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DOCOSAHEXAENOIC ACID: AN ESSENTIAL FRIEND TO HUMAN HEALTH

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ABSTRACT

Docosahexaenoic acid (**DHA**) is an omega-3 fatty acid that is a primary structural component of the human brain, cerebral cortex, skin, and retina. In physiological literature, it is given the name 22:6(n-3). It can be synthesized from alpha-linolenic acid or obtained directly from maternal milk (breast milk), fatty fish, fish oil, or algae oil.DHA's structure is a carboxylic acid (-oic acid) with a 22-carbon chain (docosa- derives from the Ancient Greek for 22) and six (hexa-) cis double bonds (-en-); with the first double bond located at the third carbon from the omega end. Its trivial name is **cervonic acid** (from the Latin word cerebrum for "brain"), its systematic name is **all-cis-docosa-4, 7, 10, 13, 16, 19-hexa-enoic acid**, and its shorthand name is **22:6(n−3)** in the nomenclature of fatty acids. Most of the docosahexaenoic acid in fish and multi-cellular organisms with access to cold-water oceanic foods originates from photosynthetic and heterotrophic microalgae, and becomes increasingly concentrated in organisms the further they are up the food chain. DHA is also commercially manufactured from microalgae: *Crypthecodinium cohnii* and another of the genus Schizochytrium. DHA manufactured using microalgae is vegetarian.

KEYWORDS: DHA, Brain Development, Central Nervous System, Omega-3- fatty Acids.

INTRODUCTION

DHA is a major fatty acid in brain phospholipids and the retina. Research into the potential role or benefit of DHA in various pathologies is ongoing, with significant focus on its mechanism in Alzheimer's disease and cardiovascular disease.[1]

Figure-1: Baby food Containing DHA.

Plant Source

1. **Chia seeds**[*Salvia hispanica*]

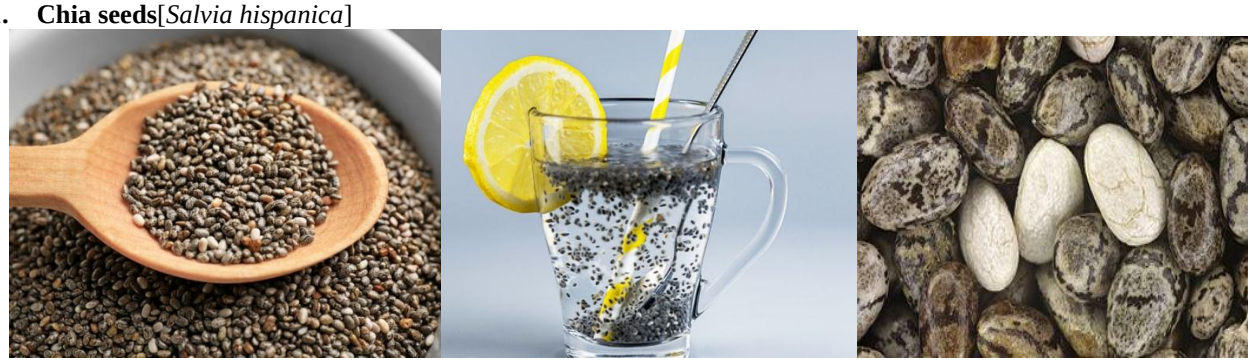


Figure-2: Chia Seeds and Chia Seed Water.

- Chia seeds are known for their many health benefits, providing a hefty dose of fiber and protein in each serving.
- They're also a great plant-based source of ALA omega-3 fatty acids.
- Studies have found that, thanks to their omega-3, fiber, and protein, chia seeds could decrease the risk of chronic disease when consumed as part of a healthy diet.
- One study in people with metabolic syndrome found that consuming a diet with chia seeds, nopal, soy protein, and oats decreased participants' blood triglycerides, glucose intolerance, and inflammatory markers.
- A 2007 animal study also found that eating chia seeds decreased blood triglycerides and increased both HDL (good) cholesterol and omega-3 levels in the blood.However, more human research needs to be conducted before a definitive conclusion can be made.
- The current daily recommended intake of ALA for adults over age 19 is 1,100 mg for women and 1,600 mg for men.
- Just 1 ounce (28 grams) of chia seeds far exceeds your daily recommended intake of omega-3 fatty acids, delivering a whopping 5,000 mg.
- You can boost your chia seed intake by whipping up a nutritious chia pudding or sprinkling chia seeds on top of salads, yogurts, or smoothies.
- Ground chia seeds can also be used as a vegan substitute for eggs. Combine 1 tablespoon (7 grams) with 3 tablespoons of water to replace 1 egg in recipes.

2. **Brussels sprouts**[*Brassica oleracea*]

Figure-3: Brussels sprouts.

- In addition to their high content of vitamin K, vitamin C, and fiber, Brussels sprouts are an excellent source of omega-3 fatty acids.
- Because cruciferous vegetables like Brussels sprouts are so rich in omega-3 fatty acids and other nutrients, they have been linked to many health benefits.
- In fact, one study found that an increased intake of cruciferous vegetables is associated with an almost 16% lower risk of heart disease.
- A half-cup (44 grams) of raw Brussels sprouts contains about 44 mg of ALA.
- Meanwhile, cooked Brussels sprouts contain three times as much, providing 135 mg of omega-3 fatty acids in each half-cup (78-gram) serving.
- Whether they're roasted, steamed, blanched, or stir-fried, Brussels sprouts make a healthy and delicious accompaniment to any meal.

3. Algal oil [*Crypthecodinium cohnii*]

- Algal oil, a type of oil derived from algae, stands out as one of the few vegan sources of both EPA and DHA.
- Some studies have even found that it's comparable to seafood in regard to its nutritional availability of EPA and DHA.
- One study compared algal oil capsules to cooked salmon and found that both were well tolerated and equivalent in terms of absorption.
- Though research is limited, animal studies show that the DHA from algal oil is especially beneficial to health.
- In fact, a recent animal study found that supplementing mice with a DHA algal oil compound led to an improvement in memory.

Figure-4: Algal Oil.

- However, more human studies are needed to determine the extent of its health benefits.
- Most commonly available in softgel form, algal oil supplements typically provide 400–500 mg of combined DHA and EPA. Generally, it is recommended to get 300–900 mg of combined DHA and EPA per day.
- Algal oil supplements are easy to find in most pharmacies. Liquid forms can also be added to drinks or smoothies for a dose of healthy fats.

4. Hemp seed [*Cannabis sativa*]

Figure-5: Hemp Seed.

- In addition to protein, magnesium, iron, and zinc, hemp seeds consist of about 30% oil and contain a good amount of omega-3s
- Studies have found that the omega-3s found in hemp seeds could benefit heart health. They may do this by preventing the formation of blood clots and helping the heart recover after a heart attack.
- Three tablespoons (30 grams) of hemp seeds contain approximately 2,600 mg of ALA.
- Sprinkle hemp seeds on top of yogurt or mix them into a smoothie to add a bit of crunch and boost the omega-3 content of your snack.
- Also, homemade hemp seed granola bars can be a simple way to combine hemp seeds with other healthy ingredients such as flaxseeds and pack in extra omega-3s.
- Hemp seed oil, which is made by pressing hemp seeds, can also be consumed to provide a concentrated dose of omega-3 fatty acids.

5. Walnuts [*Juglans regia*]

- Walnuts are loaded with healthy fats and ALA omega-3 fatty acids. In fact, walnuts are composed of about 65% fat by weight.
- Several animal studies have found that walnuts could help improve brain health as a result of their omega-3 content.

- Studies in both humans and animals have found that eating walnuts is associated with improvements in cognitive performance and memory.
- Another animal study showed that walnuts caused significant improvements in memory, learning, motor development, and anxiety in mice with Alzheimer's disease.
- More research is still needed in this area since animal studies cannot be applied to humans.

Figure-6: Walnuts.

- Just one serving of walnuts can fulfil an entire day's requirements of omega-3 fatty acids, with a single ounce (28 grams) providing 2,570 mg.
- Add walnuts to your homemade granola or cereal sprinkle them on top of yogurt, or simply snack on a handful to increase your ALA intake.

6. Flaxseed [*Linum usitatissimum*]

Figure-7: Flaxseed.

- Flaxseed is a nutritional powerhouse, providing a good amount of fiber, protein, magnesium, and manganese in each serving.
- It's also an excellent source of omega-3s.
- Several studies have demonstrated the heart-healthy benefits of flaxseed, largely thanks to its omega-3 fatty acid content.
- Both flaxseed and flaxseed oil have been shown to reduce cholesterol in multiple studies.
- Another study found that flaxseed could help significantly lower blood pressure, particularly in people with high blood pressure.
- One tablespoon (10 grams) of whole flaxseed contains 2,350 mg of ALA omega-3 fatty acids, surpassing the daily recommended amount.
- Flaxseed is easy to incorporate into your diet and can be a staple ingredient in vegan baking.
- Whisk together 1 tablespoon (7 grams) of flaxseed meal with 2.5 tablespoons of water to use it as a handy substitute for 1 egg in baked goods.
- With a mild yet slightly nutty flavour, flaxseed also makes the perfect addition to cereal, oatmeal, soups, or salads.

7. Perilla oil [*Perilla frutescens*]

- This oil, derived from Perilla seeds, is often used in Korean cuisine as a condiment and cooking oil.
- In addition to being a versatile and flavourful ingredient, it's a good source of omega-3 fatty acids.
- In one study in 20 elderly participants, researchers replaced soybean oil with Perilla oil and found that it caused ALA levels in the blood to double. In the long term, it also led to an increase in EPA and DHA blood levels.

Figure-8: Perilla Oil.

- Perilla oil is very rich in omega-3 fatty acids, with ALA making up an estimated 64% of this seed oil .
- Each tablespoon (14 grams) contains nearly 9,000 mg of ALA omega-3 fatty acids.
- To maximize its health benefits, Perilla oil should be used as a flavour enhancer or dressing, rather than cooking oil. This is because oils high in polyunsaturated fats can oxidize with heat, forming harmful free radicals that contribute to disease.
- Perilla oil is also available in capsule form for an easy and convenient way to increase your omega-3 intake.

Pathway of DHA synthesis: The synthesis pathway of DHA from ALA. The desaturase and elongase enzymes that are used to synthesize longer chain PUFA (for example DHA) are most highly expressed in the liver as compared to heart or brain corresponding to more than 30-fold higher rates of DHA synthesis in this organ. ALA is desaturated by the rate-limiting Δ6-desaturase enzyme in the endoplasmic reticulum (ER) to form 18:4n-3, followed by elongation to 20:4n-3 and desaturation by Δ5-desaturase to form 20:5n-3 (EPA). EPA can be elongated further to 22:5n-3 (docosapentaenoic acid – DPAn-3), and 24:5n-3. 24:5n-3 is desaturated by Δ6-desaturase forming 24:6n-3, which is transferred from the ER to the peroxisomes where it is β-oxidized to form 22:6n-3 (DHA). DHA is then transferred back to the ER where it can undergo esterification, lipoprotein packaging and secretion to the blood.

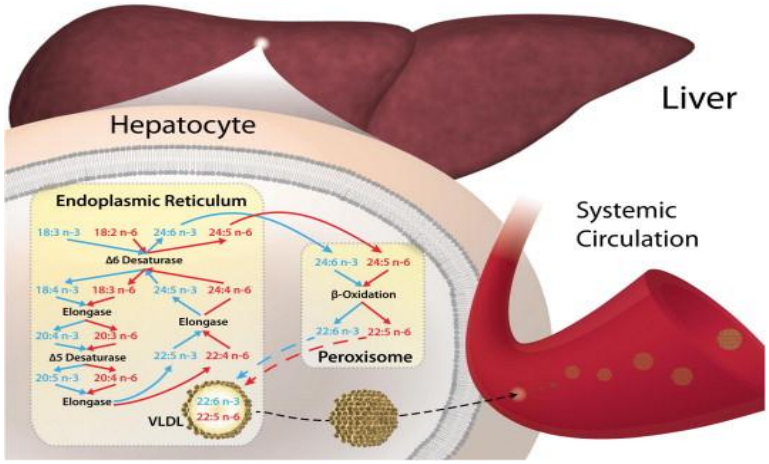


Figure-9: DHA is synthesized from ALA in the liver by a series of desaturations, elongations and a β-oxidation. Enzymes involved in the synthesis of DHA from ALA are also used by n-6 PUFA and n-9 fatty acids (not shown) leading to competition between n-3 PUFA, n-6 PUFA, and n-9 fatty acids for these enzymes. This competition is most apparent for the Δ6 desaturase, where 4 PUFA (2 n-3 PUFA and 2 n-6 PUFA) compete for a single enzyme. The desaturations and elongations occur in the endoplasmic reticulum and the β-oxidation occurs in the peroxisomes, to where 24-carbon PUFA are transferred. The final products (DHA and 22:5n-6) are then transferred back to the endoplasmic reticulum where they along with other PUFA can be esterified to lipoproteins (eg. VLDL) and secreted into the blood.

The pathway is active towards both n-3 and n-6 PUFA as well as n-9 fatty acids, resulting in potential competition for enzyme activity between the families of fatty acids. This is particularly important for the rate-limiting enzyme, Δ6-desaturase, which is active towards ALA and linoleic acid (LNA), as well as 24-carbon n-3 and n-6 PUFA. Dietary PUFA down regulate the expression and activity of the enzymes involved in DHA synthesis in the liver; thus, decreasing the hepatic DHA synthesis rat. The brain is capable of synthesizing DHA; however, brain DHA synthesis is approximately 100-fold lower than brain DHA uptake and consumption rates, indicating that brain DHA synthesis does not contribute significantly to brain DHA homeostasis. Interestingly, dietary n-3 PUFA deprivation does not affect the expression of the desaturase or elongases or the DHA synthesis rate in the brain, in contrast to increased synthesis found in the liver. DHA synthesis-secretion in the liver is at least 3–10-fold greater than brain DHA consumption rates which, combined with the finding of up-regulated hepatic DHA synthesis during n-3 deprivation, suggests that hepatic DHA synthesis is capable of maintaining brain DHA homeostasis.

Recently, alternative mechanisms for DHA synthesis have been proposed. An experiment performed in baboons determined that the Δ6-desaturase enzyme also has Δ8-desaturase activity. Based on this finding the authors proposed an alternative pathway for DHA synthesis from ALA that functions in parallel with the classical pathway and involves an initial elongation of ALA to 20:3n-3 followed by Δ8-desaturation to make 20:4n-3, which is then desaturated and elongated to become DHA . Another recent study questioned the Δ6-desaturation as the sole rate-limiting step in the synthesis pathway. The authors found that the elongation of DPA n-3 to 24:5n-3 may be another crucial control point in DHA synthesis. This reaction is catalyzed by the enzyme elovl2, and lack of expression of this enzyme in heart is believed to be the reason why heart tissue has very low DHA synthesis rates. These novel insights into DHA synthesis merit further investigation to determine how much they contribute to DHA synthesis *in-vivo*.

Estimates of DHA synthesis from ALA in humans

Evidence from ALA feeding: The simplest means of estimating DHA synthesis in humans is measuring changes in DHA status in response to acute or chronic increases in dietary ALA consumption, and these studies have been previously reviewed in detail. In general, these studies increase subjects' ALA consumption and measure DHA in the blood. While most studies report that plasma and erythrocyte EPA increase with ALA feeding, most do not detect an increase in plasma or erythrocyte DHA. Reviews of these studies have pointed out two important points pertaining to the lack of plasma DHA increases after ALA feeding. Firstly, in humans with low DHA diets (vegans and vegetarians), ALA feeding increases plasma DHA. Additionally, plasma DHA tends to increase to a greater extent when ALA consumption is increased in combination with decreased LNA consumption.

It should be recognized that these studies only measure DHA in blood lipids (plasma, erythrocytes, or leukocytes) as opposed to tissues. While plasma DHA may be a reliable marker for dietary DHA intake, the applicability of this pool to the brain is not agreed upon. This is because most of these studies measure percent composition of DHA in the esterified blood lipid pools, which are not thought to be available to the brain. A recent rodent study performed in our laboratory highlights this point. We fed rats a diet that was either low in n-3 PUFA (0.25% fatty acids as ALA) or contained either ALA or DHA. After 15 weeks on these diets, levels of DHA in the body and plasma were significantly higher in rats fed DHA compared to rats fed the ALA and control diet (2.4 and 11-fold higher, respectively, for the body and 2 and 5-fold higher, respectively, for plasma). However, brain DHA levels were not different between ALA- and DHA-fed rats, similar to previous studies in rats and non-human primates, suggesting that changes in blood DHA concentration do not necessarily reflect the magnitude of changes in brain DHA, with some exceptions. Interestingly, graded ALA deprivation from 4.6% (considered "adequate" to maintain brain function and DHA concentrations) to 0.2% (considered "inadequate" based on decreased DHA concentration and metabolism) of fatty acids in a diet lacking DHA results in decreased brain DHA only when the ALA content of the diet is decreased to 0.8% or lower . This indicates that extreme cases of ALA deprivation are required to affect brain DHA concentrations. Accordingly, the only recorded case of n-3 PUFA deficiency in humans resulted from total parenteral feeding of an emulsion containing only 0.6% of fatty acids as ALA. This supports the hypothesis that extremely low ALA intakes are required to significantly affect brain DHA levels and function, assuming however, that the neurological impairments observed with ALA deficiency is caused by decreases in brain DHA.

It is possible that though plasma esterified DHA is unchanged with chronic increases in ALA feeding, dietary ALA may be sufficient to maintain brain DHA concentrations, possibly via the plasma unsterilized fatty acid pool. The plasma un-esterified fatty acid pool is 10–100-fold smaller than the esterified pools and is maintained largely via the adipose (fasting state) and hydrolysis from plasma lipoproteins (post-prandial). Also, the DHA concentration of the plasma un-esterified fatty acid pool decreases only when extreme n-3 PUFA deprivation occurs. Moreover, few studies have examined the effect of increasing dietary DHA intake on un-esterified DHA concentrations in humans, with some studies reporting an increase and others reporting no increase. Adipose, the tissue that maintains plasma un-esterified fatty acid concentrations, has been estimated to contain 1–4 and 20–50 g of DHA in the infant and adult,

respectively. Using the previously measured brain DHA uptake rate of 3.8 mg/day in adult humans, it can be calculated that adult human adipose contains enough DHA to supply the brain for 14–36 years. It is important to note that the estimate for how long adipose DHA can supply the brain is an overestimate because DHA released from the adipose is used by other tissues as well as the brain. Therefore, to determine the actual amount of time that adipose DHA can supply the brain, the proportion of DHA that is released from the adipose and taken up into the brain (brain-body partition coefficient) must be determined.[2]

Evidence from stable isotope administration: DHA synthesis from ALA in humans has been examined by administering an oral dose of stable isotope-labeled ALA and measuring the appearance of labeled DHA in blood lipids over time. Through repeated blood sampling, concentration–time plots of the appearance of labeled n-3 PUFA are obtained, and the area under the curve (AUC) for DHA is compared to either the AUC for all labeled PUFA or expressed relative to the administered dose to calculate the fractional conversion of ALA to DHA. The fractional conversion of DHA from ALA is, therefore, a measure of the percentage of labeled n-3 PUFA that appears in the plasma as DHA or the percentage of a single oral dose of ALA administered at one time that appears in the plasma as DHA.

Estimates of fractional conversion of an oral dose of ALA to DHA using this technique have ranged from below the detection limit in one study to 9.8%, however, the majority of studies using this technique report fractional DHA conversion of <1%. Alternatively, the relative conversion of each intermediate within the pathway can be estimated by using compartmental modeling. This approach is based on the assumption that the relative concentration of pathway intermediates in plasma is representative of the relative concentrations in liver, the primary site of DHA synthesis. The amount of orally administered ALA utilized for DHA synthesis using this technique has been estimated to be between 0.01 and 0.08%. Taken together, these measures have led to a general consensus that DHA synthesis in humans is insufficient to meet DHA demands; however, care must be taken in interpreting these estimates of DHA synthesis in humans, especially in reference to the brain.

In general, there are considerations regarding the oral administration of an ALA tracer to estimate DHA synthesis, as this type of experiment represents DHA synthesis from postprandial ALA only, rather than total DHA synthesis from ALA. For example, the extent to which orally administered ALA is available for DHA synthesis is not known. Fatty acids absorbed in the intestine are packaged into lipoproteins, and the majority are transported through lymphatic circulation and secreted into the blood through the thoracic duct. Fatty acids are taken up by tissues following hydrolysis of lipids by endothelial lipase and lipoprotein lipase or by endocytosis of the lipoprotein. Approximately 72% and 64% of orally administered C-ALA is β-oxidized 168 h after dosing in humans and after 24 h in rats, respectively. This value for β-oxidation of ALA in humans is similar to that of oleic and elaidic acids, but slightly higher than LA, at least between 9 and 24 h post dose. Studies in rats demonstrate that the adipose AUC makes up 75% of the whole-body AUC for orally gavaged ^{2}H-ALA after 600 h with progressive enrichment of adipose tissue with ALA. Balance studies performed in rodents have also found that the majority of dietary ALA that is not β-oxidized accumulates in the adipose tissue. Moreover, in adult females after one week it has been estimated that upon an oral dose of labeled ALA, up to 57% of the tracer is in the adipose. The fate of ALA that is deposited into adipose tissue is not clear, however, the adipose fatty acid half-life is approximately 1 year indicating that long-term storage would make a large proportion of oral ALA tracer unavailable for DHA synthesis measures. Taken together, this indicates that the major fate of orally administered ALA tracer, that is not β-oxidized, is adipose sequestration with a long half-life. In fact, enrichment of plasma with gavaged ALA peaks at only 5% of the whole-body tracer content and progressively declines over time. Moreover, in rats, less than 5% of ^{2}H-EPA, DPAn-3 and DHA derived from gavaged ^{2}H-ALA is found in plasma with the majority found in nervous system, liver, and adipose with a progressive enrichment in nervous tissue. Thus, the amount of tracer that is found in plasma represents a very small proportion of the total tracer that is provided orally, and is likely an underestimate of the total whole-body DHA synthesized and accreted. This suggests that DHA synthesis measures from ingested ALA tracer likely represent only DHA synthesized from postprandial ALA, but do not necessarily reflect the total pool of ALA that is available for DHA synthesis. As fractional conversion of DHA from ingested ALA represents only the proportion of the dose that is found in the blood compartment, which is a very small portion of the DHA synthesized from ALA, these estimates of fractional conversion are likely underestimates of actual DHA synthesis in humans. Estimates of DHA synthesis from ALA using this method range from <0.01 to 1% of oral dose of ALA.[3]

Fractional DHA synthesis has also been estimated by comparing the plasma AUC for labeled n-3 PUFA to estimate the percentage of plasma ALA that is converted into DHA. In these studies fractional conversion is measured by determining what percentage of the total labeled n-3 PUFA that appeared in the plasma was labeled DHA. By adjusting for the appearance of labeled fatty acids, this method is less likely to underestimate fractional DHA synthesis rates by accounting for loss of label associated with adipose sequestration. The fractional conversion of ^{13}C- or ^{2}H-ALA to DHA in young men using this technique has been measured as 3.8% after 48 h and below the detection limit after 504 h in one study, and 9.2% after 504 h in young women.

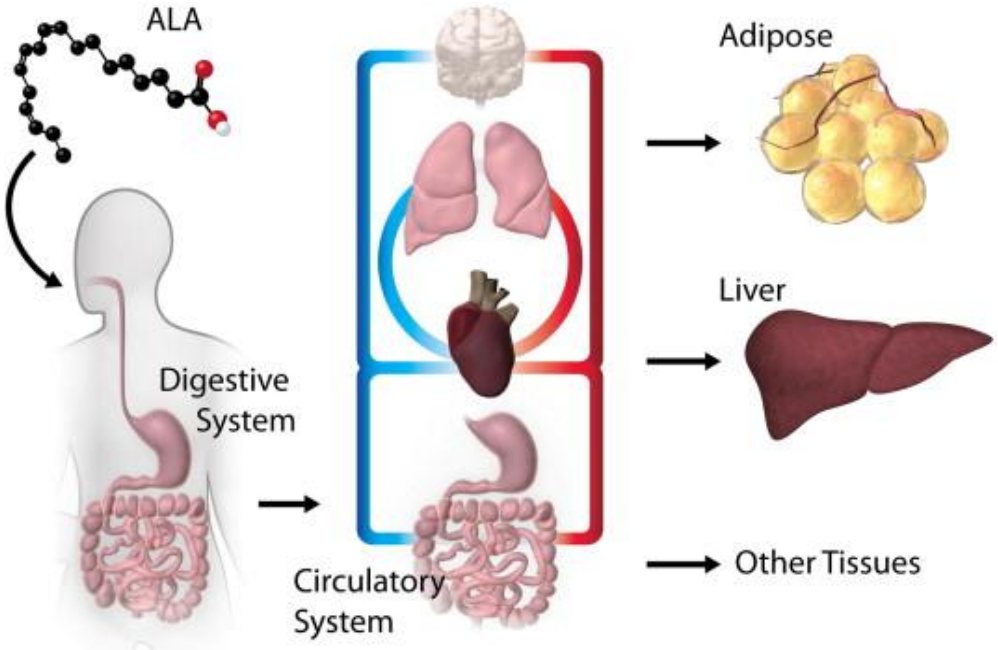


Figure-10: When ALA is administered orally it is absorbed into the lymphatic system and then deposited into systemic circulation. This is problematic for human tracer studies that administer ALA orally and measure the appearance of labeled n-3 PUFA products in the plasma, as a large portion of the tracer will get taken up into the tissues and adipose and not reach the liver for the duration of the study.

However, the extent to which the fractional conversion quantifies actual DHA synthesis is not clear, as it is only a relative measure. In addition, the AUC comparisons do not take into account differences in the plasma half-lives of the different n-3 PUFA. It has been estimated that the half-life for plasma esterified ALA is 1 h, while that of DHA is 20 h. This difference in plasma half-life would result in equal amounts of DHA and ALA eliciting a much greater AUC for DHA than that of ALA. Therefore, these methods are also susceptible to factors that affect plasma half-life of DHA, such as diet.

Compartmentalized modeling procedures are another method to determine DHA synthesis from orally administered ALA and also provide measures of rate of flow of labeled fatty acids between compartments, half-lives, loss rates, as well as conversion rates from one fatty acid to another. Compartmentalized modeling describes the flow of materials, in this case n-3 PUFA, from one compartment to another. For modeling n-3 PUFA metabolism, stable isotope-labeled ALA is provided orally and the appearance of ALA and its longer-chain derivatives, including DHA, is measured over time. Each fatty acid between ALA and DHA is considered a "compartment" in the model, and when the data is corrected for unlabeled n-3 PUFA concentrations the transfer of label from one compartment to another describes the rate constants for conversions between fatty acids within the DHA synthesis pathway. A major advantage of this type of modeling is that it can potentially yield conversion rates in μg/h rather than relative data such as percent conversion. However, numerous assumptions are required for this type of modeling that likely affect conclusions rendered from the data. For example, the kinetics that are modelled in this analysis are based on oral consumption of an ALA tracer, and as such may not represent the kinetics of all sources of ALA that compose steady-state serum ALA concentration, such as ALA secreted from adipose or liver stores. Also, the majority of the tracer is lost to uptake by adipose or other tissues and/or β-oxidation based on very low appearance of the ALA tracer in plasma after ingestion. This type of modeling is an approximation of hepatic conversion of ALA into longer-chain n-3 PUFA based on appearance of label in plasma, however, important differences in plasma and hepatic n-3 PUFA composition (eg. ratio of DHA to ALA is 2-fold higher in liver than in plasma total lipids suggest this approximation is limited. The rate constants that are calculated, therefore, represent the cumulative process involved in conversion of one plasma tracer to another, including uptake by the liver, conversion, and secretion back into the plasma. This will also lead to an underestimation of DHA synthesis as it has been reported that after the consumption of a labeled ALA tracer, approximately 15% of DHA is synthesized fully in the liver before appearing in the plasma based on comparison of compartmental DHA metabolism. Interestingly, in one study the compartmental model predicted that the amount of dietary DHA required to maintain serum DHA concentration was 2.2-fold higher than what was directly measured by food duplicate, and the authors concluded that maintenance of DHA status requires greater DHA output from body store utilization or ALA synthesis than was measured in this study. Estimates of fractional DHA synthesis from ALA using this method range from 0.01 to 0.08%.[4]

Considerations for oral stable isotope studies: A factor that contributes to the significant variation in estimates of DHA synthesis in humans, and therefore, adds significant uncertainty to conclusions regarding DHA synthesis, is heterogeneity between studies in background fatty acid intake. Dietary fatty acid composition has significant effects on the DHA synthesis rate. Specifically, DHA is known to down regulate enzymes involved in its own synthesis. In addition, n-6 PUFA may compete with n-3 PUFA for the enzymes involved in DHA synthesis. For example, higher fractional conversion of ALA into DHA has been shown in response to increased ALA: LNA ratio in the diet using compartmentalized modeling in humans.

Although methods utilizing oral administration of stable-isotope-labeled ALA to estimate DHA synthesis in humans may not directly measure a DHA synthesis rate, these measures do have utility in comparing DHA synthesis between individuals or groups in the same study. In general, conclusions can be drawn about the relative differences in DHA synthesis between groups, such as the finding that women utilize a greater proportion of n-3 DPA for DHA synthesis as compared with men. However, based on factors discussed previously, absolute DHA synthesis rates cannot be quantified with this method.Ingested fatty acid tracers also appear to poorly model the pharmacokinetics of *in situ* PUFA metabolism, in addition to having only a fraction of the tracer appear in the blood. For example, compartmental analysis revealed that stable isotope-labeled EPA is 40% less effectively utilized for DHA synthesis when ingested as compared with EPA that has been synthesized from ALA. This may also be true for ALA, in that ingested labeled ALA may poorly represent unlabeled ALA derived from body stores, although this has not been examined.

The use of stable isotope tracers to measure DHA synthesis has another general consideration, as one must by definition change the substrate concentration in the form of an administered tracer. This may increase flux through a pathway, result in substrate inhibition, or result in additional effects that might otherwise not occur under normal circumstances. Therefore, one must use the smallest amount of tracer that allow for reliable quantitation of the measure of interest so as not to influence the physiological process being measured. There is also some concern regarding deuterium exchange while using deuterium-labeled stable isotopes, in which deuterium atoms are exchanged with unlabeled hydrogen atoms. Though this exchange rate has not been quantified in DHA synthesis studies, hydrogen exchange between water and fatty acids has been found to be negligible under typical experimental conditions, suggesting that deuterium exchange is a quantitatively minor process. Also, deuterium exchange would most likely affect tracer/tracee ratio of both products and substrates in DHA synthesis (assuming all fatty acids have equal deuterium exchange rates). Therefore, studies calculating DHA synthesis as "percent of oral dose" are susceptible to underestimation if using ^{2}H-ALA, while studies calculating percent conversion based on comparisons between AUCs of ^{2}H-ALA and ^{2}H-DHA would likely be unaffected.[5]

Evidence that DHA synthesis affects blood DHA levels: In addition, there is evidence that significant changes in DHA status can occur independent of changes in n-3 PUFA intake, likely through increased synthesis of DHA from ALA. For example, women have higher DHA in plasma phospholipids and erythrocytes compared with men, which is associated with much higher rates of DHA synthesis in women. The higher DHA synthesis in women corresponds to higher hepatic expression of the Δ5- and Δ6-desaturase enzymes in female compared with male rodents. Female rats also have higher expression of fatty acid binding protein in hepatocytes, suggesting that binding and trafficking of ALA towards DHA synthesis may be higher in females as compared with males, and it is also possible that the half-life of DHA in the plasma is longer in women. Another example of DHA status being affected independent of changes in n-3 PUFA intake is altered fatty acid profiles associated with single nucleotide polymorphisms (SNP) in the human Fatty Acid Desaturase 2 gene (FADS2), the gene that encodes the Δ6-desaturase enzyme. The majority of these polymorphisms affect EPA concentrations, but not DHA concentrations, in phospholipids of plasma, serum, and erythrocytes; while analysis of a particular heliotype (with 28 SNP) has shown increased levels of DHA in plasma total lipids in the Northern Swedish Population Health Study. Also, a Δ6-desaturase SNP associated with increased Δ6-desaturase product: precursor ratios is associated with increased DHA percent composition in maternal erythrocytes during pregnancy and colostrums and a SNP with lower Δ6-desaturase activity is associated with lower levels of DHA in erythrocytes in pregnancy and breast milk. A recent study using orally administered ALA tracer found that some minor allele variants were associated with lower labeled EPA enrichment in the plasma as well as lower concentrations of ARA and EPA. These studies provide some evidence that DHA levels can be altered with no change in n-3 PUFA intake, with evidence that these changes are due, at least in part, from differences in DHA synthesis.

Forms: Triglyceride is the natural form. Basically, all supplements sold at present are in triglyceride form and some in ethyl ester and phospholipid form. However, some bioavailability of DHA or EPA in the lysophosphatidylcholine (LPC) form is more efficient than triglyceride and phosphatidylcholines (PC) according to a 2020 study.

Table-1: Base/DHA.

Base	DHA
Ethyl ester	DHA ethyl ester
Lysophosphatidylcholine (LPC, or lysoPC)	LPC-DHA, or lysoPC-DHA
Phosphatidylcholine (PC)	DHA-PC
Phosphatidylcholine (PC)	DHA-PC
Phosphatidylcholine (PC)	DHA-PC
Phosphatidylcholine (PC)	DHA-PC

Central nervous system constituent

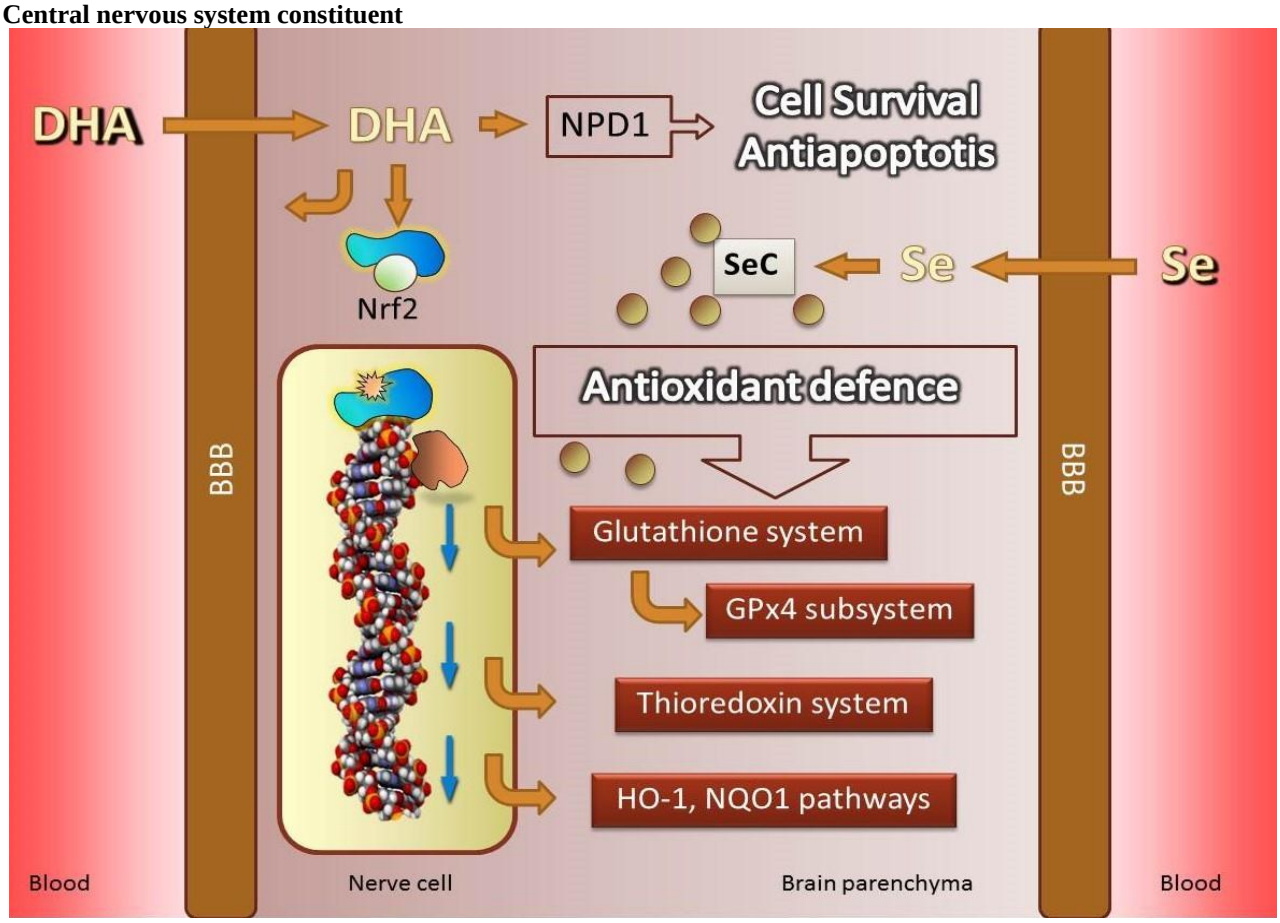


Figure-11: DHA and Its Elaborated Modulation of Antioxidant Defenses of the Brain: Implications in Aging and AD Neurodegeneration.

DHA is the most abundant omega-3 fatty acid in the brain and retina. DHA comprises 40% of the polyunsaturated fatty acids (PUFAs) in the brain and 60% of the PUFAs in the retina. Fifty percent of a neuronal plasma membrane is composed of DHA.DHA modulates the carrier-mediated transport of choline, glycine, and taurine, the function of delayed rectifier potassium channels, and the response of rhodopsin contained in the synaptic vesicles.

Phosphatidylserine (PS) – which contains high DHA content – has roles in neuronal signalling and neurotransmitter synthesis, and DHA deficiency is associated with cognitive decline. DHA levels are reduced in the brain tissue of severely depressed people.

Metabolic synthesis: In humans, DHA is either obtained from the diet or may be converted in small amounts from eicosapentaenoic acid (EPA, 20:5, ω-3) via docosapentaenoic acid (DPA, 22:5 ω-3) as an intermediate. This synthesis had been thought to occur through an elongation step followed by the action of Δ4-desaturase. It is now considered more likely that DHA is biosynthesized via a C24 intermediate followed by beta oxidation in peroxisomes. Thus, EPA is twice elongated, yielding 24:5 ω-3, then desaturated to 24:6 ω-3, then shortened to DHA (22:6 ω-3) via beta oxidation. This pathway is known as "Sprecher's shunt".

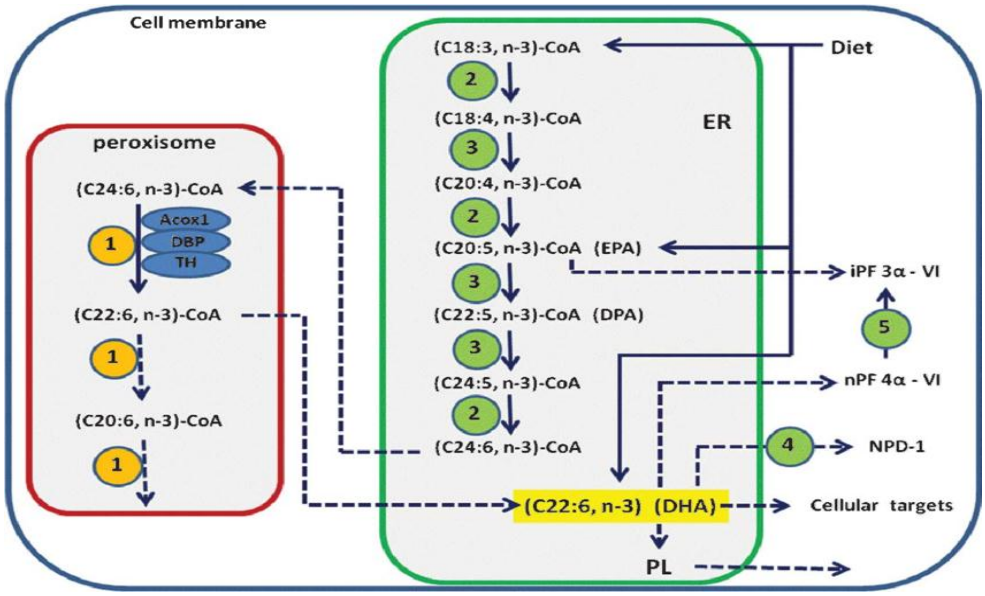


Figure-12: Metabolic synthesis pathways of DHA.

In organisms such as microalgae, mosses and fungi, biosynthesis of DHA usually occurs as a series of desaturation and elongation reactions, catalyzed by the sequential action of desaturase and elongase enzymes. One known pathway in these organisms involves:

1. A desaturation at the sixth carbon of alpha-linolenic acid by a Δ6 desaturase to produce stearidonic acid,
2. Elongation of the stearidonic acid by a Δ6 elongase to produce to eicosatetraenoic acid,
3. Desaturation at the fifth carbon of eicosatetraenoic acid by a Δ5 desaturase to produce eicosapentaenoic acid,
4. Elongation of eicosapentaenoic acid by a Δ5 elongase to produce docosapentaenoic acid, and
5. Desaturation at the fourth carbon of docosapentaenoic acid by a Δ4 desaturase to produce DHA.

Metabolism: DHA can be metabolized into DHA-derived specialized pro-resolving mediators (SPMs), DHA epoxides, electrophilic oxo-derivatives (EFOX) of DHA, neuroprostanes, ethanolamines, acylglycerols, docosahexaenoyl amides of amino acids or neurotransmitters, and branched DHA esters of hydroxy fatty acids, among others.The enzyme CYP2C9 metabolizes DHA to epoxydocosapentaenoic acids (EDPs; primarily 19,20-epoxy-eicosapentaenoic acid isomers [i.e. 10,11-EDPs]).

Potential health effects

Cardiovascular: Though mixed and plagued by methodological inconsistencies, there is now convincing evidence from ecological, RCTs, meta-analyses and animal trials show a benefit for omega-3 dietary intake for cardiovascular health. Of the n-3 FAs, DHA has been argued to be the most beneficial due to its preferential uptake in the myocardium, its strongly anti-inflammatory activity and its metabolism toward neuroprotection and resolvins, the latter of which directly contribute to cardiac function.[6]

Pregnancy and lactation: Foods high in omega-3 fatty acids may be recommended to women who want to become pregnant or when nursing. A working group from the International Society for the Study of Fatty Acids and Lipids recommended 300 mg/day of DHA for pregnant and lactating women, whereas the average consumption was between 45 mg and 115 mg per day of the women in the study, similar to a Canadian study.

Brain and visual functions: A major structural component of the mammalian central nervous system, DHA is the most abundant omega−3 fatty acid in the brain and retina. Brain and retinal function rely on dietary intake of DHA to support a broad range of cellmembrane and cell signalling properties, particularly in grey matter and retinal photoreceptor cell outer segments, which are rich in membranes. A systematic review found that DHA had no significant benefits in improving visual field in individuals with retinitis pigmentosa. Docosahexaenoic acid (DHA) is a structural constituent of membranes specifically in the central nervous system. Its accumulation in the fetal brain takes place mainly during the last trimester of pregnancy and continues at very high rates up to the end of the second year of life. Since the endogenous formation of DHA seems to be relatively low, DHA intake may contribute to optimal conditions for brain development. We performed a narrative review on research on the associations between DHA levels and brain development and function throughout the lifespan. Data from cell and animal studies justify the indication of DHA in relation to brain function for neuronal cell growth and differentiation as well as in relation to neuronal signalling.

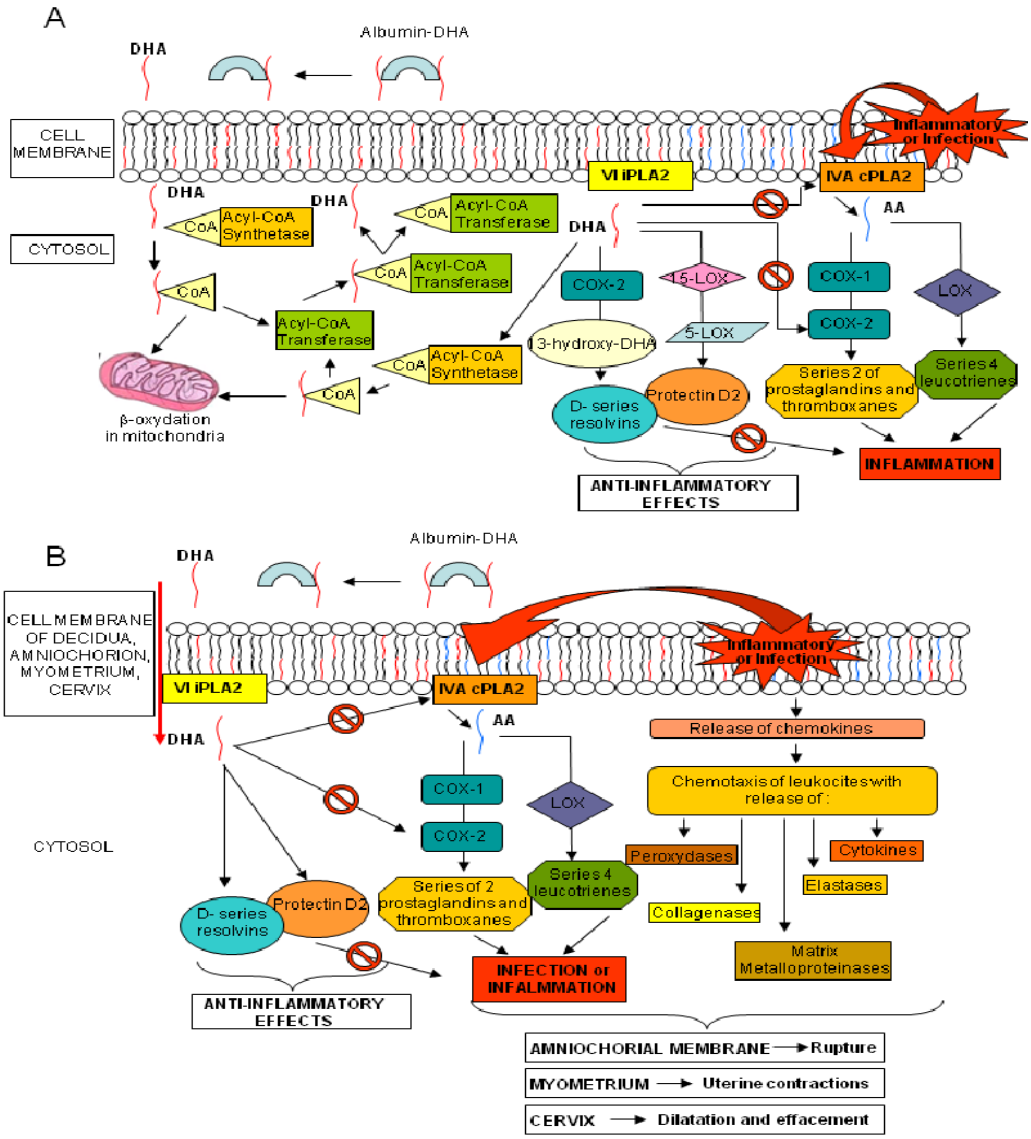


Figure-13: DHA Metabolism.

Most data from human studies concern the contribution of DHA to optimal visual acuity development. Accumulating data indicate that DHA may have effects on the brain in infancy, and recent studies indicate that the effect of DHA may depend on gender and genotype of genes involved in the endogenous synthesis of DHA.

While DHA levels may affect early development, potential effects are also increasingly recognized during childhood and adult life, suggesting a role of DHA in cognitive decline and in relation to major psychiatric disorders.[7]

Nutrition

Figure-14: DHA Supplements.

Ordinary types of cooked salmon contain 500–1500 mg DHA and 300–1000 mg EPA per 100 grams. Additional rich seafood sources of DHA include caviar (3400 mg per 100 grams), anchovies (1292 mg per 100 grams), mackerel (1195 mg per 100 grams), and cooked herring (1105 mg per 100 grams). Brains from mammals are also a good direct source. Beef brain, for example, contains approximately 855 mg of DHA per 100 grams in a serving.[8]

Discovery of algae-based DHA: In the early 1980s, NASA sponsored scientific research on a plant-based food source that could generate oxygen and nutrition on long-duration space flights. Certain species of marine algae produced rich nutrients, leading to the development of algae-based, vegetable-like oil that contains two polyunsaturated fatty acids, DHA and arachidonic acid.

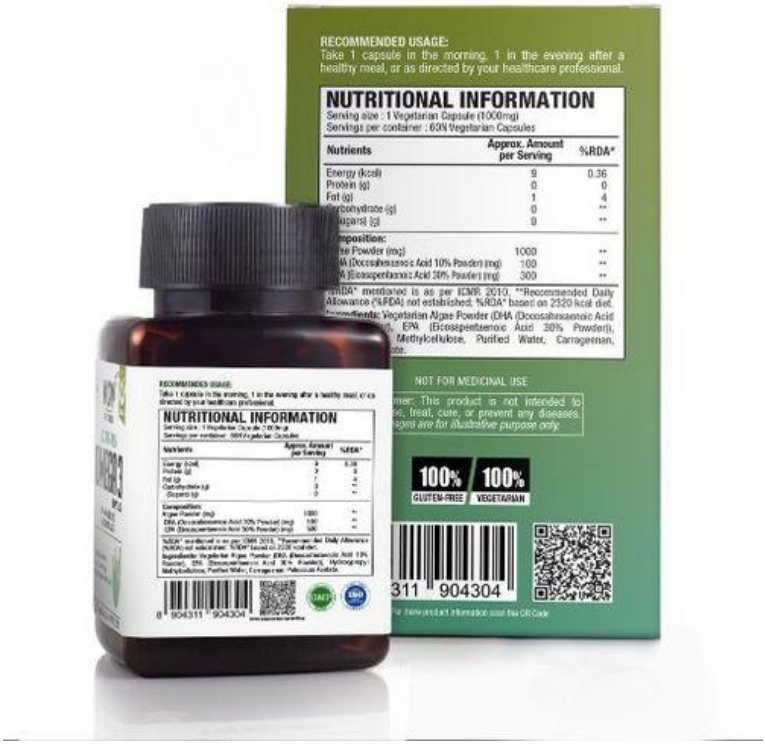
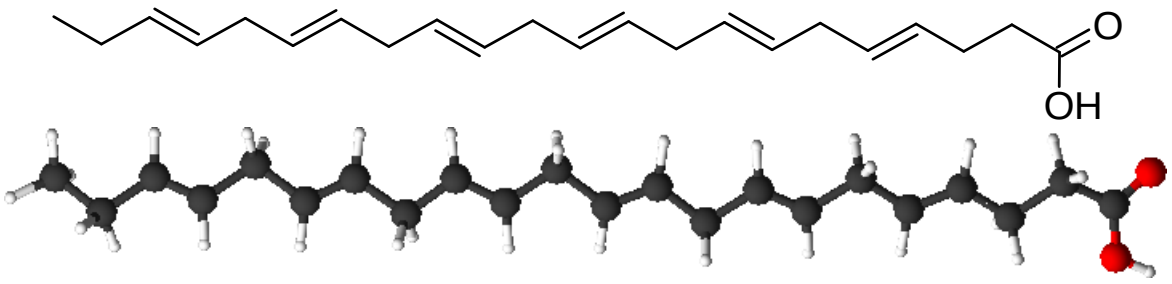


Figure-15: Algae Based DHA.

Use as a food additive: DHA [logP=6.68, IUPAC:4Z,7Z,10Z,13Z,16Z,19Z)-Docosa-4,7,10,13,16,19-hexaenoic acid, CAS: 6217-54-5] is widely used as a food supplement. It was first used primarily in infant formulas. In 2019, the US Food and Drug Administration published qualified health claims for DHA.

Some manufactured DHA is a vegetarian product extracted from algae, and it competes on the market with fish oil that contains DHA and other omega-3s such as EPA. Both fish oil and DHA are odorless and tasteless after processing as a food additive.[9]

Studies of vegetarians and vegans: Vegetarian diets typically contain limited amounts of DHA, and vegan diets typically contain no DHA. In preliminary research, algae-based supplements increased DHA levels. While there is little evidence of adverse health or cognitive effects due to DHA deficiency in adult vegetarians or vegans, breast milk levels remain a concern for supplying adequate DHA to the developing fetus.



DHA and EPA in fish oils: Fish oil is widely sold in capsules containing a mixture of omega-3 fatty acids, including EPA and DHA. Oxidized fish oil in supplement capsules may contain lower levels of EPA and DHA. Light, oxygen exposure, and heat can all contribute to oxidation of fish oil supplements. Buying a quality product that is kept cold in storage and then keeping it in a refrigerator can help minimize oxidation.[10,11]

OMEGA-9 FATTY ACIDS

Table-2: Omega-9 Fatty Acids.

oleic acid	18:1 (n-9)	9-octadecenoic acid
elaidic acid	18:1 (n-9)	(E)-octadec-9-enoic acid
gondoic acid	20:1 (n-9)	11-eicosenoic acid
mead acid	20:3 (n-9)	5,8,11-eicosatrienoic acid
erucic acid	22:1 (n-9)	13-docosenoic acid
nervonic acid	24:1 (n-9)	15-tetracosenoic acid

CONCLUSION

In organisms that do not eat algae containing DHA nor animal products containing DHA, DHA is instead produced internally from α-linolenic acid, a shorter omega-3 fatty acid manufactured by plants (and also occurring in animal products as obtained from plants). Limited amounts of eicosapentaenoic and docosapentaenoic acids are possible products of α-linolenic acid metabolism in young women and men. DHA in breast milk is important for the developing infant. Rates of DHA production in women are 15% higher than in men.

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