, while river mullet fillets are abundant in polyunsaturated fatty acids (PUFA) at 1.87%. Rayfin fillets exhibit the highest omega-6 levels at 1.1%, whereas river mullet fillets showcase the highest omega-3 content at 1.87%. Furthermore, salmon is a notable source containing 0.8% EPA, 1.6% DHA, and 12.4% total PUFA, whereas Russian sturgeon stands out with 11.3% EPA, 0.7% DHA, and 46.8% total PUFA (Kyosev and Dragoev, 2008). Despite the nutritional contribution of freshwater fish to omega-3 fatty acids, marine counterparts like salmon and russian sturgeon remain prime sources of these essential nutrients. The majority of commercially available fish oils are derived from marine species. EPA and DHA, the most crucial polyunsaturated fatty acids, are renowned for their various health advantages such as cardiovascular disease risk reduction, cancer prevention, and alleviation of inflammatory conditions linked to the immune system (Avinash Gowda *et al*., 2018; Munoz-Tebar *et al*., 2019; Goksen *et al*., 2020).

Table 1: Alpha-linolenic acid (omega-3) content of foods (g /100 g)

Foods (100 g)	ALA (g)
Cereal/millet wheat and pearl millet (bajra)	0.14
Black gram (kala chana), kidney beans (rajmah) and cowpea (lobia)	0.5
Other pulses	0.16
Green leafy vegetables	0.16
Other vegetables	0.025
Fruits	0.025
Fenugreek seed (methi)	2.0
Mustard (sarson)	10.0
Unconventional flaxseed (alsi)	20.0
Perilla seeds (bhanjira)	33.0

Source: NIN, 2011.

DHA plays a pivotal role in brain and vision development, particularly crucial during pregnancy and early childhood for optimal growth (Calder *et al*., 2010). EPA, with its distinct molecular structure, presents essential biological effects like anti-inflammatory and antithrombotic properties by substituting the proinflammatory and prothrombotic omega-6 fatty acid arachidonic acid (AA, 20:4, omega-6) in cell membrane phospholipids (Adkins and Kelley, 2010; Jump *et al*., 2012; Larsson *et al*., 2004). Tuna oil and its concentrated form (60% tuna oil) are recognized for their high EPA and DHA content. The fortification of various foods with fish oil offers an avenue to enhance omega-3 fatty acid intake. Nevertheless, a significant technological hurdle in integrating EPA and DHA into foods is the risk of oxidation and the development of an undesirable fishy taste due to lipid degradation (Feizollahi *et al*., 2018; Gumus and

Gharibzahedi, 2021). Omega-3 fatty acid-rich fish oils are distinguished by a unique flavour and scent that can influence fortified products, limiting their application (Piombo *et al*., 2006; Botelho *et al*., 2013; Waraich *et al*., 2013; Ganesan *et al*., 2014). The utilization of highly purified and odourless fish oil or encapsulated fish oil in producing omega-3-enriched foods may offer an alternative strategy to mask unwanted sensory attributes and safeguard the oil during manufacturing (Iafelice *et al*., 2008).

4.1 Animal sources

Some high-quality sources of omega-3s, along with their respective content (Nigam *et al.,* 2018) are described below.

4.1.1 Mackerel

Mackerel is a small, fatty fish commonly smoked and eaten as whole fillets. It provides 500% of the daily value (DV) for vitamin B_{12} and 130% for selenium. Omega-3 content: 4,580 mg of EPA and DHA (combined) in a 3.5 oz. (100 g) serving.

4.1.2 Salmon

Salmon is nutrient-dense, offering high-quality protein, vitamin D, selenium, and B vitamins. Regular consumption of salmon is associated with a lower risk of heart disease, dementia, and depression. Omega-3 content: 2,150 mg of EPA and DHA (combined) in a 3.5 oz. (100 g) serving.

4.1.3 Cod liver oil

Cod liver oil is a supplement extracted from cod fish livers. It is rich in omega-3s, vitamins D, and A. Omega-3 content: 2,438 mg of EPA and DHA (combined) per tablespoon.

4.1.4 Herring

Herring is a medium-sized oily fish, often cold-smoked or pickled. A 3.5 oz. (100 g) serving provides almost 100% of the DV for selenium and 779% for vitamin B_{12}. Omega-3 content: 2,150 mg of EPA and DHA (combined) in a 3.5 oz. (100 g) serving.

4.1.5 Oysters

Oysters, rich in zinc, are among the most nutritious foods and a great source of omega-3s. Omega-3 content: 329 mg per serving. Complexities of animal sources of omega-3 fatty acids and their benefits and potential risks are the point of discussion. Ponnampalam *et al.,* 2021; Tur *et al.,* 2012 reviewed the benefits and potential risks associated with animal sources of omega-3 fatty acids. Red meat, such as beef, lamb, and pork, is a common animal-derived food. While red meat contains essential nutrients, it is not a significant source of long-chain omega-3 fatty acids (EPA and DHA). Animals raised on grain-based diets, which are common in feedlots, typically have lower levels of omega-3s in their tissues. The ratio of omega-6 to omega-3 fatty acids in red meat can be unfavourable for health when consumed excessively (Lakra *et al.,* 2019). Grass-fed animals have higher levels of omega-3s due to their natural diet. In contrast, grain-fed animals (commonly found in feedlots) have lower omega-3 content. Choosing grass-fed meat may provide better omega-3 profiles. Omega-6 fatty acids are essential but can be harmful in excess. Modern diets often contain an imbalance, with higher omega-6 intake. Consuming too much omega-6 relative to omega-3 can lead to inflammation and health issues. Optimal health requires a balanced ratio of these fatty acids. Fish, especially fatty fish like salmon, mackerel, and sardines, remain the best source of EPA and DHA. Plant-based sources (such as flaxseed, chia seeds and walnuts) provide ALA, which can convert to EPA and DHA but less efficiently. Supplements (such as fish oil and algae-based) are also popular for omega-3 intake (Tur *et al.,* 2012; Lakra *et al.,* 2019).

4.2 Plant sources

The importance of vegan omega-3 fatty acids sourced from plants is getting attention. Common vegan sources are walnuts, chia seeds, flaxseeds, hemp seeds, edamame, seaweed and algae. Vegan diets may lead to deficiencies in vitamin B_{12}, calcium, zinc, iron, magnesium, high-quality protein, and omega-3. Addressing these deficiencies is essential. Research continues to explore the bioavailability and conversion rates of plant-based omega-3 sources like ALA to DHA and EPA. Omega-3 PUFAs, specifically focusing on their emerging plant and algal sources. Saini *et al.,* 2021; Gammone *et al.,* 2019; Keivani and Hosseini, 2023 review sheds light on the latest developments in obtaining these essential nutrients from sustainable and diverse sources. Chia seeds, flaxseeds, and garden cress seeds are now widely recognized for their high content of á-linolenic acid. ALA is a plant-based omega-3 that serves as a precursor for EPA and DHA. Other plant sources like *echium plantagineum, Buglossoides arvensis,* and *Ribes* sp. are explored for stearidonic acid (SDA), which is more effective than ALA in increasing EPA and DHA levels in the body. Microalgae and thraustochytrids directly supply EPA and DHA. These microbial sources are currently used for the commercial production of vegan EPA and DHA. They offer a sustainable alternative to marine-derived omega-3s. Researchers continue to explore these aspects for future advancements (Saini *et al.,* 2021). The nutritional and commercial importance of omega-3 PUFA from various sources is critical. The future of omega-3 fatty acids involves addressing sustainability concerns, embracing innovative technologies, and personalizing approaches to meet individual needs. One notable example is the startup Örlö, an Icelandic company offering plant-based omega-3. Örlö's approach uses 99% less land and water for crop cultivation compared to other producers (Saini *et al.,* 2021). Plant-based omega-3 fatty acids are described below, categorized by crop.

4.2.1 Flaxseed

Flaxseed (*Linum usitatissimum*) is a remarkable plant that offers both culinary and health benefits. It has a good connection to α-linolenic acid (ALA), an essential omega-3 fatty acid. Flaxseed is rich in ALA, which is an omega-3 PUFA. ALA is considered an essential fatty acid because it cannot be synthesized by the human body. Flaxseed oil contains approximately 50-60% ALA in its composition. ALA plays a crucial role in maintaining cardiovascular health. It helps reduce inflammation, supports brain function, and contributes to overall well-being. Consuming flaxseed or flaxseed oil is an excellent way to boost ALA intake (Raghuwanshi *et al.,* 2019; Goyal *et al.,* 2020). Flaxseed oil capsules are available as dietary supplements. Ground flaxseed can be added to baked goods, smoothies, and oatmeal. It is also used in flaxseed oil in salad dressings or drizzled-over dishes. Researchers conducted a diallel cross using six flax genotypes with varying fatty acid content. The study estimated genetic parameters related to the content of oleic acid, linoleic acid, and á-linolenic acid (Cunnane *et al.,* 1993). Additive gene effects predominantly determine the inheritance of linoleic and á-linolenic acid content. Parental lines with high linoleic acid and low á-linolenic acid content were identified for continuous improvement programs. Promising F_1 hybrids were also identified for achieving specific fatty acid profiles in linseed oil. Flaxseed oil is rich in PUFA, constituting approximately 73% of its total lipids. Major fatty acids present in flaxseed oil include ALA (40-60%), linoleic acid (12-17%), oleic acid (13-19%), palmitic acid (5-8%) and stearic acid (2-4.5%). Flaxseed lignans, along with ALA, contribute to its health-promoting properties. The n-6:n-3 fatty acid ratio in flaxseed oil is approximately 0.3:1 making it a valuable dietary component (Walkowiak *et al.,* 2022).

4.2.2 Soybean

Soybean is a major oilseed crop globally, accounting for 28% of total vegetable oil consumption in 2019. Soybean seeds contain approximately 8% ALA (omega-3) in their oil. Soybean-derived omega-3 can be an alternative source for populations at risk of inadequate omega-3 PUFA intake. Breeding aims to increase the concentration of omega-3 PUFA in soybean seeds. However, higher omega-3 PUFA content can lead to rancidity in seed oil, necessitating chemical hydrogenation (which produces trans fats). Balancing higher omega-3 PUFA levels with oil stability is crucial. Selecting soybean varieties with improved omega-3 PUFA content and identifying genetic markers associated with omega-3 PUFA traits, in addition to studying gene expression and regulation to enhance omega-3 PUFA accumulation. Developing transgenic soybeans with altered fatty acid profiles and achieving an optimal omega-6 PUFA/omega-3 PUFA ratio is essential for health. Breeding efforts focus on improving omega-3 PUFA content while maintaining a balanced ratio in progress. Researchers and breeders are working diligently to enhance the omega-3 PUFA content in soybean oil, providing a healthier dietary option without compromising stability. The journey toward better oilseed crops continues, driven by the quest for improved nutrition and well-being (Kulkarni *et al.,* 2021; Zhou *et al.,* 2023). There is a fascinating connection between soybean (*Glycine max*) and á-linolenic acid (ALA), an essential omega-3 PUFA. Previous studies reported that omega-3 fatty acid and α-linolenic acid are important compounds that prevent cardiovascular disease and cancer in humans. Soybean oil typically contains approximately 8% ALA. Wild soybeans (*Glycine soja* Sieb. and Zucc.) exhibit a remarkable trait of elevated (~15%) ALA content in their seed oil is recorded. Researchers have developed recombinant inbred lines (RILs) with increased ALA content by crossing wild soybeans (PI 483463) with a cultivar (Hutcheson). These RILs consistently maintain higher ALA content than cultivated soybeans across various growing environments. The stable ALA content in these lines makes them valuable for improving soybeans with lower linoleic acid (LA) to ALA ratios (Asekova *et al.,* 2014). Researchers achieved efficient gene silencing of the omega-3 fatty acid desaturase (FAD3) gene family in soybeans using small interfering RNA (siRNA). FAD3 is responsible for synthesizing ALA (18:3) in the polyunsaturated fatty acid pathway. This study demonstrates the potential for modifying ALA levels in soybeans through targeted gene silencing. The GmFAD3A-2 and GmFAD3C genes, encoding cytosolic FAD3 from soybean (Qihuang 29), were cloned and expressed in yeast. The transformed yeast strains produced ALA. Understanding the regulation of FAD3 genes can contribute to enhancing ALA content in soybean oil (Flores *et al.,* 2008; Zhang *et al.,* 2009). Ahmad *et al.* (2023) and Kulkarni *et al.* (2021) conducted research aiming at enhancing the nutritional quality of soybean oil by increasing its omega-3 content while maintaining a balanced omega-6/omega-3 ratio. Chemical hydrogenation (used to reduce rancidity) generates trans fats, which are associated with health risks. The demand for soybeans with reduced ALA content is growing. Researchers explore conventional breeding methods, genetic mapping, and genomics to alter the omega-3 fatty acid content. By enhancing soybean oil omega-3 content, this research contributes to better health outcomes and sustainable food production.

4.2.3 Chia seeds

The fascinating connection between chia seeds (*Salvia hispanica*) and α-linolenic acid (ALA), an essential omega-3 PUFA. Here are some relevant studies and references (Chicco *et al.,* 2008; Gabal, 2024; Knez Hrnèiè *et al.,* 2019; Oteri *et al.,* 2022; Fernandes *et al.,* 2021) which reported interesting findings. Chia seeds are rich in ALA and fiber. A study investigated the effects of dietary chia seeds on dyslipidaemia and insulin resistance induced by a sucrose-rich diet (SRD) in rats. Results showed that chia seeds prevented the onset of dyslipidaemia and insulin resistance when fed to rats on an SRD for 3 weeks. Normalized dyslipidaemia and insulin resistance in long-term SRD-fed rats when chia seeds replaced the dietary fat during the last 2 months of the feeding period. Chia seeds' ALA content played a key role in these beneficial effects. Chia seeds contain approximately 39% oil (by mass of dry seed). The major constituents of chia oil are PUFA, particularly ALA (up to 68%) and linoleic acid (LA, an omega-6 fatty acid, 19%). Chia seeds are one of the best plant sources of ALA compared to other known plant sources (Chicco *et al.,* 2008). Chia seeds' ALA content contributes to their health-promoting properties. Incorporating chia seeds into the diet can enhance the balance of omega-3 and omega-6 fatty acids (Coorey *et al.,* 2014).

4.2.4 Walnuts

Studies conducted by Fan *et al.* (2023); Kömür *et al.* (2023); Carey *et al.* (2020); Rabrenoviæ *et al.* (2011); Simopoulos (2019) revealed a fascinating connection between walnuts (*Juglans regia*) and α-linolenic acid. Walnuts have been lauded as a 'superfood,' containing a remarkable array of natural constituents that may contribute to reduced cancer risk. Walnuts are a rich source of ALA, tocopherols, antioxidant polyphenols (including ellagitannins), and prebiotics (including fiber). Among the most potent constituents of walnuts are the ellagitannins, primarily pedunculagin. After ingestion, ellagitannins are hydrolyzed at low pH to release ellagic acid (EA), which is subsequently metabolized by the gut microbiota to bioactive urolithins (hydroxydibenzo [b, d] pyran-6-ones). Several urolithins, including urolithin A, reportedly exhibit potent anti-inflammatory properties. These properties of walnuts provide a rationale for including them in a healthy diet for overall disease risk reduction, including colorectal cancer. Walnuts contain a high level of short-chain omega-6 and omega-3 PUFAs, such as linoleic acid (C18:2n-6, LA) and alpha-linolenic acid (C18:3n-3, ALA). The desirable ratio of omega-6 to omega-3 PUFA in walnuts contributes to their health-promoting effects.

4.2.5 Hemp seeds

Padilla-González *et al.* (2023) reviewed hemp (*Cannabis sativa L.*) as a versatile industrial crop with applications in various industries through omega-3 PUFA. The chemical diversity of hemp seeds has not been extensively explored. In a recent study, researchers analyzed 52 germplasm accessions of hemp seeds to identify new metabolites and link specific accessions to the presence of biologically important molecules. The study revealed large variability in polar chemistry profiles among accessions. A new compound and four structural analogues were discovered (cinnamic acid glycosyl sulphates). These novel metabolites belong to a previously unknown chemical class in hemp seeds. Variability in fatty acid profiles was also observed, with some accessions having a higher yield of ALA and variation in the ratio of linoleic acid (LA) to ALA. These findings have implications for commercial claims and breeding programs. Hemp seed oil is exceptionally rich in unsaturated fatty acids, particularly PUFA. The Hemp seed oil's nutraceutical value lies in its fatty acid composition. ALA is a precursor for synthesizing other beneficial fatty acids (Farinon *et al.,* 2020).

4.2.6 Perilla

Perilla (*Perilla frutescens* (L.) *var. frutescens*) is an oilseed crop that produces a large amount of ALA in its seeds (Kim *et al.,* 2019), ranging from 47% to 64%. Other fatty acids present include linoleic acid (LA, 18:2), which is an omega-6 fatty acid, constituting 10% to 24% and oleic acid (OA, 18:1) is an omega-9 fatty acid, ranging from 9% to 20%. The seed oil content among perilla accessions varies from 17% to 42.7% (Kim *et al.,* 2019; Singh *et al.,* 2023; Asif, 2011; Lee *et al.,* 2016).

4.3 Lesser-known plant sources rich in omega-3 fatty acids

While flaxseed, chia seeds, walnuts, hemp seeds, and perilla are well-known sources of omega-3 fatty acids (ALA), some lesser-known crops also offer these beneficial nutrients, which are explained below.

4.3.1 Sacha Inchi

Sacha Inchi (*Plukenetia volubilis*), also known as the Inca peanut, is a remarkable oilseed crop with unique nutritional properties. Its connection to ALA, an essential omega-3 PUFA is well studied by Hu *et al.* (2018). Sacha Inchi seeds contain approximately 41-54% oil. The oil is characterized predominantly by high levels of PUFA, especially ALA and LA. ALA constitutes approximately 35.2-50.8% of the total lipid fraction in Sacha Inchi seed oil. LA represents about 33.4-41.0% of the total lipid content (Ruiz *et al.,* 2013; Cisneros *et al.,* 2014). Understanding the genetic information and genome sequence of Sacha Inchi is essential for functional genomics and molecular breeding studies. Identification of candidate genes involved in ALA metabolism will aid in the genetic improvement of Sacha Inchi and potentially benefit other crops through metabolic engineering.

4.3.2 Ahiflower

Ahiflower oil from the seeds of *Buglossoides arvensis* is rich in ALA and stearidonic acid (SDA) (Seidel *et al.,* 2024). ALA and SDA are potential precursor fatty acids for the endogenous synthesis of EPA and DHA, which are n3-long chain polyunsaturated fatty acids (n3-LC-PUFA) in humans. A randomized crossover study with healthy male volunteers showed that oral ahiflower oil intake significantly improved plasma EPA levels. EPA-derived oxylipins were also increased by SDA-rich ahiflower oil. Ahiflower oil containing SDA was compared to high ALA flaxseed oil. Ahiflower oil showed promise in enhancing VLCn-3 FA contents. Ahiflower oil contains a uniquely high combination of omega-3 ALA and SDA (stearidonic acid) plus omega-6 gamma-linolenic acid (GLA). Its total polyunsaturated fatty acid (PUFA) content is about 85%, among the highest in the plant kingdom. It is the richest dietary source of SDA at about 20%.

4.3.3 Camelina

Researchers successfully engineered *Camelina sativa* to produce fish oil-like levels of DHA, an important omega-3 long-chain polyunsaturated fatty acid (omega-3 LC-PUFA) (Petrie *et al.,* 2014). Camelina seeds can produce oil containing up to 40% of the omega-3 precursor α-linolenic acid (ALA). ALA is a substrate for synthesizing other beneficial fatty acids. Camelina oil also contains high levels of PUFA and MUFA. It is a valuable source of antioxidants, including γ-tocopherol (Rajaei *et al.,* 2011). *Camelina sativa* offers a promising land-based source of ALA and other essential fatty acids. Its potential for sustainable omega-3 LC-PUFA production makes it an exciting crop for future nutrition and health applications.

4.3.4 Black currant seed oil

Black currant (*Ribes nigrum*), also known as cassis, belongs to the *Ribes* genus and the family Grossulariaceae. Black currants are known for their versatile health benefits, including being a valuable source of polyphenols, vitamin C, anthocyanins, and flavonols. They have antioxidant properties and potential protective effects against various diseases such as cancer, cardiovascular disorders, and inflammation (Allai *et al.,* 2020). Black currant seed oil contains high amounts of essential fatty acids, including stearidonic acid (SDA) which is an omega-3 fatty acid. Omega-6 fatty acids including gamma-linolenic acid (GLA), tocopherols and phytosterols. Black currant seed oil feeding has been studied for its impact on liver lipid classes and fatty acid composition. The same research reported on the effects of dietary fatty acids on liver lipid classes and metabolism. Black currant seed oil is known for its high content of ALA and SDA.

4.3.5 Echium seeds

A study by Kuhnt *et al.* (2016) compared the effects of echium oil (EO) and linseed oil (LO) on LC n-3 PUFA accumulation in blood and clinical markers. EO contains both ALA and stearidonic acid (SDA), a specific omega-3 fatty acid. Results showed that EO increased EPA and DPA levels in plasma, red blood cells (RBC), and peripheral blood mononuclear cells (PBMC) more efficiently than LO. However, neither EO nor LO maintained blood DHA status in the absence of fish/seafood consumption. Echium oil is super-rich in α-linolenic acid (ALA), gamma-linolenic acid (GLA), and stearidonic acid (SDA). These specific omega-3 and omega-6 fatty acids make it valuable in cosmetic and skin care applications. Echium oil contains both n-6 and n-3 18C-PUFA, including ALA, SDA, and GLA. Echium seeds offer a unique blend of ALA, SDA, and other beneficial fatty acids.

Promoting sustainable sources of omega-3 fatty acids involves a multi-faceted approach with microorganisms such as fungi, bacteria, and algae can be cultivated in controlled environments to produce healthy oils (Xie *et al.,* 2015). For instance, DuPont has developed a clean and sustainable source of the omega-3 fatty acid EPA through fermentation using metabolically engineered strains of *Yarrowia lipolytica*. Encouraging sustainable farming practices for omega-3-rich crops like flaxseeds and walnuts can help increase their availability. Educating consumers about the health benefits of omega-3 fatty acids and the importance of sustainable sources can drive demand for such products. Governments and regulatory bodies can play a role by setting guidelines for the sustainable production and fortification of omega-3 fatty acids. Continued research into new and efficient ways of producing omega-3 fatty acids sustainably is crucial. This includes exploring alternative pathways for omega-3 PUFA production (Qin *et al.,* 2023). Promoting sustainable sources of omega-3 fatty acids requires a combination of technological innovation, sustainable farming, consumer education, supportive policies, and ongoing research.

5. Genetics of omega-3 fatty acid

Dietary ALA increases ALA levels in the body and also increases omega-3 LC-PUFA concentration. Key genes involved in the conversion of ALA to omega-3 LC-PUFA include FADS1, FADS2, and ELOVL5. Endogenous omega-3 LC-PUFA biosynthesis from ALA is affected by substrate levels, gene expression, and product inhibition (Wang *et al.,* 2017). Peony seeds contain ALA as the most predominant fatty acid. ALA and linoleic acid (an omega-6 FA) are essential for humans, as they cannot synthesize these two FAs and must obtain them from the diet (Zhang *et al.,* 2018). Genetic polymorphisms in FADS1 and FADS2 (delta-5 and delta-6 desaturases) affect ALA and long-chain PUFA metabolism. These genetic variations may influence an infant's IQ, atopy, coronary heart disease (CHD) risk, and other health outcomes. Human studies have explored the effects of omega-3 fatty acids on gene expression related to insulin sensitivity, inflammation, and metabolic health (Ahmadi *et al.,* 2023). Researchers investigated the protein-encoding genes regulating omega-3 polyunsaturated fatty acid (PUFA) content in chicken meat (Ahmadi *et al.,* 2023). Key genes and pathways regulating omega-3 fatty acid metabolism were identified. GRB10 upregulation inhibited the mTOR signalling pathway, improving the content of EPA and DHA. FGFR3 downregulation facilitated the conversion of ALA to EPA. This study provides insights into genes and pathways regulating fatty acid content and offers a reference for nutritional regulation systems in production (Zhao *et al.,* 2023). A study investigated the effects of omega-3 fatty acids on the gene expression of PPAR-γ and serum levels of FGF-21 in individuals with different metabolic conditions.

6. Dietary requirements

Research indicates that a substantial segment of the populace fails to meet the necessary intake of long-chain omega-3 polyunsaturated fatty acids (LC omega-3 PUFA) crucial for optimal well-being (Meyer, 2011). Numerous entities, such as the food and agriculture organization (FAO), world health organization (WHO), and domestic health authorities (Table 2), have issued dietary guidance concerning omega-3 fatty acids and fish consumption to combat this insufficiency. The incorporation of oily fish and seafood in one's diet or the utilization of fish oil supplements or micro-algal EPA/DHA capsules, deemed as safe alternatives, can fulfil these recommen-dations (Pelliccia *et al.*, 2013; Marangoni and Rousseau *et al*., 1995). Despite the FDA's caution against surpassing a daily EPA and DHA intake of 2 g, recent research indicates that doses equal to or greater than 2 g/day of EPA+DHA are imperative for a notable reduction in plasma triglyceride levels, as lower intake levels of 200-500 mg/day show minimal to no effect (Agostoni *et al*., 2012). The european food safety authority (EFSA) advocates for a minimum daily EPA+DHA intake of 250 mg for adults, 100 mg of DHA for infants and toddlers (<24 months), and an additional 100-200 mg of DHA for expectant and nursing mothers. Furthermore, EFSA recommends the consumption of diverse fish species, with a suggested frequency of two servings per week, including one serving of oily fish (Jacobsen *et al*., 2010**)**. As per EFSA, EPA+DHA doses up to 5 g/day for adults and up to 1.8 g/day for EPA and DHA individually are deemed safe. To tackle concerns related to the flavour and scent of fish oil, microencapsulation methods can mitigate lipid oxidation problems rendering fish oil more agreeable (Marangoni and Rousseau, 2013). Nevertheless, fish oil is unsuitable for vegetarians and might be unappealing due to its aroma. Alternative sources of LC omega-3 PUFA consist of krill oil, calamari oil, microorganisms, and genetically engineered crops and livestock, all of which have demonstrated safety and provide satisfactory bioavailability of omega-3 LC-PUFAs.

Table 2: Recommended adequate intakes for omega-3 fatty acids

S. No.	Age	Male	Female	Pregnancy	Lactation
1	Birth to 6 months*	0.5 g	0.5 g	-	-
2	7-12 months*	0.5 g	0.5 g	-	-
3	1-3 years**	0.7 g	0.7 g	-	-
4	4-8 years**	0.9 g	0.9 g	-	-
5	9-13 years**	1.2 g	1.0 g	-	-
6	14-18 years**	1.6 g	1.1 g	1.4 g	1.3 g
7	19-50 years**	1.6 g	1.1 g	1.4 g	1.3 g
8	51+ years**	1.6 g	1.1 g	-	-

*As total omega-3 fatty acids; **As ALA. Source: Institute of Medicine, (2005), Washington, DC.

7. Pharmacological uses

Various pharmacological uses of omega-3 fatty acids are depicted in Figure 4.

7.1 Anticancer activity

Research on the anticancer properties of omega-3 fatty acids (FAs) displays potential and is continuously advancing, supported by epidemiological research indicating a reduced cancer prevalence in populations consuming omega-3 FAs-rich diets (Dydjow-Bendek and ZagoŸdŸon, 2020). Two primary areas of investigation in cancer research involve omega-3 FA and their use as complements to chemotherapy and as inhibitors of cancer cell proliferation. When utilized as adjuncts to chemotherapy, specifically EPA and DHA, omega-3 FAs aim to enhance the tolerance to chemotherapy treatment. They exhibit anti-inflammatory and antioxidant characteristics, modulate the immune response, trigger apoptosis, hinder angiogenesis, and suppress metastasis. Moreover, omega-3 FAs have demonstrated efficacy in impeding tumour development through diverse pathways by regulating the immune response, inducing apoptosis, and inhibiting angiogenesis (Yang *et al*., 2017). Furthermore, they disrupt oestrogen-induced cell proliferation, function as COX-2 inhibitors to reduce tumour microvessel density, and impact signalling cascades associated with cell cycle control and apoptosis (Klek, 2016). Omega-3 FAs have been noted to heighten the vulnerability of cancer cells to radiotherapy, diminish drug resistance, and ameliorate cancer-induced cachexia by promoting anabolic effects on nutrition and stabilizing energy consumption. These effects have been observed across various types of cancer, such as breast, endometrial, prostate, neuroblastoma, colon, pancreatic, gastric, and melanoma (Afroze *et al*., 2024). Additionally, omega-3 FAs have been proven to boost the efficacy of radiotherapy and mitigate neuropathic pain induced by chemotherapy (Ljungblad *et al*., 2022). In conclusion, omega-3 FAs exhibit potential as adjunctive therapy in cancer management and treatment.

7.2 Effect on cardiovascular diseases (CVS) and other metabolic disorders

Research consistently indicates that diets abundant in omega-3 fatty acids (FAs) provide significant cardiovascular benefits, initially observed in the Greenland Eskimo population and subsequently confirmed through various studies (Dyerberg *et al*., 1975). The effects of omega-3 FAs include reducing the risk of arrhythmias, decreasing platelet aggregation, lowering plasma triglycerides, increasing high-density lipoprotein (HDL) cholesterol levels, optimising low-density lipoprotein (LDL) particle size, reducing blood pressure, alleviating coronary restenosis, and improving vasodilation (Yashodhara *et al*., 2009). Cumulative data from large-scale trials highlight a substantial decrease in cardiovascular events linked to omega-3 FAs supplementation. Omega-3 FAs are crucial in modulating heart rate, diminishing the chances of malignant ventricular arrhythmias, and preventing sudden cardiac death. Furthermore, they aid in both primary and secondary prevention of coronary heart disease (CHD) by hindering the advancement of coronary atherosclerosis and averting restenosis post-coronary angioplasty (Dehmer *et al*., 1988). However, the evidence concerning the protective effects against ischemic stroke has been inconclusive, possibly due to variations in fish consumption patterns and preparation methods. Recent studies have not shown significant advantages of omega-3 FAs in individuals with peripheral arterial disease, except for a decrease in blood viscosity (Schiano *et al*., 2008). Despite some research indicating improvements in endothelial function, the routine use of omega-3 FAs for managing peripheral arterial disease may require further evidence to verify their effectiveness. Ongoing research efforts offer hope for providing more insights into the role of omega-3 FAs in the secondary prevention of ischemic stroke. A retrospective cohort study analyzed data from the national health and nutrition examination survey (NHANES) database (2003-2018). ALA intake was associated with different cardiovascular diseases (CVDs): Octadecatrienoic acid intake was linked to lower odds of coronary heart disease (CHD). ALA and docosapentaenoic acid (DPA) intakes were associated with lower odds of heart attack. Higher ALA intake was related to a lower risk of all-cause mortality. ALA, arachidonic acid (AA), and DPA intakes were related to a low risk of CVD-specific mortality. Ensuring adequate intake of PUFA, including ALA, may decrease the risk of mortality (Zhong *et al.,* 2023). A meta-analysis examined the effectiveness of dietary omega-3 PUFA supplementation (EPA, DHA, and ALA) in improving cardiovascular outcomes. ALA, along with EPA and DHA, plays a role in preventing cardiovascular events, arrhythmias, and stroke (Tomodio *et al.,* 2019). ALA-rich diets have been studied for their effects on obesity, metabolic syndrome, and CVDs. ALA contributes to overall health and cardiovascular well-being (Lorente-Cebrián *et al.,* 2013; Zhong *et al.,* 2023).

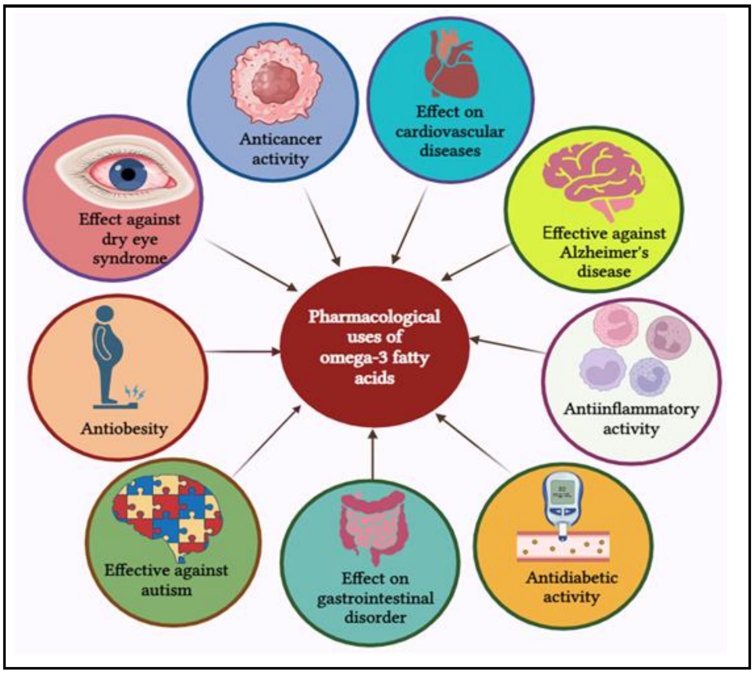

Figure 4: **Pharmacological uses of omega-3 fatty acids.**

7.3 Effective against alzheimer's disease

Alzheimer's disease (AD) is characterized by the deposition of amyloid plaques surrounding neurons and the development of neurofibrillary tangles comprised of tau protein within cells, disrupting cellular metabolic processes and resulting in cell demise, impaired neuronal function, and cognitive deterioration. Current therapeutic interventions primarily target symptomatic relief as AD remains without a cure (Patrick, 2019). Pathological mechanisms contributing to AD involve dysfunctional macrophages that exhibit reduced phagocytic capabilities, initiating cerebral inflammation and neuronal harm, alongside diminished glucose absorption in the brain. Omega-3 fatty acids have been implicated in augmenting macrophage functionality and reducing inflammation, thereby offering potential advantages in the management of AD (Lau *et al*., 2020). Specific fatty acids such as resolvin E1, E2, maresin, protectin D1, and resolvin D possess anti-inflammatory characteristics and promote the regeneration of neurons (Pifferi *et al*., 2020). The supplementation of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) has demonstrated potential in diminishing the formation and clearance of Aβ plaques, as well as regulating cerebral glucose uptake. Nevertheless, individuals carrying the APOE4 gene variant, which is linked to an elevated risk of AD, may experience challenges in the transportation of DHA to the brain. Clinical trials have yielded diverse results, possibly influenced by disparities in the sources and accessibility of DHA (Külzow *et al*., 2016).

7.4 Anti-inflammatory activity

The anti-inflammatory attributes of omega-3 fatty acids (FAs) and their derivatives, referred to as specialized pro-resolving mediators (SPMs), are well recognized. Omega-3 FAs, notably EPA and DHA, exhibit anti-inflammatory and immunoregulatory effects by integrating into cellular membranes and transforming into different eicosanoids and docosanoids. These derivatives, such as resolvins, protectins, and maresins, are generated *via* lipoxygenase, cyclooxygenase, and cytochrome P450 pathways, displaying anti-inflammatory, pro-resolving, and tissue-protective characteristics (Nesman *et al*., 2019). Omega-3 FAs compete with omega-6 FAs for identical metabolic enzymes, decreasing the generation of pro-inflammatory mediators originating from arachidonic acid. The anti-inflammatory mechanisms of omega-3 FAs encompass the reduction of inflammatory mediators like leukotrienes, prostaglandins, and thromboxanes, alongside the augmentation of anti-inflammatory and pro-resolving mediators (Rodway *et al*., 2021). Omega-3 FAs and their derivatives operate through G-protein-coupled receptors (GPR32, GPR120/FFA4, ALX) and nuclear receptors (PPARα, PPARγ) to regulate inflammatory responses and uphold liver well-being (Hathaway *et al*., 2020). Additional mechanisms involve the mitigation of reactive oxygen species, adhesion molecule expression, leukocyte-endothelial cell interaction, and the inhibition of the NF-κB pathway (Rogero *et al*., 2020). ALA, along with its derivatives EPA and DHA, has anti-inflammatory properties. These effects have been studied in classic inflammatory cells such as monocytes, macrophages, neutrophils, and endothelial cells. ALA and its metabolites reduce cellular activation, decrease the production of inflammatory cytokines, and increase pro-resolving lipid mediators. These actions contribute to vascular protection and overall cardiovascular health. ALA and other omega-3 PUFA modulate the immune response. They suppress the production of pro-inflammatory cytokines and promote the synthesis of specialized pro-resolving mediators (SPMs). SPMs, such as resolvins and protectins, play a crucial role in resolving inflammation and maintaining tissue homeostasis. ALA-rich diets have been associated with reduced inflammation in various conditions, including cardiovascular disease, arthritis, and neuroinflammation. The anti-inflammatory effects are mediated by multiple mechanisms, including SPMs, inhibition of NF-κB signaling, and modulation of immune cell function.

7.5 Antidiabetic activity

The principal benefit of omega-3 fatty acids (FAs) in individuals diagnosed with type 2 diabetes mellitus is associated with the improvement of their highly atherogenic lipid profile, which may result in decreased insulin resistance. Though certain research studies have not shown substantial changes, others have suggested enhanced insulin sensitivity in individuals treated with omega-3 FAs (Hartweg *et al*., 2008). For example, the diabetes autoimmunity study in the young (DAISY), focusing on children with an elevated risk of developing type 1 diabetes, demonstrated a significantly reduced prevalence of pancreatic islet-cell autoimmunity in those given omega-3 FAs. These encouraging results are presently undergoing further scrutiny to guide the formulation of preventive measures for this significant and incurable medical condition (Norris *et al*., 2007). The effects of á-linolenic acid (ALA), an essential omega-3 polyunsaturated fatty acid (PUFA), on insulin sensitivity. Here are some relevant studies and references (Brown *et al.,* 2019): A systematic review and meta-analysis investigated the effects of increasing ALA and other PUFA on diabetes diagnosis and glucose metabolism. Long-chain omega-3 (EPA and DHA) had little or no effect on diabetes diagnosis or glucose metabolism. ALA-rich diets were associated with improved lipid profiles, reduced inflammation (measured by C-reactive protein), and reduced cardiovascular diseases (CVDs) and all-cause mortality. ALA is metabolized to oxylipins through various pathways, contributing to its beneficial effects. However, the exact contributions of ALA, its oxylipins, or other dietary components remain a topic of investigation (Cambiaggi *et al.,* 2023; Brown *et al.,* 2019). While rodent studies support the insulin-sensitizing effects of n-3 PUFA, human intervention studies have been inconclusive. Observational studies in humans are encouraging, but most intervention trials fail to demonstrate consistent benefits in type 2 diabetes or insulin-resistant non-diabetic individuals Lalia and Lanza*,* 2016). Human studies have explored the effects of omega-3 fatty acids on gene expression related to insulin sensitivity. Although the evidence remains mixed, there is potential for ALA to improve insulin sensitivity (Brown *et al.,* 2019).

7.6 Effect on gastrointestinal disorders

Although the supplementation of omega-3 fatty acids (FAs) in the diet has exhibited potential in ameliorating disease activity and facilitating weight increase among patients suffering from active ulcerative colitis, recent results from a meta-analysis fail to advocate for their regular usage in maintaining remission (Stenson *et al*.,1992). Even though enteric-coated omega-3 FAs capsules were considered safe and efficient for sustaining remission in individuals with crohn's disease in a limited investigation, larger randomised controlled trials did not reveal significant advantages (Feagon *et al*., 2008). While regular intake of omega-3 FA supplements might provide certain benefits for cystic fibrosis patients with minimal adverse reactions, it is impossible to recommend routine supplementation due to inadequate data. Furthermore, even though specific cohort studies have hinted at a potential decrease in the risk of colorectal cancer associated with the consumption of dietary omega-3 FAs from fish, there is a lack of comprehensive large-scale data to confirm this issue (Geelen *et al*., 2007).

7.7 Effect against autism

Autism spectrum disorder (ASD) is a developmental condition that typically emerges during early childhood, often linked to the insufficiency of fragile X mental retardation protein, a genetic component. Regrettably, ASD is a condition that lacks a definitive cure, thus prompting researchers to delve into potential nutritional interventions (Schiavi *et al*., 2022). Studies in epidemiology have brought to light diminished levels of EPA and DHA in the bloodstream of children diagnosed with autism. Examination of these studies implies that the supplementation of omega-3 fatty acids could potentially alleviate symptoms related to autism, such as challenges in speech, difficulties in social interactions, repetitive behaviours, and restricted interests (Von Schacky *et al*., 2021). Recent investigations suggest that the supplementation of omega-3 PUFA in a fragile X messenger ribonucleoprotein 1 knock-out model, designed to imitate autistic characteristics, could reinstate an equilibrium in neuro-inflammatory processes and ameliorate impaired cognitive functions as well as social interactions (Schiavi *et al*., 2022).

7.8 Antiobesity

A comprehensive review discusses the effects of omega-3 fatty acids on obesity, metabolic syndrome, and cardiovascular diseases. ALA contributes to overall health and plays a role in preventing obesity-related metabolic pathologies. Studies have reported lower insulin levels in the presence of marine lipid-derived omega-3 fatty acids. The blood pressure-lowering and anti-inflammatory properties of these fatty acids may provide cardioprotection. Recommendations for omega-3 intake vary based on specific pathologies, and more clinical trials are needed to determine effective dosages (Gray *et al.,* 2013). Omega-3 fatty acids, including á-linolenic acid (ALA), play a significant role in adipose tissue physiology. Let's explore their effects: Studies have shown that omega-3 fatty acids, especially ALA, can reduce the number of macrophages in adipose tissue. Macrophages are immune cells that infiltrate adipose tissue during obesity and contribute to inflammation. Omega-3 fatty acids may modulate macrophage function and reduce their pro-inflammatory activity (Michael Spencer *et al.,* 2013). Omega-3 fatty acids have anti-inflammatory properties. They can suppress the production of pro-inflammatory cytokines in adipose tissue. By reducing inflammation, omega-3s may help maintain healthy adipose tissue function. Some studies suggest omega-3 fatty acids can improve insulin sensitivity in adipose tissue. Enhanced insulin sensitivity is beneficial for overall metabolic health. Omega-3s can influence gene expression in adipocytes. They may affect the expression of genes related to lipid metabolism, inflammation, and adipokine production. In summary, omega-3 fatty acids have multifaceted effects on adipose tissue, impacting inflammation, immune response, and metabolic health.

7.9 Effect against multiple sclerosis

The etiology of multiple sclerosis (MS) is predominantly ascribed to persistent inflammation within the central nervous system (CNS), which culminates in demyelination and the gradual onset of impairments in afflicted individuals. Although, the efficacy of EPA and DHA in ameliorating the autoimmune reaction in MS is constrained, it introduces novel avenues for therapeutic interventions. Recent investigations endeavoured to amplify the production of omega-3 fatty acids in MS murine models by upregulating desaturase expression, leading to heightened remyelination, with a specific emphasis on EPA (Siegert *et al*., 2017). Furthermore, a combined investigation incorporating omega-3 and omega-6 fatty acids alongside various vitamins (A and E) exhibited the capacity to impede the progression of disability in MS. Subsequently, a comparable formulation was subjected to evaluation as an adjunct therapeutic approach in parkinson's disease (PD) (Pantzaris *et al*., 2021).

7.10 Effect against dry eye syndrome

Dry eye syndrome (DES) arises from inadequate tear production or drainage, leading to ocular discomfort and inflammation. Studies have suggested that omega-3 fatty acids (FAs) such as EPA and DHA are crucial for maintaining tear equilibrium and reducing eye inflammation (Sharma and Hindman, 2014). Nonetheless, the efficacy of omega-3 FAs in DES treatment remains uncertain. Several clinical trials have produced conflicting outcomes regarding the benefits of omega-3 FAs for DES. While some research has demonstrated enhancements in parameters like the ocular surface disease index (OSDI) and reduced inflammation, others have shown no notable alleviation of DES symptoms (Singh *et al*., 2022). The impact of factors like the type and dosage of supplements used can influence the effectiveness of omega-3 FAs (Ng *et al*., 2022). Discrepancies in the bioavailability of oral supplements, including re-esterified omega-3 FAs, may affect their capability to mitigate DES symptoms. Further investigation is required on variants such as phospholipid EPA and DHA. The contribution of dietary sources rich in omega-3 FAs, especially those abundant in DHA, has not received sufficient attention in research, potentially impacting outcomes in DES therapy (Ng *et al*., 2022). Uncertainty surrounds the optimal dosage of omega-3 FAs, with divergent findings from various studies, including observations of gastrointestinal disturbances at higher doses. Subsequent inquiries could consider exploring alternative administration strategies, such as topical solutions like novatears + omega-3, which have exhibited the potential to ameliorate DES symptoms (Jacobi *et al*., 2022). In conclusion, additional research is imperative to elucidate the significance of omega-3 FAs in DES management and to address discrepancies in clinical observations.

8. Applications of omega-3 fatty acids from plant sources in food technology

Food fortification and encapsulation for omega-3 fatty acids strategies play a crucial role in enhancing the nutritional quality of food products (Yadav *et al.,* 2020). Essential fatty acids (EFAs), particularly omega-3s, are actively considered for fortification by food and beverage companies. Omega-3s impart known health benefits and value addition to food products. To increase the omega-3 content in foods, techniques such as fortification and encapsulation are employed. Fortification involves adding omega-3s to food products such as yoghurt, juices, grains, nuts, and baby food. Bioengineered plants and algae aquaculture is a new promising area. Microalgae serve as primary sources of very long-chain PUFA (VLC-PUFA). Algal oil or algal tablets provide direct or indirect omega-3 intake. Algae aquaculture yields high LC PUFA-containing fish oils, potentially conserving fish stocks (Walker *et al.,* 2015). Fortified foods address multiple deficiencies due to poor-quality diets. They benefit growing children and women of fertile age. Widely distributed and consumed fortified foods can improve the nutritional status of both poor and wealthy populations. Fortification requires no changes in existing food patterns or individual compliance (Panse and Phalke, 2016). Microencapsulation involves enclosing omega-3-rich fish oils within food-grade delivery systems. This method protects omega-3s from oxidation, enhances stability, and ensures controlled release. Microencapsulated omega-3s can be added to various food products, contributing to their health benefits. Researchers have developed novel stabilized emulsified formulations containing omega-3 fatty acids and micronutrients. These formulations can be readily used for food fortification. They offer a practical approach to enhancing the nutritional quality of food products (Jagtap, 2021). Food fortification and encapsulation provide innovative ways to incorporate omega-3s into our diets, promoting health and well-being.

The encapsulation and protection of omega-3-rich fish oils using food-grade delivery systems are reviewed (Venugopalan *et al.,* 2021). Omega-3 fatty acids help in reducing inflammation and are associated with lower risks of cardiovascular diseases, diabetes, arthritis, and ulcerative colitis. These fatty acids are particularly high in biological activity. Functional food products are fortified with omega-3 PUFA due to their potential nutritional and health benefits. PUFA face challenges due to their low water solubility, rapid oxidation and variable bioavailability. Encapsulation involves incorporating omega-3 oils into well-designed colloidal particles made from food-grade ingredients. Examples of colloidal particles include liposomes, emulsion droplets, nanostructured lipid carriers and microgels. It has numerous benefits such as protecting against oxidation, enhancing stability, controlling the release of bioactive components and facilitating handling, storage, and shelf life (Chang and Nickerson, 2018).

Omega-3 fatty acids due to their limited stability in response to environmental and processing factors, there is growing interest in microencapsulating them to enhance stability (Feizollahi *et al.,* 2018; Perez-Palacios *et al.,* 2022). Microencapsulation involves entrapping labile compounds (the core) within a protective shell (the wall). Wall materials and procedures significantly impact the quality of microencapsulates. Microcapsules are analyzed for size, microencapsulation efficiency, morphology, moisture content, *in vitro* digestion properties, flowing properties and yield percentage. While microencapsulation prevents the loss of omega-3 fatty acids during storage, challenges like changes in texture and colour (*e.g.,* in bread) need consideration. Efforts should focus on maximizing stability and developing cost-effective methods for extensive use in the food industry. While Goyal *et al.* (2016) reported fortification of *dahi* (Indian yoghurt) with omega-3 fatty acids using microencapsulated flaxseed oil microcapsules. Research on stabilized omega-3 fatty acids and micronutrient-emulsified formulations designed for food fortification revealed several interesting facts. Jagtap *et al.* (2021) provide valuable insights into the development, characterization, and potential applications of such formulations. This study aimed to create a novel stabilized emulsified formulation containing both omega-3 fatty acids and micronutrients. These formulations are intended for use in food fortification, enhancing the nutritional quality of food products. The researchers developed the formulation considering human requirements for omega-3 fatty acids and recommended daily allowances of essential micronutrients. The formulation was characterized for various parameters, including physical appearance, pH, specific gravity, colour measurement, fatty acid analysis, oxidative stability assessment, rheological evaluation, particle size, microscopic analysis and stability tests. The stabilized formulations provided 500-1300 mg of alpha-linolenic acid (ALA) per serving. Oxidative stability assessment showed stability comparable to raw flaxseed oil. The rheological evaluation indicated a non-newtonian system with shear thickening behaviour. Microscopic analysis confirmed the stable and homogeneous nature of the formulation. Acute oral toxicity study demonstrated safety. *In vivo,* a bioavailability study confirmed better bioavailability of omega-3 fatty acids metabolites (eicosapentaenoic and docosahexaenoic acids) compared to flax oil and similar bioavailability to fish oil. These stabilized emulsified formulations offer a practical approach to fortifying foods with essential omega-3 fatty acids and micronutrients. They can contribute to improving overall health and well-being through fortified food products (Jagtap *et al.,* 2021).

9. Bioengineered plants with omega-3 fatty acids

Marine fish are major dietary sources of long-chain omega-3s. However, increasing fish oil demand puts pressure on declining marine stocks. Sustainable alternatives are needed to meet recommended daily intake levels. Recent advancements in transgenic plant technology offer exciting possibilities (Lakra *et al.,* 2019). Plants can be genetically modified to produce health-beneficial molecules. These include multicomponent botanical drugs, plant-derived pharmaceuticals, functional foods, dietary supplements, and recombinant proteins. Bioengineered plants can complement conventional pharmaceuticals and enhance agriculture. Microalgae serve as a primary source of very long-chain PUFA (VLC-PUFA). Algal oil or algal tablets can provide omega-3s directly or indirectly. Algae aquaculture may also yield high LC-PUFA containing fish oils, potentially saving fish stocks from depletion (Amjad Khan *et al.,* 2017). Bioengineered plants hold promise as a sustainable and efficient source of omega-3 fatty acids. By harnessing genetic modifications, we can enhance human health while minimizing environmental impact.

10. Industrial applications of omega-3 fatty acids

Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have found significant industrial applications.

Figure 5: Percent share of industrial applications of omega-3 fatty acids.

10.1 Dietary supplements

Approximately 60% of the omega-3 oils rich in DHA and EPA are used for dietary supplements. These supplements are consumed by individuals who may not get enough omega-3 from their diets. These supplements come in many different forms, from regular fish oil to mammalian oil. Omega-3 fatty acids are very important for health (Nigam *et al.,* 2018). The best way to ensure an adequate intake of omega-3s is by consuming whole foods rich in these fatty acids, such as fatty fish.

10.2 Functional foods

About 20% of omega-3 oils are used in functional foods. These are foods fortified with omega-3 fatty acids to provide health benefits beyond basic nutrition. Omega-3-enriched foods are quite popular, especially beverages, and there are large areas of growth for omega-3 products in countries with both small and large existing omega-3 markets. Fortification and encapsulation are the most common methods used for the addition of omega-3 fatty acids to food products such as yoghurt, juices, grains, nuts, fresh produce, oil, and baby food (Yadav *et al.,* 2020).

10.3 Animal feed

Around 7% of omega-3 oils are used in animal feed (Hamilton *et al.,* 2015). This is particularly important in aquaculture, where fish are often fed diets rich in omega-3 to increase their omega-3 content.

10.4 Pharmaceuticals

Omega-3 fatty acids are also used in the pharmaceutical industry, accounting for about 6% of the total usage (Hamilton *et al.,* 2015). They are used in medications for conditions like high triglyceride levels.

10.5 Infant and clinical nutrition

The remainder of omega-3 oils are used in infant and clinical nutrition. For instance, infant formulas are often fortified with DHA to support brain development. It can help the immune system by protecting the child against allergies in early childhood and it is good for bone health. Omega-3 fatty acids are particularly important for the formation of a fatty sheath around nerves and for the development of vision during the perinatal period (Devarshi *et al.,* 2019). The deficiency or imbalance of LC-PUFA has been associated with poorer child development reflected in domains such as language ability, communication, gross motor and fine motor skills, problem-solving, and personal/social and verbal fluency.

10.6 Biotechnology

Biotechnology is being used to produce omega-3 fatty acids sustainably. For example, the marine diatom *Phaeodactylum tricornutum* has been genetically modified to accumulate up to 30% of the omega-3 long-chain polyunsaturated fatty acid (LC-PUFA) eicosapentaenoic acid (EPA), making it a good source for the industrial production of EPA (Hamilton *et al.,* 2015).

11. Future thrust of plant-based sources of omega-3 fatty acids

The future of plant-based sources of omega-3 fatty acids holds exciting possibilities. As we strive for sustainability, health, and innovation, here are some key thrusts.

11.1 Sustainable oilseed crops

Genetically engineered oilseed crops are approved for large-scale cultivation. These crops can meet the increasing market demand for aquaculture and human nutrition. Examples include omega-3 LC-PUFA producing oilseed crops.

11.2 Bioavailability and conversion enhancement

Researchers continue to explore ways to improve the bioavailability of plant-based omega-3s. Strategies include optimizing conversion efficiency from ALA to EPA and DHA. Innovations in food processing and formulation can enhance absorption.

11.3 Personalization and nutritional deficiency mitigation

Tailoring omega-3 recommendations based on individual needs. Addressing potential nutritional deficiencies through targeted supplementation. Customized approaches for optimal health outcomes are to be focussed.

11.4 Innovative technologies and start-ups

Companies like Örlö offer plant-based omega-3 solutions that are ready with promising technologies. Leveraging technology to produce sustainable, land-efficient sources is needed.

The future involves a blend of science, sustainability, and consumer demand, ensuring that plant-based omega-3s remain accessible and beneficial for all.

12. Future thrust of omega-3 fatty acids for human health

Omega-3 fatty acids have been extensively studied for their health benefits and are known to be crucial for human health. Here are some potential future directions for the study and application of omega-3 fatty acids.

12.1 Depression and anxiety

Omega-3 supplements may help treat and prevent depression and anxiety. Future research could focus on understanding the mechanisms behind this benefit and optimizing the use of omega-3s in mental health treatment.

12.2 Eye health

Omega-3 fatty acids, particularly DHA, are essential for eye health. Future studies could explore how omega-3 supplementation could help prevent age-related macular degeneration and other vision problems.

12.3 Brain health during pregnancy and early life

Omega-3s are crucial for brain growth and development in infants. Future research could focus on determining the optimal intake of omega-3s during pregnancy and early life to promote cognitive development and reduce the risk of developmental delay.

12.4 Heart health

Omega-3 fatty acids have been tied to numerous benefits for heart health. Future research could focus on understanding the specific roles of different types of omega-3s (EPA, DHA) in heart health and determining the optimal intake for cardiovascular disease prevention.

12.5 Chronic diseases

Higher intakes of omega-3 PUFA, especially EPA and DHA, are associated with a lower incidence of chronic diseases characterized by elevated inflammation, including cardiovascular diseases. Future research could focus on understanding the molecular and cellular actions of EPA and DHA.

12.6 COVID-19 therapy

In addition to their antioxidant and anti-inflammatory roles, omega-3 fatty acids are considered to regulate platelet homeostasis and lower the risk of thrombosis, which together indicate their potential use in COVID-19 therapy.

12.7 Sustainable alternatives

As the demand for omega-3 fatty acids increases, future research will need to explore sustainable alternatives to fish-derived omega-3 fatty acids.

These are just a few of the potential future directions for omega-3 research. As our understanding of these essential nutrients continues to grow, we can expect to see even more applications for human health in the future.

13. Conclusion

In conclusion, omega-3 fatty acids; namely, ALA, EPA, and DHA, are essential nutrients for human health. They are obtained from a variety of animal and plant sources, with fish and algae being rich in EPA and DHA, and flaxseeds, walnuts, and edible seeds being high in ALA. The fortification of food with omega-3 fatty acids is a growing trend that aims to enhance the nutritional quality of food and provide health benefits. However, despite these efforts, omega-3 fatty acid deficiency remains a concern, leading to various health issues. The applications of omega-3 fatty acids are vast, influencing numerous biological systems and playing a crucial role in the function of cell receptors. Therefore, ensuring adequate intake of omega-3 fatty acids, whether through diet or fortification, is of paramount importance. Future research should focus on understanding the implications of omega-3 fatty acid deficiency and determining the optimal intake levels. This comprehensive review highlights the importance of omega-3 fatty acids and emphasizes the need for further exploration in this field.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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