



# Omega-3: Nutrition and Application Insight

## Executive Summary

Aug-2023

Omega-3 long-chain polyunsaturated fatty acids (PUFAs) have numerous positive health benefits and are among the most extensively studied nutrients. However, in many regions worldwide, there remains a substantial proportion of the adult population that does not consume adequate levels of Omega-3s. This deficiency could have significant implications for public health.

This white paper cites research and market data to highlight the

crucial role of Omega-3 in **cardiovascular health, Alzheimer's disease, and its anti-inflammatory and immune-modulating functions.**

Additionally, this article explores the applications of CABIO's Omega-3 in prenatal nutrition, dietary supplementation, and in food and beverage solutions.

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## Introduction

The exploration of Omega-3 fatty acids (also known as Omega-3s) dates back to the early 20th century when Danish biochemist Hans Christian Hansen discovered that fish oil was abundant in fatty acids that promoted human health. Over the ensuing decades, scientists conducted extensive research on various fatty acids. It was not until the latter half of the 20th century that a significant amount of research confirmed Omega-3s as a healthy human food. These studies focused primarily on epidemiology, animal research, clinical trials, and mechanisms at the cellular and molecular levels.

It took scientists a considerable amount of time to discover the importance of Omega-3s for the human heart, brain, eyes, and immune system, as well as their potential for treating inflammation and cognitive functions of the brain. These findings have led people to delve deeper into the world of Omega-3s, emphasizing the importance of consuming adequate amounts.

## There are three types of important omega-3 fatty acids:

### ALA

The primary source of this substance is from plants grown on land. Perilla and flaxseeds are two types of plant seeds that are rich in alpha-linolenic acids. The ALA content in flaxseed and perilla seed oils is between 50% to 60%, whereas other oils like walnut, soybean, and canola oil contain around 10%. ALA plays a crucial role in regulating blood lipid levels, improving memory and learning functions, and controlling inflammation. It can help manage dyslipidemia in patients with metabolic syndrome by reducing LDL levels and increasing HDL levels. Moreover, consuming omega-3 fatty acids is linked to a lower risk of cardiovascular disease, particularly sudden cardiac death.

### EPA

High-fat abyssal fishes are the primary source of EPA. Some planktonic algae also contain high levels of this compound. EPA is known to have various physiological benefits, including anti-platelet agglutination, tumor growth inhibition, and anti-inflammatory properties. Additionally, it can reduce platelet aggregation, dilate blood vessels, lower blood pressure, and decrease cholesterol and TG levels. This leads to an improvement in blood lipid profile and blood pressure in patients with metabolic syndrome while preventing the occurrence of atherosclerosis, myocardial infarction, and cerebral infarction.

### DHA

DHA is a vital component found in deep-sea fishes and seaweeds in nature. It is an important element for the human brain and retina, serving multiple physiological functions, including enhancing brain development, preventing cognitive decline, regulating blood lipid levels, combating inflammation, and protecting eyesight. When combined with EPA, DHA can also help improve dyslipidemia and hypertension in patients with metabolic syndrome. This combination can reduce TG levels, blood pressure, platelet aggregation, and inflammation, while increasing HDL levels. Consuming a diet rich in DHA and EPA can also lead to a lower mortality rate associated with cardiovascular diseases.

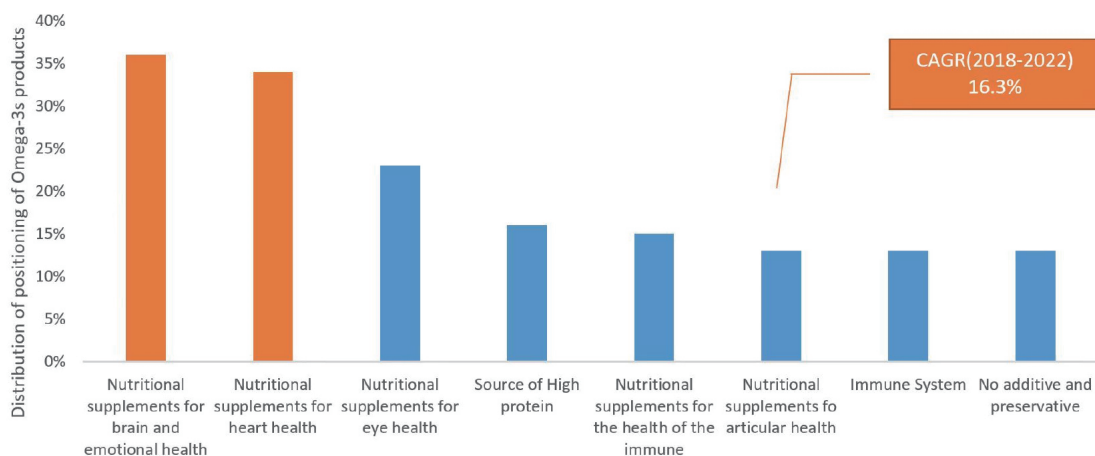
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## Omega-3s Consumer Insights and Demand Analysis

As people become increasingly aware of the benefits of Omega-3s on cardiovascular, cerebrovascular, articular, and ocular health, the demand for Omega-3 products is on the rise. This heightened consciousness about health is making consumers pay greater attention to the positive effects of Omega-3s.

### Globally, brain health, emotional health and heart health are the most common focus of Omega-3s-containing products

(Global distribution of positioning of new Omega-3s products by function (2018-2022))

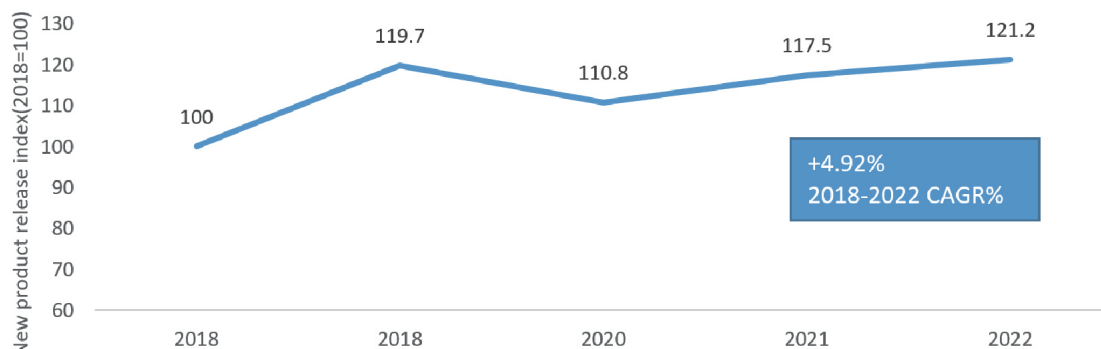


Source: Innova Market Insight

Consumers have seen the introduction of several new and innovative products in the market. For instance, plant-sourced Omega-3s products like linseed oil, algal oil, among others, are becoming increasingly popular as substitutes for traditional fish oil supplements. Such novel products cater to the needs and preferences of different consumer groups, thereby expanding the market.

### The trend in global release of new Omega-3s products has grown since the 2020 drop ends

(The trend in global release of new Omega-3s products(2018-2022))



Source: Innova Market Insight

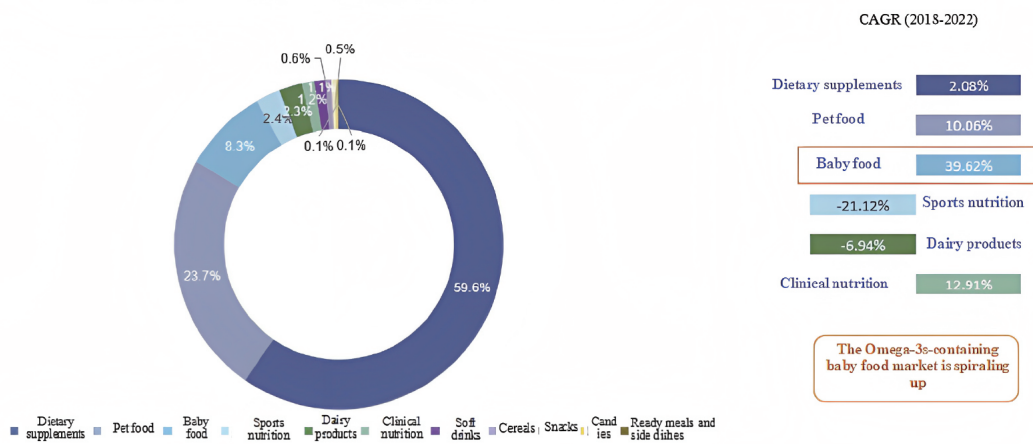
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The global market for Omega-3s in 2022 was worth USD 2.43 billion. Experts predict a Compound Annual Growth Rate (CAGR) of up to 7.8% from 2023 to 2030, which is higher than most other nutritional products. Food and drink companies are increasingly focusing on the functionality of their products by adding Omega-3s to them. This makes it easier for consumers to get the necessary nutritional supplements from their everyday diets.

Consumers have certain preferences when it comes to Omega-3s. They prefer products that are easy to carry and consume, such as supplements and soft gels made from fish oil. Quality and purity are also important to them, as they tend to choose certified products that have been proven to be effective. Furthermore, they are concerned about the source of the products and their sustainability. For instance, they prefer Omega-3s that come from plants or are sustainably sourced through fishing.

## New Omega-3s products are mostly dietary supplements at the global level

Distribution of newly released Omega-3s-containing products at the global level (2018-2022)



Source: Innova Market Insights

Regarding consumption patterns, consumers in certain markets such as Europe and North America exhibit a greater willingness to embrace Omega-3 products and tend to favor high-end options. However, in some developed countries, there is a lower demand due to a lack of awareness about the benefits of Omega-3.



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## N-3 polyunsaturated fatty acids and cardiovascular health

With the improvement of the socioeconomic level and the deepening of globalization and urbanization, people's dietary habits and other lifestyles have undergone significant changes. In addition, as the world is now witnessing an accelerated aging process, there is growing evidence that non-communicable diseases, especially cardiovascular diseases (CVD), have emerged as significant contributors to the global burden of disease [1-2]. The Global Burden of Disease Study 2019 (GBD) shows that CVD has caused a total of 18,562,100 deaths worldwide in 2019 and has become the number one cause of human death globally.

It is well known that the pathological basis for the occurrence of cardiovascular disease is atherosclerosis, and the risk factors for the occurrence of atherosclerosis are related to obesity, hyperlipidemia (high triglycerides, high cholesterol, high LDL cholesterol, etc.), blood viscosity, etc. Many individuals commonly regulate their dietary intake of fat and cholesterol to reduce blood chole-

sterol and LDL cholesterol levels. However, it is often observed that high triglyceride levels and LDL cholesterol coexist, posing additional risk factors for the development of atherosclerosis [2]

The role of different types of dietary fatty acids for chronic diseases has long sparked interest. Dietary fats consist of saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), and polyunsaturated fatty acids (PUFAs), with the PUFAs primarily being composed of n-3 PUFAs and n-6 PUFAs. The elevated ratio of n-6 PUFA to n-3 PUFA in modern human diets has been linked to numerous chronic diseases, including hyperlipidemia, hypertension, atherosclerosis, obesity, cardiovascular and renal diseases, inflammatory disorders, and more.

## Physiological functions of n-3 PUFAs

Three major food-derived n-3 PUFAs include alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). EPA and DHA are mainly found in seafood and vegetable oils, such as deep-sea fish oil and algal oil. ALA is the metabolic precursor of EPA and DHA in the human body, which is only found in vegetable oils such as flaxseed oil, hemp seed oil, and perilla seed oil.

It has been demonstrated that the intake of three n-3 PUFAs, i.e. ALA, EPA and DHA, has a positive effect on the prevention and treatment of cardiovascular diseases.

The structural characteristics of n-3 PUFAs and their biological properties allow them to play different roles in membrane structure and function, tissue metabolism, and genetic regulation. Experiments have demonstrated that the effects of n-3 PUFAs include regulating the membrane structures and functions of cells and organelles, ion channels and cellular electrophysiology, nuclear receptors, transcription factors, and arachidonic acid (AA)-derived eicosanoids.

Because of their long hydrocarbon chains and multiple double bonds, ALA, EPA, and DHA all modify the properties of lipid membranes. A clinical study has confirmed that high doses of ALA (with 5.2% of energy derived from ALA) have a significant and effective impact on markers of endothelial cell activation, such as VCAM-1 and ICAM-1. In cultured mouse lymphocytes, DHA can alter the distribution and size of lipid rafts and specify the structural domains of lipids in the cell membrane. In cultured

human T cells, EPA can also affect lipid raft composition and function, and n-3 PUFAs can regulate ion channels. In the HEK293 cell model, ALA, EPA, and DHA can inhibit the activity of Na-Ca<sub>2</sub> exchangers. Many ion channels are concentrated in lipid rafts, and the physical properties of membranes and lipid rafts can modulate ion channel activity. DHA can inhibit the sensitivity of kainate receptors in neuronal ion channels, as well as modify membrane protein function through close-range interactions.

Long-chain n-3 PUFAs are natural ligands for several nuclear receptors that regulate gene expression, including peroxisome proliferator-activated receptor (PPAR), hepatocyte nuclear factor (HNF), liver x receptor (LXR), and retinoid x receptor (RXR), and also alter the expression of certain transcription factors such as sterol regulatory element binding protein (SREBP) and carbohydrate response element binding protein (CREBP). These gene expressions contribute to the physiological effects of n-3 PUFAs on lipid metabolism.

N-3 PUFAs can regulate the metabolism of AA-derived eicosanoids. Research has demonstrated that depletion of n-3 PUFAs can reduce the synthesis of some eicosanoids in cells in vitro, and these substances like PGE<sub>2</sub>, LTB<sub>4</sub>, and thromboxane B<sub>2</sub> (ThromboxaneB<sub>2</sub>), are "pro-inflammatory cytokines" that exacerbate inflammation. This effect is due to the fact that n-3 PUFAs can replace AA to regulate the gene of eicosanoid synthesis and compete with AA for its metabolic enzymes.

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## • Possible mechanisms and the cardiovascular system's protective effects of n-3 PUFAs [4-6].

### Regulation of blood fats

N-3 PUFAs reduce blood triglycerides (TG) and very low-density lipoprotein cholesterol (VLDL-c) while mildly increasing high-density lipoprotein cholesterol (HDL-C). How n-3 PUFAs regulate blood fats are unknown, and the mechanisms are probably like this: n-3 PUFAs inhibit cholesterol synthesis and uptake, and downregulate hepatocyte LDL receptor expression; n-3 PUFAs have a high affinity for acetyl coenzyme A - a cholesterol acetyltransferase - and thus interfere with the esterification and release of other fatty acids to reduce TG production; n-3 PUFAs preferentially synthesize phospholipids via the phospholipid bypass,

whereas other fatty acids prefer the TG pathway for TG synthesis; n-3 PUFAs heighten the oxidation of fatty acids by activating PPAR to boost fatty acid metabolism; n-3 PUFAs increase lipoprotein lipase (LPL) activity, decrease the secretion of TG-rich VLDL-C particles, and promote TG clearance; n-3 PUFAs accelerate the conversion of VLDL to LDL and increase large granular LDL-Cs that are less likely to cause atherosclerosis; n-3 PUFAs can inhibit endogenous HMG-CoA reductase and cholesteryl ester transporter protein (CETP).

### Anti-atherosclerosis

Clinical studies have demonstrated that the supplementation of n-3 PUFAs in patients with coronary artery disease can result in the reduction of coronary plaque size, a decrease in intraplaque macrophages, the facilitation of IV-type fibrous cap formation that can resist plaque rupture, and a decrease in the formation of thin V-type inflammatory caps. After correcting for smoking, diabetes, blood lipids, the pre-existing history of myocardial infarction, and other factors, Harris found that plasma EPA and DHA levels were independent risk factors for the development of acute coronary syndromes. The inhibitory effects of n-3 PUFAs on atherosclerosis may be attributed to their ability to regulate blood lipid levels, exhibit anticoagulant properties, inhibit platelet aggregation, reduce inflammatory responses, improve

endothelial cell function, decrease synthesis of growth factors, and inhibit smooth muscle cell proliferation. In addition, DHA activates PPAR and inhibits the progression of atherosclerosis through mechanisms such as improving insulin resistance and reducing the oxidative stress response. Recent studies suggest that endothelial cell damage in patients with cardiovascular disease is associated with cellular functional aging and that telomerase is involved in the process of cellular senescence. Several studies have found that telomerase length shortening plays an important role in atherosclerosis. n-3 PUFAs regulate the telomerase length to slow down the progression of AS by inhibiting telomerase retroelement activity.

### Antiplatelet and anti-inflammation

N-3 PUFAs compete with arachidonic acids for cyclooxygenase and lipoxygenase, resulting in decreased production of prostaglandin I<sub>2</sub>, thromboxane A<sub>2</sub>, and leukotrienes and increased production of prostaglandin I<sub>3</sub> and thromboxane A<sub>3</sub>, so as to inhibit platelet aggregation, lower blood viscosity, and relax blood vessels. Some studies have shown that n-6 PUFAs mainly produce prostaglandin I<sub>2</sub>, thromboxane A<sub>2</sub>, leukotriene B<sub>4</sub>, and other bioactive substances with pro-inflammatory and thrombogenic effects via the arachidonic acid pathway; n-3 PUFAs compete with n-6 PUFAs, and an imbalance in the ratio of the two can lead to thrombosis. Follow-up studies on health suggest that a high intake of n-6 PUFAs does not affect the cardiovascular protective effects of n-3 PUFAs, and increasing the intake of n-3

PUFAs is more important than maintaining an appropriate n-6 PUFAs/n-3 PUFAs ratio. N-3 PUFAs metabolism in vivo can produce anti-inflammatory mediators such as lipoxin, properdin, and neuroprotective factor D1 that can regulate the inflammatory response. Studies have confirmed that n-3 PUFAs can stimulate endothelial cells to produce nitric oxide and nitroalkene derivatives and improve endothelial function while inhibiting cytokine synthesis, decreasing the expression of E-selectin, cell adhesion molecule-1, and vascular cell adhesion molecule-1, and reducing the adhesion of monocytes and vascular endothelium.

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## Antiarrhythmia

Calo et al. found that administration of 2.0 g/d of n-3 PUFAs to patients after coronary artery bypass grafting significantly reduced the incidence of postoperative atrial fibrillation. Dhein et al. found through research that the perfusion of EPA and DHA to isolated rabbit hearts brought about negative dromotropic action. Ligation of the left main coronary artery in dogs resulted in 60% fatal arrhythmias, and earlier use of n-3 PUFAs clearly reduced the incidence of malignant arrhythmias. A meta-analysis of animal experiments shows that n-3 PUFAs decrease cardiac events that cause deaths due to malignant arrhythmias such as ventricular tachycardia and ventricular fibrillation. A recent meta-analysis of clinical studies shows that intake of fish oil has no significant antiarrhythmic effect, although it reduces death from cardiac events. During a FAAT study, 402 patients wearing implantable cardioverter defibrillators (ICDs) were randomly given 2.6 g/d of n-3 PUFAs or placebos, with the former significantly reducing the time of first ICD discharge, which was more beneficial to patients with coronary artery disease. For a SOFA study, 546 patients with ICD were enrolled and given 2.0 g/d of fish oil or placebo, and the results showed no significantly

difference in the primary endpoint, that is, fish oil could not reduce the frequency of sustained ventricular tachycardia and ventricular fibrillation episodes in patients wearing an ICD for new-onset sustained ventricular arrhythmias; however, there was a trend toward a therapeutic benefit in the subgroup that had experienced myocardial infarction, with 28% of the patients given fish oil experiencing life-threatening arrhythmias or death compared with 35% in the placebo group. N-3 PUFAs antiarrhythmic effects are not known by mechanism and may be associated with the ionic channel on the membrane that regulates cardiomyocytes, particularly voltage-gated Na<sup>+</sup> channels and L-type Ca<sup>2+</sup> channels. N-3 PUFAs have the ability to prolong the refractory period of action potential, increase the action potential threshold induced by depolarizing currents, decrease membrane potential excitability; reduce intracellular free calcium levels in the myocardium to prevent calcium overload, and lessen oxidative stress during myocardial ischemia-reperfusion, thereby decreasing reperfusion arrhythmias.

## Lowering blood pressure and decreasing heart rate

A meta-analysis of 36 trials shows that intake of a moderate dose (3.7 g/d) of fish oil lowers systolic pressure by 2.1 mm Hg (1 mm Hg = 0.133 kPa) and diastolic pressure by 1.6 mm Hg. N-3 PUFAs may exert their hypotensive effects through the following mechanisms: affecting the formation of prostaglandin and mediating vasodilation; increasing the proportion of EPA and DHA in membrane phospholipids to enhance systemic arterial compliance, decreasing responsiveness to vasoconstrictive substances, and improve endothelial function; and affecting the renin-angiotensin system to drop blood pressure. Another meta-analysis of 30 randomized, double-blind, placebo-controlled trials shows that fish oil slows down the heart rate by 1.6 beats/min compared with the placebo group. O'Keefe et al. found that n-3

PUFAs (EPA+DHA, 0.8g/d) significantly reduced the heart rate and improved heart rate variability. N-3 PUFAs may ease down the heart rate by a mechanism related to its function of increasing the acetylcholine level in the brain, heightening parasympathetic action, and relatively weakening sympathetic action.

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## N-3 fatty acids and Alzheimer's disease

Memory turns into quicksand, loved ones become strangers, the mind is like a child, and the world reverts to zero. According to data, one third of China's elderly population over 85 years old suffers from Alzheimer's disease (AD), commonly known as "dementia". For people with AD, it is a phantom process; for their loved ones, it is a near-irreversible challenge that requires extra care.

### ■ The incidence of Alzheimer's disease is on the rise, highlighting the importance of prevention measures

Alzheimer's disease was first described in 1906 by Alzheimer, a German psychiatrist and neuropathologist, after whom the disease is named. AD occurs in people over 65 years old, but there are rare cases of early-onset AD.

AD is a common neurodegenerative disorder of the elderly that is characterized by memory loss and recognition impairment, along with a variety of neurological symptoms and behavior disorders. The most common symptom in the early stages of the disease is the inability to remember recent events. As the disease progresses, symptoms will include loss of long-term memory, irritability, emotional instability, and gradual loss of physical function, and lead to death in the end.

The pathogenesis of AD is not clear, and there are several hypotheses. The more recognized ones are theories of cytoskeletal alteration,  $\beta$ -amyloid, central neurotransmitter metabolism disorder, gene mutation, free radical loss, calcium metabolism disorder, etc. It is complex and may be the result of multiple factors.

There is growing evidence that good nutrition (e.g. fruit, vegetable, fish) and healthy dietary patterns are important for improving cognitive performance and are associated with reduction of AD risks. Importantly, advances in science and technology have improved our ability to fully understand the unique neuroprotective mechanisms of specific nutrients that may drive these positive outcomes. Some dietary components selectively accumulate in the brain and perform important physiological functions.

Current treatments for Alzheimer's disease only help to alleviate the symptoms of the disease; there are no treatments to stop or reverse the course of the disease. Traditional therapeutic drugs such as acetylcholinesterase blockers and neuron protectors are often supplemented by other symptomatic medications such as sleeping pills, antipsychotics, and antidepressants. As research into Alzheimer's disease has intensified, the use of various nutritional components to aid in the prevention and treatment of the disease has been increasingly studied [5].

### ■ RCT: The synergistic benefits of n-3 fatty acids, carotenoids, and vitamin E have been shown to improve memory in the elderly population

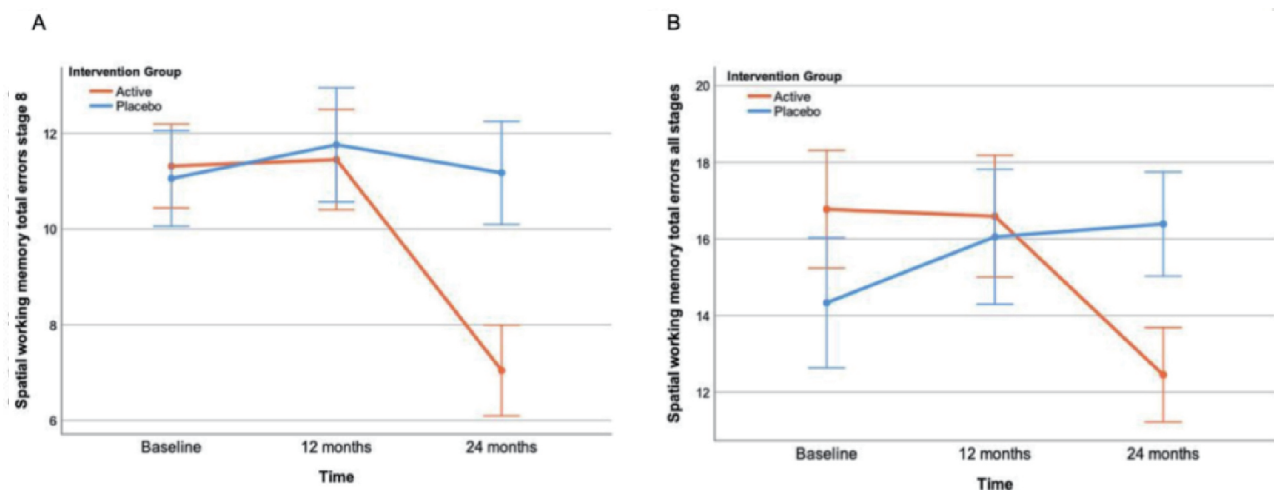
A cognitive impairment study (CARES) published by Clinical Nutrition investigated the combined effects of n-3 FA, carotenoids and vitamin E supplements on cognitive performance in older adults, assessing whether they had the ability to improve memory <sup>[4]</sup>. Researchers asked healthy older adults aged 65 and above to take 1 g of fish oil (containing 430 mg of docosahexaenoic acid and 90 mg of eicosapentaenoic acid), 22 mg of carotenoids (10 mg of lutein, 10 mg of endoxanthin, and 2 mg of zeaxanthin), and 15 mg of vitamin E daily for treatment, while a similar cohort of older patients was recruited for placebo-controlled treatment.



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The results show that after 24 months of supplementation with relevant nutritional agents, patients in the treatment group performed better than the placebo group in terms of memory capacity compared with individuals receiving a placebo (n=30; aged 69.77±3.74; 70% females), although the cognitive load in working memory tasks increased. Statistically significant improvements in tissue carotenoid concentrations, serum lutein carotenoid concentrations, and plasma n-3 FA concentrations were also observed in the treatment group compared with the placebo. Therefore, additional supplementation with n-3 fatty acids, carotenoids, and vitamin E is of benefit.

## Line chart of changes in spatial working memory errors over 24 months



This study demonstrates improvements in working memory after 24 months of supplementation with n-3 fatty acids, lutein carotenoids, and vitamin E in cognitively healthy older adults. These results support a biologically plausible theory that these nutrients work in concert and improve cognitive performance in a dose-dependent manner. These findings suggest the importance of nutritional enrichment in improving cognition and enabling older adults to continue to live independently and highlight how the combination of n-3 fatty acids and lutein carotenoids may prove beneficial in reducing cognitive decline and/or delaying the onset of Alzheimer's disease in later life.

## • DHA in the prevention and supporting treatment of Alzheimer's disease

Several epidemiological studies have revealed a link between DHA and Alzheimer's disease. Kalmijn et al. first reported that fish intake reduced the risk of Alzheimer's disease in 1997 [6]. High saturated fatty acid and cholesterol intakes as well as low unsaturated fatty acid intake increase the risk of cardiovascular disease, which is associated with AD. In this study, 5,386 participants aged 55 and above were screened, and their dietary habits were evaluated using a semiquantitative food frequency questionnaire. Then, follow-up visit was performed 2.1 years later, and patients with AD were screened using a three-step principle

including clinical examination, and the risk of AD was assessed by logistic regression analysis. Ultimately, by correcting for age, sex, education, and energy intake, it is found that participants who consumed fish had a negative association with the incidence of general dementia (RR=0.495%; CI=0.2-0.9), and an even more significant negative association with the risk of AD (RR=0.395%; CI=0.1-0.9); in contrast, the incidence of general dementia was significantly higher in participants who frequently took in saturated fatty acids and cholesterol.

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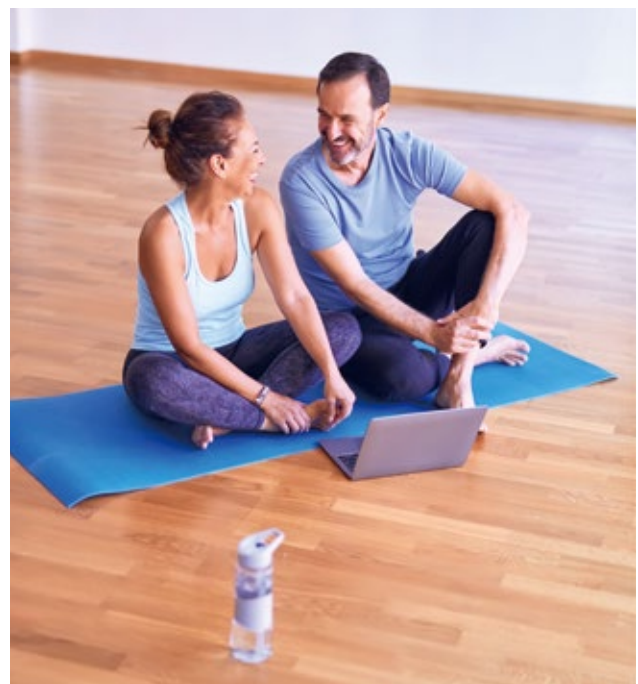
The association between high-fat diet and dementia may be confounded by other factors, such as educational background, smoking, and alcohol abuse, and the above conclusions were still tenable after correcting for these factors. The reason for this is that fatty acids are an important component of the cardiovascular system, especially n-3 polyunsaturated fatty acids, which play an important role in the composition of the nervous system, and DHA also has an anti-inflammatory response. Fish is the "producer" of n-3 polyunsaturated fatty acids, and therefore subjects who ate fish regularly showed a lower incidence of AD.

In a community study in Chicago, Morris et al. evaluated and followed 815 residents aged 65-94 by self-questionnaire for 3.9 years, and 131 participants had AD. Those participants who ate fish only once a week had a statistically significant 60% lower risk of developing AD compared to those who rarely or never ate fish regularly (RR=0.495%; CI=0.2-0.9). The intake of n-3 and DHA alone, without EPA, was strongly associated with a decreased risk of developing Alzheimer's disease. This means that even a daily intake of 30 mg of DHA/EPA from fish slowed cognitive deterioration considerably more than those who did not eat fish.

In 2006, a group from Karolinska University Hospital in Stockholm published a randomized double-blind controlled trial of DHA and EPA for the treatment of 174 patients with mild and moderate AD symptoms who received 1.7 g of DHA and 0.6 g of EPA daily or placebo for six months. For the next six months, all participants took DHA/EPA supplements. After the first six months, there was no significant difference in cognitive decline between the two groups. However, in the next experimental group with AD, cognitive decline was remarkably slowed down in the DHA/EPA treatment group. The placebo group also showed a slight deceleration of cognitive decline. These findings suggest that patients with mild AD benefit from consuming a diet containing DHA and EPA.

Animal experiments have also demonstrated the therapeutic efficacy of DHA for AD. Calon et al. studied the efficacy of n-3 polyunsaturated fatty acids for AD in transgenic rats in 2004 and 2005. These rats exhibited memory loss and  $\beta$ -amyloid deposition. In both experiments, adult rats were fed different levels of n-3 polyunsaturated fatty acids for 100 days. The control group was fed an n-3 polyunsaturated fatty acid-deficient diet, and the other control group was supplemented with DHA. The results show that n-3 polyunsaturated fatty acid-deficient control group had deficits in neuro synaptic markers critical for cognition. In contrast, the control group supplemented with DHA drastically improved these cognitive and behavioral deficits and reduced  $\beta$ -amyloid deposition. E Trofimiuk et al. studied the ability of DHA to combat negative cognitive deficits in rats following restraint

stress. In the experiments, male Wistar rats were fed blank sunflower oil, DHA-added sunflower oil, and fluoxetine added sunflower oil, and all rats were then placed in specially designed, very compact tubes to produce restraint stress effects and consequently cognitive and spatial deficits. After 21 days of experimentation, the DHA experimental group was effective in preventing cognitive impairment ( $p < 0.01$ ) and spatial memory impairment ( $p < 0.01$ ) caused by restraint stress in the rats. Min Xiao et al. used an APP/PS1 transgenic mouse model in which age-related accumulation of plaques and tangles developed in the brain to mimic AD-related symptoms, and assessed the effect of DHA supplementation on cognitive performance in AD mice by Morris water maze and open field tests (related DHA nutritional mixture provided by CABIO)<sup>[7]</sup>. Compared to the AD control group, DHA supplementation improved spatial learning, memory capacity, and anxiety in mice; inhibited the accumulation of A $\beta$  oligomers and the formation of neurofibrillary tangles. The research confirms that DHA can significantly improve cognitive impairment and depressive/anxious behavior in mice with Alzheimer's disease and alleviate AD symptoms and suppress pathological features in mice with AD by improving blood fats, suggesting that DHA supplementation may be an effective option to treat Alzheimer's disease.



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## ■ Possible mechanism

DHA may act in the following ways for the prevention and adjunctive treatment of AD.

Lowering cholesterol and apolipoprotein subtype E. High plasma cholesterol levels have been experimentally shown to be associated with AD. Also, some form of the APOE gene - a potential cholesterol transporter gene in the brain - has been strongly associated with a high risk of AD. Dietary supplementation of DHA has been shown through experiments to lower plasma cholesterol levels, and the effect of DHA is thus considered to be a mechanism for its role in AD prevention and adjunctive therapy.

Anti-inflammatory effects on the brain. AA coexists with DHA in cell membrane phospholipids. AA is associated with inflammatory responses. It is excised and released from cell membrane phospholipids by phospholipase A2 (PLA2) and later converted by COX-2 into pro-inflammatory response lipid mediators such as prostaglandins. In the brain of AD patients, PLA2 and COX-2 levels go up, whereas DHA and the neuroprotective mediator D1 reduce COX-2 levels. In recent experiments, PLA2 and COX-2 expression levels increased in mice after 15 weeks of n-3 polyunsaturated fatty acid-deficient feeding. Thus, the efficacy of DHA in AD may be related to its anti-inflammatory effects.

Neuroprotective effect. DHA can act as a neuroprotective molecule to improve cell survival. Lukiw, Akbar, Florent, Rao et al. have revealed the efficacy of DHA in AD from the protective effects of DHA on the nervous system via multiple pathways in independent experiments, either cell culture or animal experiments.

In the context of population aging, the disease burden of AD in China will continue to aggravate for some time in the future, and there is a long way to go in terms of prevention and treatment. In addition to dietary supplements such as n-3 fatty acids, a well-matched diet, regular work-rest cycle, more social activities, and mind-body exercises can help lower the risks of the disease. In addition, regular physical examination and diagnosis are also important, and pharmacological interventions for early-stage patients can delay the progression of Alzheimer's disease to a greater extent.

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## The role of DHA in anti-inflammation and immune regulation

### Long-chain polyunsaturated fatty acids affect immune function and development

On January 30, 2020, the WHO declared the outbreak of COVID-19 to be a public health emergency of international concern. At that time, less than 100 cases of coronavirus disease had been reported outside of China, and no deaths had been reported. On March 11 of the same year, the WHO officially declared the COVID-19 outbreak as a pandemic. More than three years later, the COVID-19 pandemic has claimed nearly 7 million lives. During the early stages of the COVID-19 outbreak, Professor Kang Jingxuan, a renowned lipid medicine scientist and president of the International Society for Omega-3 Research (ISOR), was one of the first to propose the importance of systemic treatment targeting inflammation in addition to antiviral strategies. He emphasized that anti-inflammatory measures should be considered as a fundamental treatment approach for COVID-19. Professor Kang suggested that increasing the level of Omega-3 fatty acids in the body through appropriate nutritional interventions could restore lipid metabolism balance, mitigate pro-inflammatory factors, and promote the production of anti-inflammatory factors.

The n-3 fatty acid family (ALA, DHA, EPA, DPA, etc.) is an essential fatty acid for human body, a vital nutrient for life and an important substance for cell formation. It is widely accepted that enhancing one's immune function is currently the most effective approach in combating viruses. Experts recommend that we can bolster our immune system through physical exercise and proper nutrition, including the supplementation of n-3 fatty acids, which can enhance our ability to resist diseases.

Globally, there are current some study reports on n-3 against influenza viruses. In 2013, the journal *Nature Medicine* published a noteworthy article titled "Potential treatment for severe influenza found in n-3 fatty acids." The study conducted by Harvard researchers involved injecting mice with the H1N1 influenza virus, which caused the swine-origin flu pandemic in 2009. The results showed that n-3 fatty acids produced a substance called protectin D1, which significantly increased the survival rates of mice infected with various strains of influenza, including H1N1.

Japanese researchers also found that in a culture dish of human lung cells, protectin D1 could reduce the virulence of the influenza virus by preventing viral mRNA from exiting the cell nucleus. This could lead to a sharp decline in cell-to-cell infection rate. It is

commonly believed that these naturally occurring components have protective effects on the lungs, brain and other organs. Protectin D1 is not only a derivative of n-3 fatty acids, but also a family member of fatty molecules with distinct anti-inflammatory and antibiotic properties. The research was done by Japanese scientists and published in the journal *Cell*.

In her nutritional monograph *The Omega Diet: The Lifesaving Nutritional Program Based on the Diet of the Island of Crete*, Dr. Artemis P. Simopoulos, President of the Center for Genetics, Nutrition and Health, writes that we know that n-3 fatty acids can put a brake on a runaway immune system. One of the methods they use is to slow the replenishment rate of white blood cells. When an infection occurs in one part of the body, the white blood cells that are battling viruses and bacteria need to be directed to that area. To mark the pathway, a chemical marker is produced in the body, and n-3 fatty acids undermine the attractiveness of the marker for the pathway, thus cutting down the number of white blood cells that reach the infected area.

Docosahexaenoic acid (DHA), commonly known as brain gold, is a crucial member of the n-3 unsaturated fatty acid family. Extensive research indicates that DHA possesses the ability to enhance the body's immune function. In numerous studies, it has been observed that n-3 fatty acids derived from sources such as fish, algae, or others show beneficial effects on the respiratory system. These effects include a reduction in the symptoms or markers of asthma and other allergic conditions. Several studies, including randomized clinical trials evaluating the supplementation of fish oil or algal oil DHA in pregnant women or children, as well as experiments involving infant formulas enriched with DHA and ARA, have reported a decrease in respiratory infections.

Data on the various mechanisms through which long-chain polyunsaturated fatty acids influence immune function and development offer fresh insights into the role of n-3 unsaturated fatty acids in the initiation and resolution of inflammatory responses. Further studies should focus on identifying the optimal dietary sources and dosage of long-chain polyunsaturated fatty acids for specific age groups, with the aim of promoting respiratory health and immune system development in newborns, infants, and children.

# Omega-3: Nutrition and Application Insight

## ■ Potential mechanisms that n-3 fatty acids work to prevent and treat allergic diseases

In clinical practice, some medical practitioners advocate equal emphasis on prevention and treatment of allergic reactions and suggest that the body's immunity and inflammatory factor tolerance should be improved by dietary nutritional modifications. Among these areas of research, the preventive and therapeutic effects of n-3 fatty acids on allergic asthma and respiratory diseases and injuries caused by smog have emerged as a significant area of interest.

The role of n-3 PUFA (EPA and DHA) in allergic asthma is mainly based on the theory of its immunomodulatory effects:

### Regulation of Metabolic Hormones

N-3 PUFA can be lipid-oxidized to produce the less inflammatory leukotriene 5 series hormones (LTB<sub>5</sub>, C<sub>5</sub>, D<sub>5</sub>, E<sub>5</sub>), while n-6 PUFA is oxidized to produce the inflammatory leukotriene 4 series hormones (LTB<sub>4</sub>, LTC<sub>4</sub>, D<sub>4</sub>, E<sub>4</sub>). Increasing n-3 PUFA intake can inhibit and balance the release of potent inflammatory mediators such as LTB<sub>4</sub> and LTC<sub>4</sub>.

### Modulation of cytokines

The n-3 PUFA component can modulate the activation ability of relevant transcription factors (such as nuclear factor  $\kappa$ B or NF- $\kappa$ B) to attenuate the cellular response to bacterial lipopolysaccharide, interleukin (IL), and tumor necrosis factor (TNF), thereby reducing the secretion of highly inflammatory cytokines.

### Other mechanisms

N-3 PUFA can alter cell membrane fluidity, bring down intracellular calcium ion levels, prevent rapid cellular calcium transfer, thereby regulating intracellular signaling pathways to control immune system responses. Other studies have also identified two classes of compounds, namely resolvins and protectins, derived from the metabolism of EPA and DHA in n-3 PUFAs. These compounds not only possess potent anti-inflammatory properties but also exhibit activities in promoting inflammatory resolution and repair. However, the mechanisms underlying these effects are not yet fully understood.

Some clinical studies have also shown that n-3 PUFA has a protective mechanism for allergic respiratory diseases (allergic asthma). Meanwhile, studies have revealed that maternal supplementation of n-3 PUFAs during pregnancy can reduce the secretion of Th2 cytokine IL-13 in newborns. This, in turn, leads to decreased activation of B cells during the allergic process, signifying the potential influence of LC-PUFAs on early-life immune system development. Interventions aimed at reducing the occurrence of

allergic reactions or mitigating the severity of allergic reactions through the immunomodulatory effects of n-3 PUFAs are indeed feasible.

During the initial outbreak of the COVID-19 pandemic, a majority of the diagnosed cases were elderly individuals and patients with pre-existing medical conditions, who are well-known to have compromised immune systems. People with poorer immunity are more likely to have symptoms of colds, allergies, and infectious diseases in their daily lives. Therefore, in the context of virus rampage, we need to do the necessary protection, but more importantly, we need to enhance our immune systems through proper nutrition and overall immune support. Moreover, excessive inflammatory responses are a primary trigger for common complications in ICU patients. The balance between pro-inflammatory and anti-inflammatory responses plays a crucial role in determining whether systemic immune reactions occur in the body.

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Djuricic I, Calder PC. Beneficial Outcomes of Omega-6 and Omega-3 Polyunsaturated Fatty Acids on Human Health: An Update for 2021. *Nutrients*. 2021; 13(7):2421. <https://doi.org/10.3390/nu13072421>

# Omega-3: Nutrition and Application Insight

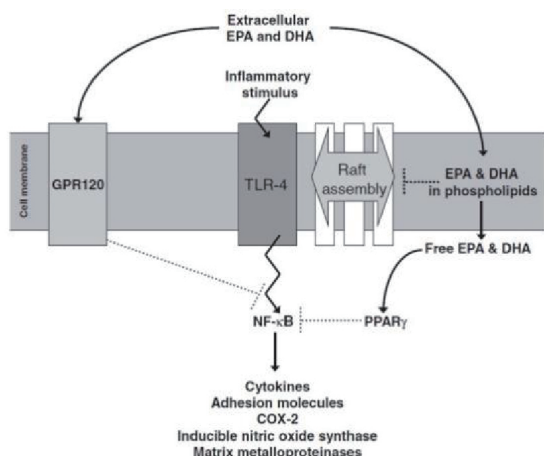
DHA exerts its anti-inflammatory and immunomodulatory functions mainly by acting on immune cells and cytokines. Philips et al. discovered that the consumption of foods supplemented with DHA by healthy subjects could reduce the concentrations of C-reactive protein (CRP) and interleukin-6 (IL-6), thereby alleviating exercise-induced inflammation. A study conducted by Ouyang Jingyi revealed that fetal serum DHA levels have a positive regulatory effect on fetal serum IgG and Th1 cytokine IFN- $\gamma$  levels. It was further concluded that increasing DHA intake levels and reducing the n-6/n-3 PUFA intake ratio are advantageous for promoting the maturation of fetal immune functions. In children with asthma, a one-month treatment with fish oil capsules led to increased plasma DHA levels, inhibited NF- $\kappa$ B activity, and reduced interleukin 12 and interleukin 13 levels. As a result, pulmonary function was improved.

In another cellular experiment conducted by Han Lirong et al., it was found that DHA exhibited immunomodulatory activity. DHA was observed to promote macrophage proliferation and phagocytic activity while enhancing the activity of related enzymes within the cells. Additionally, it was shown to upregulate the protein expression of three pathways in the MAPKs family to a certain extent. In a study conducted by Weiming Kong et al. on

the effects of DHA on dendritic cells (DCs), it was observed that DHA could maintain the immature phenotype of bone marrow-derived DCs by preventing the upregulation of MHCII and co-stimulatory molecules. Additionally, DHA was found to preserve high levels of cellular endocytic activity. Moreover, DHA demonstrated the ability to inhibit the production of pro-inflammatory cytokines by activating PPAR $\gamma$  and inhibiting the nuclear translocation of NF- $\kappa$ B p65 (specifically within the IL-12 cytokine family). Correspondingly, similar conclusions were drawn from experiments conducted on mice.

Numerous studies have provided evidence that n-3 polyunsaturated fatty acids (PUFAs) accumulate in cell membranes, thereby increasing the proportion of EPA and DHA fatty acids. This alteration in fatty acid composition affects intracellular signaling and inhibits the transcriptional activity of the inflammation-associated transcription factor NF- $\kappa$ B. Consequently, the expression of pro-inflammatory cytokines including TNF- $\alpha$ , IL-6, and IL-8 is reduced. In addition, EPA and DHA can act as precursors of Resolvins and Protectins, and experimental studies have shown that Resolvins and Protectins play an important anti-inflammatory role in a variety of inflammatory diseases.

## In terms of the inflammation and immunity effects and mechanisms of n-3 polyunsaturated fatty acids, Philip Calder summarized relevant research findings



**Table 1.** Summary of the effects of n-3 fatty acids (EPA - DHA) on immune and inflammatory cells

Cell type	Effects seen
Endothelial cells	Decreased adhesion molecule expression Decreased adhesion of leucocytes Decreased production of inflammatory cytokines
Neutrophils	Decreased chemotaxis Decreased adhesion to endothelial cells Decreased respiratory burst Increased production of eicosanoids from arachidonic acid
Monocytes and macrophages	Decreased chemotaxis Decreased adhesion molecule expression Decreased adhesion to endothelial cells Decreased respiratory burst Increased phagocytosis Decreased production of eicosanoids from arachidonic acid Decreased production of inflammatory cytokines
Antigen presenting cells	Decreased MHC I and II expression Decreased antigen presentation
T-cells	Decreased adhesion molecule expression Decreased adhesion to endothelial cells Decreased production of T-helper 1 type cytokines Decreased proliferation

**Table 2.** Summary of the mechanisms of action of n-3 fatty acids (EPA - DHA) on immune and inflammatory cells

Effect	Mechanism(s) likely to be involved
Decreased production of eicosanoids from arachidonic acid	Decreased arachidonic acid in membrane phospholipids Inhibition of arachidonic acid metabolism Decreased expression of cyclooxygenase-2 gene (via decreased activation of NF- $\kappa$ B)
Increased production of (weakly inflammatory) eicosanoids from EPA	Increased EPA in membrane phospholipids
Increased production of inflammation resolving resolvins and protectins	Increased EPA and DHA in membrane phospholipids Inhibition of arachidonic acid metabolism
Decreased production of inflammatory cytokines	Decreased expression of inflammatory cytokine genes (via decreased activation of NF- $\kappa$ B) - Induction and activation of PPAR $\gamma$ - Decreased generation of intracellular signals due to disruption of membrane lipid rafts - Activation of G-protein signaling
Decreased leucocyte chemotaxis	Decreased production of some chemoattractants
Decreased T-cell reactivity	Decreased expression of chemoattractant receptors Decreased generation of intracellular signals due to disruption of membrane lipid rafts
Decreased antigen presentation	Decreased MHC expression due to disruption of membrane lipid rafts

The European Society for Parenteral and Enteral Nutrition and the American Society for Parenteral and Enteral Nutrition unanimously recommend early supplementation of n-3 PUFA enteral nutrient solution for surgical patients. Similarly, experts in nutritional support for critically ill COVID-19 patients recommend immunomodulatory nutritional preparations rich in n-3 polyunsaturated fatty acids, glutamine, and nucleotides because they can promote recovery of critically ill patients by suppressing inflammatory response and improving immune function. As an essential polyunsaturated fatty acid with many physiological functions, DHA plays an important role in human immune system.

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# Omega-3: Nutrition and Application Insight

## CABIO DHA Algae Oil Nutrition during Pregnancy

Omega-3 DHA is the most important fatty acid during pregnancy because it is a key component of the baby's brain, retina and nervous system. In addition to being associated with the development of the baby, it is also essential for mothers-to-be. DHA contributes to supporting healthy childbirth and delivery outcomes. Additionally, research has indicated that it helps promote maternal emotional well-being postpartum.

The average recommended daily intake of DHA for the maternal population by different agencies is shown in the following table:

Institution	DHA intake
Chinese Nutrition Society	200 mg/d <sup>[1]</sup>
National Institutes of Health (NIH)	300 mg/d <sup>[2]</sup>
Food and Agriculture Organization (FAO)	200 mg/d
World Health Organization (WHO)	200 mg/d

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Djuricic I, Calder PC. Beneficial Outcomes of Omega-6 and Omega-3 Polyunsaturated Fatty Acids on Human Health: An Update for 2021. *Nutrients*. 2021; 13(7):2421. <https://doi.org/10.3390/nu13072421>

# Omega-3: Nutrition and Application Insight

To meet the need for DHA dietary supplementation of sensitive populations such as pregnant and lying-in women, we provide pure, high-quality, non-polluting DHA algae oil products that accord with the food safety standards of domestic and international baby-formula grade ingredients.

Item	Standard requirements	CABIO DHA Algae Oil			
		Batch in 2021	Batch in 2022	Batch in 2023	
Heavy metals	Arsenic (As)	0.1 mg/kg	< 0.01	< 0.02	< 0.01
	Lead (Pb)	0.08 mg/kg	< 0.01	< 0.01	< 0.01
Glycidyl ester (measured in glycidol)		500 µg/kg (EU 2020/1322)	< 100	< 100	< 100
Sum of 3-chloro-1, 2-propanediol and 3-chloro-1, 2-propanediol fatty acid esters (measured in 3-chloro-1, 2-propanediol)		750 µg/kg (EU 2020/1322)	170	191	131
Plasticizer	DBP	0.3	< 0.3	< 0.3	< 0.3
	DEHP	1.5	< 1.5	< 1.5	< 1.5
	DINP	9.0	< 9.0	< 9.0	< 9.0
Mineral oil	MOAH	1 mg/kg (EU 2017/84)	< 1	< 1	< 1
	MOSH	10 mg/kg	< 3.7	< 2.7	< 3.2

According to the above table, CABIO DHA algae oil meets the latest domestic and international requirements for contaminants in baby formula, and provides the purest and highest quality DHA nutrition for mothers and babies. There are various ways to supplement DHA during pregnancy, including formulated milk powder for pregnant and lying-in women, powdered drinks, DHA algae oil capsules, DHA algae oil oral solution, etc.

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# Omega-3: Nutrition and Application Insight

## CABIO DHA Algae Oil and Dietary Supplement

In developed countries like Europe and the United States, the majority of adults regularly or sporadically consume one or multiple dietary supplements. Common dietary supplements include vitamins, minerals, herbs, amino acids, enzymes (preparations), and a variety of other products. Dietary supplements come in a variety of forms, including pills, tablets, capsules, powders, and liquids. Currently, the most widespread and popular dietary supplements such as vitamins, fish oil, probiotics, collagen, and herbs target a variety of popular functional areas like immune health, gut health, brain health, eye health, skin health, and cardiovascular health.

DHA, a lifelong dietary nutrient, has been proven by several studies that the body needs adequate DHA supplementation during infancy and childhood, adulthood, and maturation and old age. DHA not only helps to promote the normal development of the brains and retinas of infants and children, but it also plays a beneficial role in regulating blood sugar and blood fat levels, enhancing memory, stabilizing mood, boosting immune function, and alleviating symptoms of Alzheimer's disease. DHA products, derived from either fish oil or algae oil, are widely available in the dietary supplement market.

DHA dietary supplements are commonly available in soft gel form. To ensure that consumers can visually appreciate the clarity and purity of the oil content, producers of encapsulated dietary supplements often have strict requirements for the transparency of DHA oils.

Catering specifically to softgel customers, CABIO provides highly clarified winterized oils to meet their specific product application needs. Winterization of oils and fats involves a cooling process where glycerides with a high freezing point crystallize, leading to the separation of oil from solid fat. By utilizing winterization techniques, oils and fats can maintain their clarity under low temperature conditions, such as during the winter season, thereby ensuring the preservation of product appearance. Thanks to ongoing optimization and refinement, CABIO has successfully developed a unique winterization process that guarantees the clarity and absence of sediment in DHA algae oil for a minimum of 4 days at 0°C. This specially winterized algae oil is exceptionally well-suited for use in dietary supplement formulations, particularly those in soft gel dosage form.

Dietary supplements are frequently chosen as an ideal dosage form for DHA raw materials due to their ability to provide high levels of DHA. Additionally, their effective blockage of air

prevents the oxidation of DHA, making them a popular and well-regarded choice among consumers. The pandemic has had a profound impact on the global dietary supplement market, as consumers have become more aware of the importance of nutrition and have once again heightened their health concern. With the continuous advancement and application of DHA algae oil processing technology in dietary supplement products, more consumers can now enjoy the benefits of higher-quality products for their overall health.



CABIO's DHA algae oil gel candy

# Omega-3: Nutrition and Application Insight

## CABIO DHA Algae Oil and Food and Beverage

CABIO algae oil DHA is an Omega-3 polyunsaturated fatty acid synthesized using single-celled algae. The production process takes place in a closed and clean environment. It has received approval from the U.S. FDA GRAS and is certified organic in the United States. The production of this algae oil is carried out in a manner that prioritizes food safety, quality control, and traceability. Moreover, the production is not limited by resources, making it a sustainable and environmentally friendly supply chain method. CABIO algae oil DHA includes three product series: oil, powder and algae powder. The oil and powder products are primarily utilized in areas such as infant formula and dietary supplements. They are also commonly employed in the preparation of health foods, including but not limited to prepared milk powder, soft gels, solid drinks, drops, soft sweets, dietary foods, special medical foods, baked goods, and processed meat products. This application serves to enhance the health value of these products. Algae powder is mainly used in the field of animal nutrition.

### 1. Application in softgels

About 10% of infants and children suffer from different degrees of ADHD and developmental delay because of malnutrition. Many producers of infant formula milk powder want to promote brain development by adding DHA, but the actual amount of DHA supplementation is insufficient. With the prevalence of unhealthy work and lifestyle habits, as well as the fast pace of modern life, the number of individuals experiencing insomnia and neurological depression exceeds 15% of the population. Furthermore, as individuals age, the incidence of conditions such as amnesia and

CABIO algae oil DHA has good sensory attributes and high stability levels. Throughout the refining process, the oils and fats are meticulously handled to meet stringent process requirements, effectively preventing and controlling oxidation from light, oxygen, temperature, and metal ions. This is particularly emphasized through a stable and efficient deodorization process aimed at removing odor-causing small molecules. Furthermore, the combination of appropriate packaging materials and packaging techniques ensures the optimal sensory quality and stability of CABIO algae oil products. In addition, through the utilization of microencapsulation technology, DHA algae oil can be transformed into powder form, effectively isolating it from external factors such as oxygen, moisture, light, and temperature. This not only helps prevent oxidation and deterioration, preserving the physiological activity of DHA but also masks the inherent flavor of DHA algae oil, thereby enhancing its acceptability. As a result, the application of DHA in various foods can be significantly expanded.

Alzheimer's disease continues to rise steadily.

With the improvement of living standards and the maturation of health awareness, individuals are increasingly capable and willing to invest in their own well-being. Simultaneously, as the concept of DHA becomes more established, there is a growing demand for supplements that are high in content and safety. Currently, the DHA market is experiencing rapid growth and demonstrates tremendous potential.

### 2. Application in soft sweets

In the Dosage Forms and Technical Requirements of Health Food Filing (2021 version) published by the State Administration for Market Regulation, food-like gel candy has been firstly included as one of the filed dosage forms for health food. The filing process for gelatinized confections was officially launched in June 2021, according to reports. This signifies that soft sweets can now swiftly obtain the "blue hat" status of health food through the filing system, thus offering consumers a wider range of experiential options. Importantly, as an innovative product dosage form, the application of soft sweets can encompass most popular functional ingredients and quickly become an important food carrier for health and nutritional functionality. With its dual

functionality as both a "nutritional supplement" and a "snack," health food in the form of soft sweets and similar snacks has become a new favorite among contemporary young people. Embracing a "life with sugar," these individuals appreciate the convenience provided by these products. Amway, By-Health, Sirio, Aland, Jiannuo and other leading companies have also laid out in this field, and most of them also offer functional gummy candy products specifically designed for children. Moreover, foreign brands have a significant presence in the market due to their early entry. For instance, Australia's Nature's Way and Blackmores, U.S.-based brands like Yummy Bear and Lil Critters.

# Omega-3: Nutrition and Application Insight

## 3. Application in powdered drinks

In recent years, powdered drinks have emerged as the fastest-growing product type, owing to their small size, the convenience of consumption, portability, and extended shelf life. DHA is prone to oxidation, and factors such as oxygen, moisture, and light can accelerate this process. As a result, DHA exhibits greater stability and extended shelf life in dry systems as compared to liquid systems. DHA microencapsulated powder

possesses excellent water solubility and is encapsulated to effectively isolate oxygen. As a result, it exhibits enhanced stability in comparison to DHA oil. It is worth noting that incorporating DHA in the form of microencapsulated powder is the optimal choice for developing DHA-infused powdered drinks with an extended shelf life.

### DHA and protein powder

While seeking to increase protein intake, one may be tempted to turn to animal-based foods due to their high protein content. However, these options often come with high levels of saturated fatty acids and cholesterol. While increasing protein intake, it is important to consider the accompanying increase in fat and cholesterol intake. It is evident that relying solely on animal-based foods for protein supplementation is not advisable. Instead, it is preferable to opt for protein products with high protein content and low levels of fat and cholesterol. Unfortunately, there is still a lack of such food or protein supplements in China. Therefore, in line with this trend, it is imperative to develop natural, green, and pure protein powders with low fat and cholesterol contents and high protein content. The addition of DHA strengthens the functional and nutritional properties of protein, which can help supplement protein and polyunsaturated fatty acids at the same time.

### DHA and powdered juice

Fruits are rich in vitamins, minerals, dietary fibers, and some beneficial biological components such as polyphenols and flavonoids. Advanced technology is adopted to extract the natural vitamins, minerals and other nutrients from fruits to make powder without destroying their activity while retaining their natural original taste, and the powdered juice produced using this method is favored by consumers. The application of DHA to powdered juice can improve the added value of the product on the one hand, and the natural aroma of the powdered juice can mask the characteristic smell of DHA on the other hand.

### DHA and composite powdered drinks

Composite powdered drinks typically incorporate health-promoting ingredients such as chrysanthemum, wolfberry, hawthorn, red dates, eucommia, kudzu, spirulina, and various vegetables. These ingredients possess certain health benefits and have become a focal point of recent research in the field. Li Jinghua et al. [10] blended DHA with hawthorn juice, carrot juice, sodium alginate, and other raw materials by a certain ratio to make a functional composite powdered drink. Hu Zemin et al. [11] developed a powdered drink for infants and children that facilitates sleep and clears heat with raw materials such as hawthorn powder, Spina date seeds, malt flour, lily root flour, lotus nut flour, tuckahoe extract powder, honeysuckle extract powder, mulberry extract powder, chrysanthemum extract powder, oligofructose, and DHA through crushing, stirring, granulating, drying, and other steps.

# Omega-3: Nutrition and Application Insight

## 4. Application in cookies

Cookies are a combination of functions such as nutrition, convenience and leisure in baked goods, and have a long shelf life. The cookie industry in China shows a good momentum of development. There is a strong tendency to develop new products with health as the theme in the cookie industry abroad, and the addition of nutritional ingredients to produce cookies with health-promoting functions has been a great success. The concept of healthy cookies is not absent in China, but there is still a gap in DHA nutritional fortification. DHA-fortified cookies can better meet the needs of health and mental development and are more easily accepted by consumers, which therefore have a great market potential.



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