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Role of Omega 3 Fatty Acid in Human Health

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Abstract: ***In this paper based on doctrinal research, the article highlight the three types of omega−3 fatty acids involved in human physiology are α-linolenic acid (ALA), found in plant oils, and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both commonly found in marine oils. Marine algae and phytoplankton are primary sources of omega−3 fatty acids. Common sources of plant oils containing ALA include walnut, edible seeds, clary sage seed oil, algal oil, flaxseed oil, Sacha Inchi oil, Echium oil, and hemp oil, while sources of animal omega−3 fatty acids EPA and DHA include fish, fish oils, eggs from chickens fed EPA and DHA, squid oils, and krill oil. Dietary supplementation with omega−3 fatty acids does not appear to affect the risk of death, cancer or heart disease. Furthermore, fish oil supplement studies have failed to support claims of preventing heart attacks or strokes. Omega−3 fatty acids are important for normal metabolism. Mammals are unable to synthesize omega−3 fatty acids, but can obtain the shorter-chain omega−3 fatty acid ALA (18 carbons and 3 double bonds) through diet and use it to form the more important long-chain omega−3 fatty acids, EPA (20 carbons and 5 double bonds) and then from EPA, the most crucial, DHA (22 carbons and 6 double bonds). The ability to make the longer-chain omega−3 fatty acids from ALA may be impaired in aging. In foods exposed to air, unsaturated fatty acids are vulnerable to oxidation and rancidity.***

Keywords: Omega-3, Mammals, Phospholipids, metabolism, eicosapentaenoic

1. Introduction

Omega−3 fatty acids, also called **ω−3 fatty acids** or ***n*−3 fatty acids**, are polyunsaturated fatty acids (PUFAs). The fatty acids have two ends, the carboxylic acid (-COOH) end, which is considered the beginning of the chain, thus "alpha", and the methyl ($-CH_3$) end, which is considered the "tail" of the chain, thus "omega". One way in which a fatty acid is named is determined by the location of the first double bond, counted from the tail, that is, the omega (ω-) or the n- end. Thus, in omega-3 fatty acids the first double bond is between the third and fourth carbon atoms from the tail end. However, the standard (IUPAC) chemical nomenclature system starts from the carboxyl end [1].

The three types of omega−3 fatty acids involved in human physiology are α-linolenic acid (ALA), found in plant oils, and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both commonly found in marine oils. Marine algae and phytoplankton are primary sources of omega−3 fatty acids. Common sources of plant oils containing ALA include walnut, edible seeds, clary sage seed oil, algal oil, flaxseed oil, Sacha Inchi oil, *Echium* oil, and hemp oil, while sources of animal omega−3 fatty acids EPA and DHA include fish, fish oils, eggs from chickens fed EPA and DHA, squid oils, and krill oil. Dietary supplementation with omega−3 fatty acids does not appear to affect the risk of death, cancer or heart disease. Furthermore, fish oil supplement studies have failed to support claims of preventing heart attacks or strokes [2].

Omega−3 fatty acids are important for normal metabolism. Mammals are unable to synthesize omega−3 fatty acids, but can obtain the shorter-chain omega−3 fatty acid ALA (18 carbons and 3 double bonds) through diet and use it to form the more important long-chain omega−3 fatty acids, EPA (20 carbons and 5 double bonds) and then from EPA, the most crucial, DHA (22 carbons and 6 double bonds). The ability to make the longer-chain omega−3 fatty acids from ALA may be impaired in aging. In foods exposed to air, unsaturated fatty acids are vulnerable to oxidation and rancidity [3].

List of omega−3 fatty acids
This table lists several different names for the most common omega−3 fatty acids found in nature.

Common name	Lipid name	Chemical name
Hexadecatrienoic acid (HTA)	16:3 (*n*-3)	*all-cis*-7,10,13-hexadecatrienoic acid
α-Linolenic acid (ALA)	18:3 (*n*-3)	*all-cis*-9,12,15-octadecatrienoic acid
Stearidonic acid (SDA)	18:4 (*n*-3)	*all-cis*-6,9,12,15-octadecatetraenoic acid
Eicosatrienoic acid (ETE)	20:3 (*n*-3)	*all-cis*-11,14,17-eicosatrienoic acid
Eicosatetraenoic acid (ETA)	20:4 (*n*-3)	*all-cis*-8,11,14,17-eicosatetraenoic acid
Eicosapentaenoic acid (EPA)	20:5 (*n*-3)	*all-cis*-5,8,11,14,17-eicosapentaenoic acid
Heneicosapentaenoic acid (HPA)	21:5 (*n*-3)	*all-cis*-6,9,12,15,18-heneicosapentaenoic acid
Docosapentaenoic acid (DPA), Clupanodonic acid	22:5 (*n*-3)	*all-cis*-7,10,13,16,19-docosapentaenoic acid

Docosahexaenoic acid (DHA)	22:6 (*n*-3)	*all-cis*-4,7,10,13,16,19-docosahexaenoic acid
Tetracosapentaenoic acid	24:5 (*n*-3)	*all-cis*-9,12,15,18,21-tetracosapentaenoic acid
Tetracosahexaenoic acid (Nisinic acid)	24:6 (*n*-3)	*all-cis*-6,9,12,15,18,21-tetracosahexaenoic acid

Forms

Omega−3 fatty acids occur naturally in two forms, triglycerides and phospholipids. In the triglycerides, they, together with other fatty acids, are bonded to glycerol. Phospholipid omega−3 is composed of two fatty acids attached to a phosphate and choline, versus the three fatty acids attached to glycerol in triglycerides.

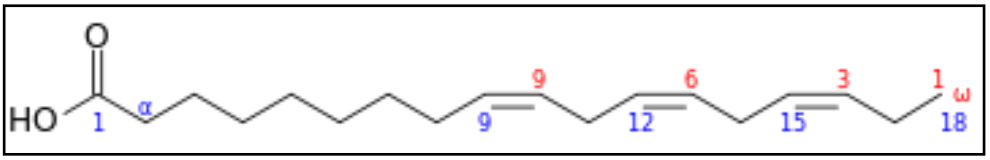
The triglycerides can be converted to the free fatty acid or to methyl or ethyl esters, and the individual esters of omega−3 fatty acids are available [4].

Biochemistry

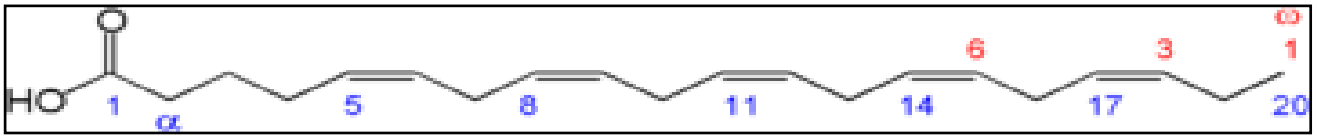
Transporters

DHA in the form of lysophosphatidylcholine is transported into the brain by a membrane transport protein, MFSD2A, which is exclusively expressed in the endothelium of the blood–brain barrier.

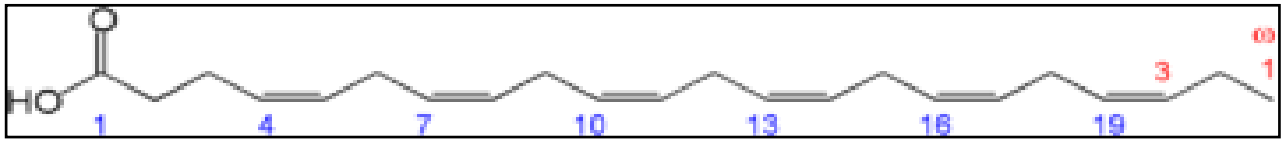
Chemistry



Chemical structure of alpha-linolenic acid (ALA), an essential omega−3 fatty acid, (18:3Δ9c,12c,15c, which means a chain of 18 carbons with 3 double bonds on carbons numbered 9, 12, and 15). Although chemists count from the carbonyl carbon (blue numbering), biologists count from the *n* (ω) carbon (red numbering). Note that, from the *n* end (diagram right), the first double bond appears as the third carbon-carbon bond (line segment), hence the name "*n*-3". This is explained by the fact that the *n* end is almost never changed during physiological transformations in the human body, as it is more energy-stable, and other compounds can be synthesized from the other carbonyl end, for example in glycerides, or from double bonds in the middle of the chain [5].



Chemical structure of eicosapentaenoic acid (EPA)



Chemical structure of docosahexaenoic acid (DHA)

An omega−3 fatty acid is a fatty acid with multiple double bonds, where the first double bond is between the third and fourth carbon atoms from the end of the carbon atom chain. "Short chain" omega−3 fatty acids have a chain of 18 carbon atoms or less, while "long chain" omega−3 fatty acids have a chain of 20 or more.

Three omega−3 fatty acids are important in human physiology, α-linolenic acid (18:3, *n*-3; ALA), eicosapentaenoic acid (20:5, *n*-3; EPA), and docosahexaenoic acid (22:6, *n*-3; DHA).

Health effects

Supplementation does not appear to be associated with a lower risk of all-cause mortality [6].

Cancer

The evidence linking the consumption of marine omega−3 fats to a lower risk of cancer is poor. With the possible exception of breast cancer, there is insufficient evidence that supplementation with omega−3 fatty acids have an effect on different cancers. The effect of consumption on prostate cancer is not conclusive. There is a decreased risk with higher blood levels of DPA, but an increased risk of more aggressive prostate cancer was shown with higher blood levels of combined EPA and DHA. In people with advanced cancer and cachexia, omega−3 fatty acids supplements may be of benefit, improving appetite, weight, and quality of life [7].

Cardiovascular disease

Evidence in the population generally does not support a beneficial role for omega−3 fatty acid supplementation in preventing cardiovascular disease (including myocardial infarction and sudden cardiac death) or stroke. However, omega−3 fatty acid supplementation greater than one gram daily for at least a year may be protective against cardiac death, sudden death, and myocardial infarction in people

who have a history of cardiovascular disease. No protective effect against the development of stroke or all-cause mortality was seen in this population. Eating a diet high in fish that contain long chain omega−3 fatty acids does appear to decrease the risk of stroke. Fish oil supplementation has not been shown to benefit revascularization or abnormal heart rhythms and has no effect on heart failure hospital admission rates.[22] Furthermore, fish oil supplement studies have failed to support claims of preventing heart attacks or strokes.

Evidence suggests that omega−3 fatty acids modestly lower blood pressure (systolic and diastolic) in people with hypertension and in people with normal blood pressure. Some evidence suggests that people with certain circulatory problems, such as varicose veins, may benefit from the consumption of EPA and DHA, which may stimulate blood circulation and increase the breakdown of fibrin, a protein involved in blood clotting and scar formation. Omega−3 fatty acids reduce blood triglyceride levels but do not significantly change the level of LDL cholesterol or HDL cholesterol in the blood. The American Heart Association position (2011) is that borderline elevated triglycerides, defined as 150–199 mg/dL, can be lowered by 0.5-1.0 grams of EPA and DHA per day; high triglycerides 200–499 mg/dL benefit from 1-2 g/day; and >500 mg/dL be treated under a physician's supervision with 2-4 g/day using a prescription product [8].

ALA does not confer the cardiovascular health benefits of EPA and DHAs. The effect of omega−3 polyunsaturated fatty acids on stroke is unclear, with a possible benefit in women. **Inflammation**: A 2013 systematic review found tentative evidence of benefit for lowering inflammation levels in healthy adults and in people with one or more biomarkers of metabolic syndrome. Consumption of omega−3 fatty acids from marine sources lowers blood markers of inflammation such as C-reactive protein, interleukin 6, and TNF alpha [9].

Developmental disabilities
Although not supported by current scientific evidence as a primary treatment for attention deficit hyperactivity disorder (ADHD), autism, and other developmental disabilities, omega−3 fatty acid supplements are being given to children with these conditions.

One meta-analysis concluded that omega−3 fatty acid supplementation demonstrated a modest effect for improving ADHD symptoms. A Cochrane review of PUFA (not necessarily omega−3) supplementation found "there is little evidence that PUFA supplementation provides any benefit for the symptoms of ADHD in children and adolescents", while a different review found "insufficient evidence to draw any conclusion about the use of PUFAs for children with specific learning disorders". Another review concluded that the evidence is inconclusive for the use of omega−3 fatty acids in behavior and non-neurodegenerative neuropsychiatric disorders such as ADHD and depression.

Fish oil has only a small benefit on the risk of premature birth. A 2015 meta-analysis of the effect of omega−3 supplementation during pregnancy did not demonstrate a decrease in the rate of preterm birth or improve outcomes in women with singleton pregnancies with no prior preterm births. A systematic review and meta-analysis published the same year reached the opposite conclusion, specifically, that omega−3 fatty acids were effective in "preventing early and any preterm delivery" [10].

Mental health
There is some evidence that omega−3 fatty acids are related to mental health, including that they may tentatively be useful as an add-on for the treatment of depression associated with bipolar disorder. Significant benefits due to EPA supplementation were only seen, however, when treating depressive symptoms and not manic symptoms suggesting a link between omega−3 and depressive mood. There is also preliminary evidence that EPA supplementation is helpful in cases of depression. The link between omega−3 and depression has been attributed to the fact that many of the products of the omega−3 synthesis pathway play key roles in regulating inflammation such as prostaglandin E3 which have been linked to depression.[48] This link to inflammation regulation has been supported in both in vitro and in vivo studies as well as in meta-analysis studies. The exact mechanism in which omega−3 acts upon the inflammatory system is still controversial as it was commonly believed to have anti-inflammatory effects. [11]

There is, however, significant difficulty in interpreting the literature due to participant recall and systematic differences in diets. There is also controversy as to the efficacy of omega−3, with many meta-analysis papers finding heterogeneity among results which can be explained mostly by publication bias. A significant correlation between shorter treatment trials was associated with increased omega−3 efficacy for treating depressed symptoms further implicating bias in publication. [12]

Risk of deficiency
People with PKU often have low intake of omega−3 fatty acids, because nutrients rich in omega−3 fatty acids are excluded from their diet due to high protein content.

Asthma
As of 2015 there was no evidence that taking omega 3 supplements can prevent asthma attacks in children.

Mechanism of action
The 'essential' fatty acids were given their name when researchers found that they are essential to normal growth in young children and animals. The omega−3 fatty acid DHA, also known as docosahexaenoic acid, is found in high abundance in the human brain. It is produced by a desaturation process, but humans lack the desaturase enzyme, which acts to insert double bonds at the ω_6 and ω_3 position. Therefore, the ω_6 and ω_3 polyunsaturated fatty acids cannot be synthesized and are appropriately called essential fatty acids.

In 1964 it was discovered that enzymes found in sheep tissues convert omega−6 arachidonic acid into the inflammatory agent called prostaglandin E_2 which both causes the sensation of pain and expedites healing and immune response in traumatized and infected tissues. By

1979 more of what are now known as eicosanoids was discovered: thromboxanes, prostacyclins, and the leukotrienes. The eicosanoids, which have important biological functions, typically have a short active lifetime in the body, starting with synthesis from fatty acids and ending with metabolism by enzymes. If the rate of synthesis exceeds the rate of metabolism, the excess eicosanoids may, however, have deleterious effects. Researchers found that certain omega−3 fatty acids are also converted into eicosanoids, but at a much slower rate. Eicosanoids made from omega−3 fatty acids are often referred to as anti-inflammatory, but in fact they are just less inflammatory than those made from omega−6 fats. If both omega−3 and omega−6 fatty acids are present, they will "compete" to be transformed, so the ratio of long-chain omega−3:omega−6 fatty acid directly affects the type of eicosanoids that are produced. [13]

Aims and Objectives

It is a review article of Omega-3 Fatty Acids has been use from ancient time for the purpose of health benefits. Different marketed products of Aloe very are use to improve different health condition as well as cosmetology product. From that background this review work has been selected to find out the role of Aloe Vera on human health.

The main aims of the paper are

- To investigate the therapeutic potential of omega-3 fatty acids.
- This article aims to present science-based benefits of omega-3 for the human body and what are the food sources of these fatty acids.
- To search out the effect of Aloe Vera on heart, brain and other body organ function.
- To collect the information how aloe Vera use effective for skin related problem.

Ultimately this study has been focused on the safe use of Aloe Vera in our community at present.

2. Review of Literature

Omega-3 PUFA Efficacy in the Cardiovascular Field

The predominant field of omega-3 PUFA research in the past decades has been that of cardiovascular medicine and prevention. This is the field in which the hypothesis of a protective effect of omega-3 PUFA was founded, and a large clinical study establishing a benefit was the basis for approval of omega-3 PUFA as secondary prevention in patients after myocardial infarction. The GISSI-Prevention trial was performed as an open-label trial in the 1990s in 11324 patients shortly after myocardial infarction. Participants in the omega-3 PUFA group received 1 g/d omega-3 PUFA (ratio of EPA/DHA 1: 2, with a total amount of EPA + DHA of approximately 850 mg) for 3.5 years. There were no systematic fatty acid measurements performed in the participants, but, as an indication of omega-3 PUFA uptake, triglycerides were lower in the omega-3 PUFA group. Treatment with omega3 PUFA significantly lowered the risk of death, including cardiovascular death. This area has seen some good examples of translational research, particularly with regard to the ant arrhythmic effects attributed to omega-3 PUFA. Leaf was a pioneer in the field of omega-3 PUFA research showing that these FA can block proarrhythmogenic effects of adrenal agents, calcium, and other substances in isolated cardiomyocytes, continuing with studies in animals, and finally concluding his research in a large human multicenter trial. The concept of cardio protection through omega3 PUFA supplementation has been firmly engrained into the canon of medical knowledge and clinical thinking, as is evidenced by the AHA guidelines recommending intake of omega-3 PUFA. [13]

However, while preclinical data regarding the anti arrhythmic effect of omega-3 PUFA were strongly beneficial, the double-blind intervention study by Leaf et al. [14] does not show a clear benefit. A relevant problem of the study was the high noncompliance rate (35% of enrollees, similar in fish oil and olive oil groups), probably due to the high capsule load (2600 mg fish oil per day). Treatment with daily fish oil or olive oil for 12 months in patients with implanted cardio verter/defibrillators (ICDs) did not lead to a significant difference for the primary end point (time to first ICD event for ventricular tachycardia (VT) or death from any cause). However, there was a significant effect in participants who were at risk of fatal ventricular arrhythmias and, after staying on protocol for at least 11 months, showed a significant risk reduction of 38%. Phospholipid fatty acid content of red blood cells was compared in a subset of participants in the study, and omega-3 PUFA content increased significantly from 3.4% to 7.6% of total fatty acids, while it remained at 3.5% in the olive oil control group. [19]

There are two more randomized, double-blind, place bocontrolled trials with omega-3 PUFA supplementation performed in patients with ICDs and at high risk of high-grade arrhythmic events. In one, 200 patients with an ICD and a recent episode of sustained VT or ventricular fibrillation (VF) received either 1300 mg/d omega-3 PUFA or placebo and were followed up for 2 years. While patients on fish oil hadanincreaseinthemeanpercentageofomega-3PUFAin red blood cell membranes from 4.7% at baseline to a steady state maximum of 8.3% at 3 months, there was no protection from VT/VF events . The third study did not find a significant advantage for omega-3 PUFA supplementation in ICD patients receiving 2 g/d of fish oil (n = 273) versus prevention. This is the field in which the hypothesis of a protective effect of omega-3 PUFA was founded, and a large clinical study establishing a benefit was the basis for approval of omega-3 PUFA as secondary prevention in patients after myocardial infarction. The GISSI-Prevenzione trial was performed as an open-label trial in the 1990s in 11324 patients shortly after myocardial infarction. Participants in the omega-3 PUF A group received 1 g/d omega-3 PUFA (ratio of EPA/DHA 1 : 2, with a total amount of EPA + DHA of approximately 850 mg) for 3.5 years. There were no systematic fatty acid measurements performed in the participants, but, as an indication of omega-3 PUFA uptake, triglycerides were lower in the omega-3 PUFA group. Treatment with omega3 PUFA significantly lowered the risk of death, including cardiovascular death. This area has seen some good examples of translational research, particularly with regard to the anti arrhythmic effects attributed to omega-3 PUFA.

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In addition to these high-quality data sets showing uncertainty regarding the anti arrhythmic effect of omega-3 PUFA, several large studies followed up on the initial positive GISSI-P results. The GISSI-HF investigated the effect of 1 g/d omega-3 PUFA in patients with heart failure in a randomized, double-blind, placebo-controlled trial with 6975 participants. Over approximately 4 years there was a small significant advantage in the omega-3 PUFA group for death from any cause and admission to hospital for cardiovascular reasons with a number needed to treat of 56 to prevent one death.

A multicenter, double-blind, placebo-controlled trial with 4837 patients after a myocardial infarction tested 40 months of fatty acid supplementation in the form of margarines, either adding a small amount of approximately 400 mg/d EPA + DHA, 2 g/d of ALA, both EPA + DHA and ALA, or placebo fat. Neither EPA-DHA nor ALA reduced the primary endpointofa major cardiovascular event. Fatty acids were measured in plasma cholesterol esters of subgroups, and supplementation with EPA + DHA increased EPA by 53.3% and DHA by 28.6%, as compared with placebo after 20 months. Unfortunately, fatty acid composition of red blood cell membranes was not measured in this study.

The study is the study that failed to show a clear benefit of omega-3 PUFA supplementation for cardiovascular health. This study, conducted in a patient population with dysglycemia, led many physicians to conclude that the relationship between dietary omega-3 and cardiovascular health needs to be viewed with caution. In this double-blind study 12536 dysglycemic patients at high risk forcardiovascularevents wereassignedtoeither900mg/d omega-3 PUFA or placebo.

The low omega-3 index was described to be associated with higher mortality in patients with cardiovascular disease However; so far, there has been no single well-accepted and uniformly performed blood test for the omega-3 PUFA status in human studies, complicating the comparison and interpretation of different studies. The current states of evidence for the effects of omega-3 PUFA in human studies regarding cardiovascular diseases and the contrasting outcomes have been summarized in Tabl e 3. Additional possible reasons for the controversies in the field are reported in Section 6. Last but not least, it should be noted that the effect of omega-3 PUFA in the cardiovascular field can also be viewed in the context of their role as precursors of highly potent physiologically beneficial lipid mediators. A cytochrome P450 epoxygenase-dependent metabolite of EPA, namely17(R), 18(S)-epoxyeicosatetraenoic acid (17(R), 18(S)-EETeTr), was found to exert negative chronotropic effects and can protect neonatal rat cardiomyocytes against Ca2+-overload. Another EPA-metabolite, 18-hydroxyeicosapentaenoic acid (18-HEPE), was recently shown to inhibit macrophage mediated proinflammatory activation of cardiac fibroblasts in vitro, while in vivo administration of 18-HEPE led to resistance to pressure overload-induced maladaptive cardiac remodeling in mice. [17]

Omega-3 Efficacy in Inflammatory Diseases

Research data accumulated to date indicate that omega-6 PUFA play a significant role in the biology of inflammation Work on the biochemistry of omega-6 led to the identification of prostaglandins and leukotrienes as key players in the physiology of inflammation. Moreover, this work elucidated the cascade of the molecular mediator system arising from the omega-6 PUFA arachidonic acid and led to mechanistic understanding and further development of the most widely prescribed drug class worldwide, the cyclooxygenase (COX-) inhibitors. Early workonomega-3PUFA identified the antagonism between omega-6 and omega-3 PUFA. It was postulated that, by competitive inhibition of COX and other enzymes, omega3

PUFA could serve as anti-inflammatory agents. Indeed, it has been found that a high omega-3 intake was associated with a lower risk of inflammatory disease mortality.

Omega-3 Efficacy in Cancer

Mechanisms Involved in Omega-3 PUFA Anticancer Action. Most of the studies performed either in vitro or using animal models of cancer have demonstrated the possible preventive and therapeutic role of omega-3 PUFA against several types of cancer. These studies have also shed light on multiple molecular pathways modulated by these fatty acids in cancer cells and implicated in the regulation of several cell processes involved in cancer development and progression, such as cell proliferation, survival, differentiation, thus leading to increased legend-induced receptor demonization and phosphorylation along with its internalization and degradation. These changes, in turn, resulted in the disruption of the EGFR-Ras-ERK1/2 signaling cascade and the inhibition of cell proliferation A second main possible direct route for the omega-3 PUFA action is related to their high peroxidability that makes them optimal substrates for oxidants inside the cells. Through this route, these fatty acids may induce alterations of the cell oxidative status and modulation of oxidative stress dependent molecular pathways related to cell proliferation, apoptosis, or inflammation.

Moreover, a third main direct route for the omega-3 PUFA action is related to their possible metabolic conversion into bioactive molecules with powerful anti-inflammatory and proresolving action (i.e., resolvins, protectins, etc.). Receptors binding specifically to both these bioactive molecules (such as ChemR23, leukotriene B4 receptor 1, LTB4R1, and G protein coupled receptor, GRP32) [51] as well as to omega-3

Omega PUFAs and eye health

One of the fields which need further investigation and evidence as related to the effects of n-3 omega PUFAs is on eye health. One disease of the eye which has been most studied is age related macular degeneration (ARMD), an illness that progressively degenerates the back of the eye (macula). There is also insufficient evidence with few prospective studies and no randomized clinical trials to support n-3 omega PUFAs routine consumption for ARMD prevention. Claim in their study that weekly consumption of two or three portions of fatty fish can be beneficial for ARMD patients. The claim is based on an 8-year study of 3000 patients who were given n-3 omega supplements and monitored for the possible development of macular degeneration. Findings determined ARMD 25% less likely among participants consuming a diet rich in omega 3 fatty acids, EPA and DHA. The authors concluded that the combined consumption of a diet rich in omega 3 with low glycemic index carbohydrates such as whole bread products rather than processed may diminish the risk of progression of the disease to the advanced state. Deficiency of n-3 omega PUFAs was also shown to be adversely effective especially on visual and neural function in preterm infants which may need to be supported by n-3 omega formulas since n-3 omega PUFAs rich formula supports for visual and cortical function significantly in such infants.

Omega-3 PUFA in Colon Cancer

Dietary omega-3 PUFA has attracted considerable interest for their potential to prevent the development and progression of colorectal cancer (CRC) [8,]. An impressive body of evidence has been obtained in preclinical studies using in vivo CRC models, consistently supporting the antineoplastic role of omega-3 PUFA [8,], in spite of the high variability of the models and experimental conditions used [52]. Among all these data only very few were in conflict with a protective effect of the omega-3 PUFA, but in these cases extremely high doses of LC-omega-3 PUFA were administered (about 3–7 g EPA + DHA/kg body weight in mouse or 12 g EPA + DHA/kg body weight in rat; for the calculation used, see. These high doses may generate vast amounts of oxidized products with high prooxidant and carcinogenic activity. Many in vitro studies [8,] activity of omega-3 PUFA and, as discussed in the previous section, allowed identification of possible biological and molecular mechanisms [53]. Remarkably, among the in vitro studies [54] are those that recently investigated thepossibleeffectsofomega-3PUFAoncolorectalcancer stem cells (CCSC). It is believed that CCSC may drive colon tumorigenesis, being principal targets of tumorigenic genetic alterations, due to their long lifespan and capacity for selfrenewal. Moreover, they have also been related to cancer relapse, acquisition of chemotherapy resistance, and metastasis [55]. CCSC are characterized for lacking specific markers of colonic epithelium differentiation, such as cytokeratin 20 (CK20) or mucin 2 (MUC2), and expressing instead specific clusters of differentiation, such as CD133 or Lgr5 antigens (labeling undifferentiated cells. Moreover, most of cancer stem cells form spheres when cultured in serum free conditions that are highly tumorigenic if injected in immunodeficient mice.

Skin disorders

In one clinical study, 13 people with a particular sensitivity to the sun known as photo dermatitis showed significantly less sensitivity to UV rays after taking fish oil supplements. Still, research indicates that topical sunscreens are much better at protecting the skin from damaging effects of the sun than omega-3 fatty acids In another study of 40 people with psoriasis, those who were treated with medications and EPA supplements did better than those treated with the medications alone. In addition, many clinicians believe that flaxseed which contains omega-3 fatty acids is helpful for treating acne.

3. Discussion

Several reasons may be responsible for the discrepancies registered among the outcomes of human studies. First of all, it should be considered that even though omega-3 PUFA can be regarded as medication and high-dose preparations are approved as prescription drugs in many parts of the world, omega-3 PUFA are essential part of our diet. Their intake can vary widely from population to population and even within the same person, depending on actual dietary habits or short term dietary changes (eating seafood during vacations on the coast). Often, the epidemiological observational studies, particularly the early studies, refer to Food Frequency Questionnaire and Diet Records to establish fish consumption.

A number of other variables may contribute to this scarce correlation, such as the individual capacity to absorb and make the PUFA bioavailable at the serum level, the fat content of the diet, or the omega-3/omega-6 PUFA dietary ratio. Moreover, different methods are used to calculate dietary fats or specific FA in the diets. Often the questionnaires refer only to fish servings per week, without considering the serving size or the kind of fish consumed (lean fish or fatty fish). It is known that there exists an extreme variability in fish intake among populations, and if we consider the amount of fish ingested by the "low fish consumers" among the populations at high fish intake, it may correspond to or be even higher than the amount consumed by the "high fish consumers" in the populations at low fish intake. As a matter of fact, positive association between dietary intake of omega3 PUFA and health effects has been registered mainly among population eating fish at high levels. Some intrinsic weaknesses of questionnaire studies could thus be addressed by actually measuring omega-3 PUFA in the participants. Some more recent studies have directly evaluated the levels of omega-3 PUFA in serum, in different plasmatic lipid classes, or in erythrocytes. Whereas it has been argued that measuring the omega-3 PUFA level only in one class of plasma lipids may be misleading it has been suggested that erythrocyte EPA and DHA content (named "omega-3 index") may better reflect the omega-3 PUFA status of the subjects. [18]

This is because the plasma-based measurements merely represent the short-term availability of omega-3 PUFA, being susceptible to artificial elevation following an acute omega-3 PUFA load [13]. Indeed, it has been recently reported that an acute single dose (3.4–4 g/d) of omega-3 PUFA, in the form of either prescription medication or dietary supplements, peaked plasma EPA + DHA levels asearlyas5hafteradministration,where as the EPA plus DHA concentrations in erythrocyte membranes were only increased by approximately 10 orders of magnitude less than the concurrent plasma (3% versus 30%) from baseline at 24 h [15]. Therefore, even if a single evaluation may be confounding, since serum FA are powerfully affected by feeding/fasting cycles and by the lipid content of the last meal consumed [27], one possibility of overcoming the discrepanciesinomega-3PUFAresearchistocallforactuacorrelation of questionnaire-based calculations of omega3 PUFA intake with at least one actual measurement per participant in order to obtain some biochemical information regarding actual omega-3 PUFA levels. Moreover, we ask if intervention studies administering defined amounts of omega-3 PUFA may solve this problem. At least these studies exactly define the amount of omega-3 PUFA administered.

This is a concept obviously radically different from synthetic drug studies and something that has always to be taken into account when assessing intervention studies. In such studies, the animals/subjects have been treated with specific and controlled amounts of omega-3 PUFA. But most of these studies neither established baseline omega-3 PUFA body content in the participants nor monitored omega-3 PUFA during the study, making proper interpretation of the obtained results difficult. A recent study properly addressing these issues was the Welcome Trial in NASH patients, in which interpretation of the data focused on the correlation of measured DHA enrichment with liver fat content, as well as on pure ITT analysis of the treatment group. It demonstrated a statistically significant linear correlation between decreased liver fat content and increased DHA enrichment, but no significant effect in the ITT treatment group analysis [64]. Therefore, as in observational studies intervention trials should perform biochemical analyses of omega-3 PUFA content to (1) define baseline levels in the different groups and (2) determine actual changes in the different groups due to the treatment as compared to the placebo group, where some of the participants might actually contaminate the results by starting to consume a high fish diet during the trial period.

4. Conclusion

It is conclude that review of the omega-3 PUFA research literature prompts us to conclude that the animal and in vitro data have been remarkably consistent in showing health benefits, particularly through mechanisms dampening inflammation and proliferation in different tissues. These results have established potential protective effects of omega-3 PUFA in diseases ranging from cardiac arrhythmia and inflammatory conditions (atherosclerosis to airway inflammation, colitis, pancreatitis, steatohepatitis , arthritis, etc.) to tumorigenesis (particularly colon and liver tumors, but also breast and prostate cancer). On the other hand, the outcomes of human studies have been so far quite controversial. Therefore, in order to shed more light on this point and better understand if the divergences were ascribable to possible methodological weaknesses in human studies or, alternatively, to different responses of human cells/tissues to the incorporation of omega-3 as compared to those of laboratory animal species, it is suggested that all future studies in this field should perform blood FA measurements in trial participants. These evaluations should be preferably performed in blood cells, and, whenever possible, at baseline as well as at different time-points during the study. This procedure would also be extremely helpful to (1) monitor the effect of the huge omega3 PUFA supplement industry in the western world on omega3 PUFA content in humans, (2) understand the effect of other FA in the context of omega-3 PUFA interventions, and (3) recognize variations in individual responses to omega-3 PUFA supplementation.

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