Research Article

Omega-3 Fatty Acids: A Review of Its Wide Range of Applications and Possible Mechanisms of Action

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ABSTRACT

Consumption of fish/fish oil has been reported to modulate the symptoms in cardiovascular disease, inflammatory responses, cancer, and neurological disorders. The objective of this review is to provide therapeutic role of polyunsaturated fatty acids (PUFA) with practical evidences carried out in recent years. Literature studies were selected using the Google, Pub Med and Medline database on the basis of the following criteria: (1) significance of omega-3-fatty acid in nutrition and disease (2) randomized controlled design, placebo controlled studies using Eicosapentaenoic acid and Docosahexaenoic acid. Imbalance in fatty acid composition is thought to be the major risk factor for the development and progression of various diseases. Omega-3 fatty acid up regulates anti-inflammatory and anti-apoptotic gene expression. It also competes with enzymes essential for ω-6 PUFA derived pro-inflammatory eicosanoid mediators. In addition, it reduces blood pressure, angiogenesis process. Interactions of PUFA with signal transduction pathways reverse the symptoms associated with depression whereas transcription factors modulates tumor metabolism. Consumption of fatty fish/ fish oil is associated with reduced risk for cardiovascular disease, inflammatory responses, cancer and neurological disorders.

Keywords: ω-3 polyunsaturated fatty acids, Eicosapentaenoic acid, Docosahexaenoic acid, biopharmaceuticals, health disorder.

INTRODUCTION

Fatty acids are chains of hydrocarbons with carboxylic acid (COOH) at one end and an methyl group at the other end. Human and mammalian system cannot place a double bond at the third carbon position or in the sixth carbon position from the methyl end or omega end of the fatty acid (FA) chain. For this reason, linoleic acid (LA, 18:2) and alpha- linolenic acid (ALA, 18:3) are called as essential fatty acids (EFA). Polyunsaturated fatty acids (PUFAs) include the family of ω-3 and ω-6 fatty acids. Omega-3 series are derived from ALA and omega-6 from linoleic acid. Alpha-linolenic acid is converted into long chain ω-3 PUFA such as Eicosapentaeonic acid (EPA, 20:5, ω-3) and Docosahexaenoic acid (DHA, 22:6, ω-3). Similarly, LA can be sequentially converted via biosynthetic pathway into other ω -6 fatty acids i.e Gamma-linolenic acid (GLA, 18:3, ω−6), Arachidonic acid (AA, 20:4, ω−6) and Di-homo-gamma-linolenic acid (DGLA, 20:3, ω-6). Since Burr and Burr's[1] discovery of EFA namely ω-6 LA and ω -3 ALA, the subject on PUFAs has opened to a better understanding of their role in public health and disease [Figure 1].

Although mammalian cells cannot synthesize LA and ALA they can be formed by the introduction of double bonds (desaturation step) via Δ^5 and Δ^6 desaturase and by increasing the acyl chain (elongation) via elongases [Figure2]. Consequently, LA is converted to GLA by the action of Δ^6 desaturase and GLA is elongated to form DGLA, the precursor of the 1 series prostaglandins (PGs). Dihomo-gamma-linolenic acid is further converted into AA (20:4, ω-6) by Δ^6 desaturase. Arachidonic acid is the precursor of 2 series of PGs, thromboxanes, 4 series of Leukotrienes (LT). Using the same series of enzymes as those used to metabolize ω-6 PUFAs (elongases, Δ^5 and Δ^6 desaturases), ALA is converted to EPA (20:5, ω-3) by Δ^5 and Δ^6 desaturase. Eicosapentaenoic acid is the precursor of 3 series of PGs, 5 series of LT and resolvins. Since LA and ALA compete for the same set of enzymes abundant of one reduces the metabolism of the other. Under an ideal physiological ratio of 1:4, Δ^5 and Δ^6 desaturases and elongases have higher affinity to metabolize ω-3 over ω-6 PUFAs. Eicosapentaenoic acid further gets converted to DHA by elongases and Δ^6 desaturase respectively. Only 8-20% of ALA is converted into EPA in humans, ALA to DHA is less or around 0.5-9%. This lower rate of conversion is unlikely to provide sufficient levels of EPA and DHA for normal health and therefore mammalian system is dependent on dietary sources rich in polyunsaturated fatty acid. In recent years, tremendous work has been carried out worldwide to elucidate the therapeutic importance of PUFAs, in general, and omega-3-fatty acids, in particular, in human health care. This review gives compilation of theoretical and practical evidences published on this topic for the past five years for the benefit of scientific and unscientific society.

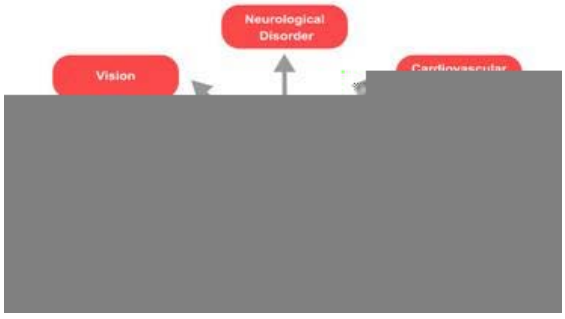

Figure 1: Properties of omega-3-fatty acid

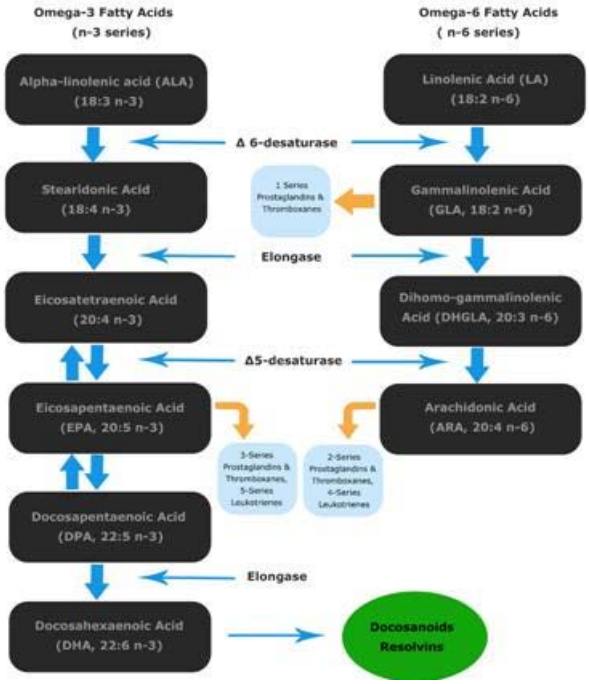

Figure 2: Biosynthetic pathway of polyunsaturated fatty acid and their mediators

SOURCES OF PUFA

Seaweeds and unicellular phytoplankton are the major sources of ω-3 FA (EPA & DHA). Marine fishes are enriched with long chain PUFA (LC-PUFA) as they consume phytoplankton and get transferred to different levels of species through food chain[2] (table 1). Cold water oily fishes such as salmon, herring, mackerel and sardines are also rich in EPA & DHA. Oil from red and brown algae is a good source of ω-3 PUFA[3]. Breast milk comprises of all PUFAs essential for infant growth[4]. Linoleic acid and ALA are present in significant amounts in vegetable oils and in other natural sources[5] (table 2 and table 3).

Table 1

Fish / sea food	Gram to provide 1g EPA and DHA per day
Fresh tuna	70–360
Sardines	60–90
Salmon	60–135
Mackerel	60–250
Herring	45–60
Rainbow trout	90–105
Halibut	90–225
Cod	375–750
Haddock	450
Catfish	450–600
Flounder	210
Oyster (Pacific / eastern / farmed)	75 / 195 / 240
Lobster	225
Crab, Alaska King	255
Shrimp	330
Clam	375
Scallop	525

Amounts (g) of few sea fish foods which should be consumed to provide 1 g EPA and DHA; Source: Ward & Singh (2005)

Table 2

Vegetables and oils	Fat content (g/100 g)	EPA + DHA (g/ 100 g)	Fat content (EPA + DHA) EPA + DHA (g 100 g)
Eel	24.5	0.83	29.51
Hering	17.8	2.72	6.54
Sprat	16.6	3.23	5.14
Tuna	15.5	3.37	4.6
Salmon	13.6	2.86	4.76
Mackerel	11.9	1.75	6.8
Carp	4.8	0.3	16
Sardine	4.5	1.39	3.24*
Swordfish	4.4	1.79	2.45*
Trout	2.7	0.59	4.58
Halibut	1.7	0.51	3.33*
Cod	0.6	0.18	3.33*
Haddock	0.6	0.16	3.75*
Lobster	1.9	0.2	9.5
Shrimp	1.4	0.3	4.66
Mussels	1.4	0.15	9.33
Anchovy	2.3	0.5	4.6
Sardine	13.9	2.44	5.7

Table 3

Fat content (g 100g)	ALA (g 100g)	Fat content / ALA (g 100g)	Fat content (g 100g)
Butter	83.2	1.2	69.3
Lard	100	0.98	102.04
Linseed oil	100	54.2	1.84
Soybean oil	100	7.7	12.98
Rapseed oil	100	9.15	10.93
Walnut oil	100	13.5	7.40*
Olive oil	100	0.86	6.25
Vegetable oil	80	2.4	33.3
Almonds	54.1	0.26	208.07
Hazelnut	61.6	0.15	410.6
Walnuts	62.5	6.8	9.19
Kale	0.9	0.35	2.57*
Lettuce	0.22	0.07	3.14*
Parsley	0.36	0.12	3*
Potato	0.11	0.02	5.5*
Cauliflower	0.18	0.1	1.8*
Spinach	0.3	0.13	2.31*
White cabbage	0.2	0.09	2.22*
Wheat bran	4.65	0.16	29.06

Fat content / EPA + DHA (g 100 g) and fat content / ALA (g 100 g) ratio of some various fish, marine products, vegetables and oils; Source: Sauci et al (1994)

*Food which appears as perfect from the point of omega 3 content

OMEGA FATTY ACIDS AND NEUROLOGICAL DISORDERS

There appears to be sufficient evidences on the importance of PUFAs in brain function. A preponderance of this research has focused on DHA, that is preferentially deposited in brain phospholipids and has been linked to Dementia, Parkinson disease, Alzheimer disease (AD), Huntington's Disease, Cognition, Suicide, Depression, Bipolar disorders, Schizophrenia and Mood disorders, Anxiety, Aggression[6-16] etc.

Depression and Mental Disorders

Interestingly, ω-3 PUFA has been reported to be effective against depressive disorders. Imbalance in FA composition is the leading cause of mood disorders. Docosahexaenoic acid helps in the maintenance of neuronal membrane stability and regulates the function of serotonin and dopamine transmission, the key components for depression.

In a double blind (DB) intervention study, supplementation of 2.5g/day of ω-3 PUFA for two months significantly reduced depressive symptoms among elderly patients suffering from major depression/dysthymia and resulted in significant decrease in AA/EPA ratio in red blood cells membrane and improved phospholipid FA profile[17]. In a nine week randomized, masked, placebo-controlled [PC] study, combination therapy (2gms containing a blend of 900mg EPA, 200mg DHA, and 100mg other ω-3 fatty acids twice daily plus citalopram (a selective serotonin uptake inhibitor) displayed significant improvement in ameliorating signs and symptoms of major depression disorder in forty two subjects than monotherapy (2 grams olive oil per day plus citalopram) [18]. Evidences from randomized, DB, PC study suggests that compared to placebo, supplementation/diet enriched with ω-3 PUFA may protect elderly patients with mild cognitive impairment from cognitive decline and ameliorate depressive symptoms and the risk of progressing to dementia[19-21]. Supplementation of EPA ≥ 60% of total EPA + DHA (200-2200 mg/d) was effective against primary depression[22].

Increased suicide risk is associated with lower intake of PUFA in Japanese women compared to men[23]. Lower levels of PUFA concentrations (DHA and AA) are seen in erythrocyte membranes of schizophrenia patients[24]. In a two DB, PC pilot studies on schizophrenia patients, EPA treatment benefited persons suffering from schizophrenia compared to DHA[25]. Supplementation of 1g/day of ω-3 PUFA showed positive effect on the patients suffering from persistent depression[26]. According to a case study, proportion of ω-6/ ω-3 ratio, plasma DHA, HDL is associated with mental retardation in mentally retarded children in Korea[27].

Alzheimer disease

Studies suggest that, apolipoprotein-E polymorphism is the major genetic risk factor for the development of sporadic Alzheimer's disease[28]. Several epidemiological studies and clinical trials suggest that ω-3 PUFA in general and DHA in particular has emerged as a potential tool against Alzheimer's disease.

Docosatriens (10, 17s) also known as Neuroprotectin D1 (NPD1) are conjugated triene structures derived from DHA (Figure 3). They possess immune-regulatory and neuroprotective properties[8]. Addition of nano molar concentration of DHA to primary co-cultures of human neurons and glial cells have resulted in 20-25% decrease in amyloid β (aβ) production, accompanied with NPD1 biosynthesis and 50% decrease in apoptosis caused by aβ. This neuroprotective property is due to upregulation of anti-inflammatory and anti-apoptotic genes namely anti-apoptotic Bcl-2 & Bcl- XL[29].

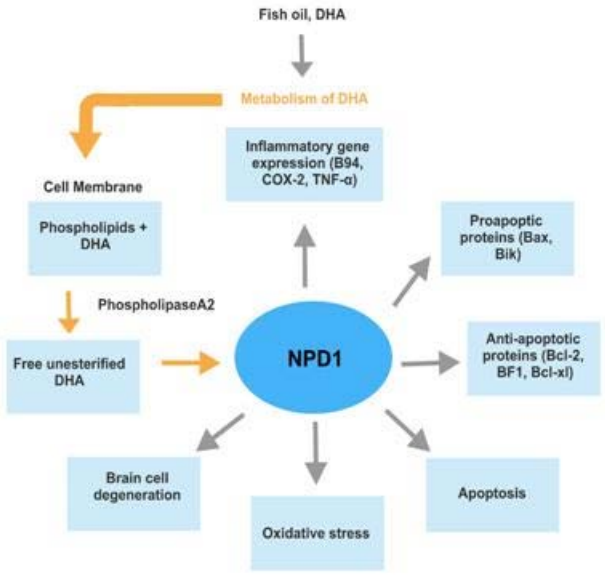

Figure 3: Neuroprotectin D1 biosynthesis and its function

In a randomized DB, PC OmegAD study, dietary administration with either 1.7 g of DHA and 0.6 g EPA or placebo for 6 months to 174 AD patients resulted in downregulation of genes involved in inflammation regulation, neurodegeneration and significantly improved plasma EPA & DHA levels[30].Evidences from randomized, DB, PC study suggests that compared to placebo, supplementation/diet enriched with ω-3 PUFA may protect elderly patients with mild cognitive impairment from cognitive decline and ameliorate depressive symptoms and the risk of progressing to dementia. However, supplementation of LC-PUFA showed no benefit on cognitive function in cognitively healthy older people and in patients with mild to moderate Alzheimer disease[31- 33]. Addition of 5-20 μM DHA inhibits A*β* fibrillation under *in vitro* and *in vivo* conditions. This function attributes to anti-amyloid properties of docosahexaenoic acid. Overall these results suggest that DHA & EPA may be used as a potential therapeutic agent against mild cognitive impairment and ALZ disease[34-36]. Conversely, compared to placebo, supplementation of algal DHA (2g/d) for 18 months did not slow the rate of cognitive and functional decline in patients with mild to moderate Alzheimer disease[37].

OMEGA-3 FATTY ACIDS AND CARDIOVASCULAR DISEASES (CVD)

Cardiovascular disease is a leading cause of mortality and morbidity worldwide today. Decreased risk of CVD was observed in Greenland Eskimos who consumed fish enriched with ω-3 fatty acids[38, 39]. According to the World Health Organization recommendations, the optimal ratio of ω-6 to ω-3 PUFAs is 5-8:1. At this ratio, consumption of LC-PUFA in food or in the form of drugs can act as potent antagonists to ω-6 PUFA synthesis and acts as membrane protectors, inhibiting the synthesis of AA from linoleic acid and competing with AA for the binding to cell membrane phospholipids[40, 41].

Cardiovascular protective nature of LC-PUFA is attributed to its property of reducing cholesterol and thus the risk of myocardial infarcation (MI), serum triglyceride in blood serum level of hyperglycemia patients, decreasing plasma triacylglyceride, blood pressure, platelet aggregation, inflammation, easing blood circulation[42-48]. Supporting evidences followed by expanded interest on omega-3-index indicates that persons having omega-3-index <4% are at a tenfold higher risk to CVD than individuals with an omega-3-index >8%[49]. In a case control study, intake of ω-3 PUFA significantly decreased plasma lipid hydroperoxide level and thereby reduced the level of oxidative damage among elderly patients with MCI[50]. Addition of EPA and DHA (50-300μM) helps in down regulating cholesterol absorption genes such as NPC1L1 and its protein expression in human enterocytes *in vitro* [51]. Supplementation of ω-3 PUFA showed beneficial effects in the prevention of atrial fibrillation recurrence[52, 53]. Conversely, in a randomized, DB, multicentre study, treatment with PUFA did not reduce recurrent atrial fibrillation[54, 55].Treatment with DHA (200mg/kg) attenuated the expression of TNF-α-induced vascular cell adhesion molecule 1 (VCAM-1) and NF-κB activation in TNF-α-treated human aortic endothelial and thereby contributing to the prevention of atherosclerosis in mice[56].

OMEGA -3 FATTY ACIDS AND CELL PROLIFERATION

Ecological studies have shown that high per capita fish consumption is correlated with a lower incidence of cancer in the population[57]. Indeed, epidemiological studies suggest that Eskimos and Alaskans who consume large quantities of fish have a low risk for cancer[58].

Several molecular mechanisms whereby ω-3 PUFA potentially inhibits carcinogenesis have been proposed[59].

These mechanisms include

1) Inhibition of eicosanoids derived AA
2) Modulation of transcription factor, gene expression and signal transduction which leads to changes in tumor metabolism, proliferation and differentiation
3) Changes in estrogen metabolism
4) Decreasing the levels of free radicals and reactive oxygen species
5) Expression of apoptotic inducing B_{ax}, p53 proteins
6) Reduction in angiogenesis process

Prostate cancer is the most commonly diagnosed cancer and is one of the leading cause of death among men in America[60]. Addition of ALA/DHA to gastric epithelial cells inhibited oxidative stress induced cellular events such as glucose oxidase mediated apoptosis, DNA fragmentation, induction of p53 and B_{ax} proteins[61].Omega-3-fattyacids post-transcriptionally regulates over expression of Zeste Homologue2 (EZH2), a polycomb group protein in breast cancer cells[62].Recently EPA has shown to be beneficial in anti-cachexia therapy[63]. In a prospective cohort study on Shanghai women fed with diet lower in ω-3 PUFA suggest that, two fold increase in breast cancer risk in women compared to subjects consuming diets enriched with ω-3 PUFA[64]. Intake of ω-3 PUFA from fish has inverse relation with postmenopausal breast cancer risk[65].

Recent studies reports that, LC-PUFA may be used as a therapeutic agent for the chemoprevention of human pancreatic cancer[66, 67]. Increase intake of food and supplements rich in PUFA is associated with reduced risk of endometrial cancer[68]. Docosahexaenoic acid inhibits the process of tumor establishment[69]. Furthermore, ω-3 PUFA has shown to reduce angiogenesis, decreases nuclear factor–κβ (NF-κβ) activation[70-72]. Increasing body of evidence has shown that, supplementation of DHA upregulates syndecan-1 (SDC-1, a tumor suppressor molecule), which induces apoptosis through activation of PPARγ and inhibits MEK/Erk/Bad signaling under *in vitro* and *in vivo* conditions[73, 74].

OMEGA-3 FATTY ACIDS AND RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation of the joints. *In vitro* study test on various PUFAs showed that ω-3 PUFAs not ω -6 PUFAs are able to markedly decrease mRNA expression level of key initial cartilage degrading proteinases (ADAMTS-4& -5) and Cox-2 and also reduced the levels of inflammatory cytokines, TNF-α, IL-1α and IL-1β[75].

Molecular mechanism by which ω-3 PUFAs may help to reduce the symptoms of RA are as follows[76]:

1. Compete with enzymes essential for ω-6 PUFA derived pro-inflammatory eicosanoid mediators
2. Reduce the gene expression of Cox-2 enzyme, cytokines, TNF-α, IL-1α, IL-1β
3. Reduce the gene expression of key initial cartilage degrading proteinases such as ADAMTS-4 and -5, matrix metalloproteinases -3 and -13

The above supporting evidences indicate that, supplementation of EPA helps in the reduction of pro-inflammatory agents which plays a key orchestral role in causing inflammation in rheumatoid arthritis.

CONCLUSION

Polyunsaturated fatty acids are the precursors to a variety of potential mediators with diverse biological function. However, molecular mechanisms behind these specific biologically active molecules in various cells and tissues processes still remain unclear. Furthermore, when these fatty acids are incorporated into the cell membrane they tend to alter its properties including composition of fatty acids, fluidity, that in turn helps in the modulation of the number and affinity of various receptors, ligands to their respective growth factors, co-factors, enzymes, hormones, peptides and proteins. Yet another action is their ability to form complexes with other biologically active molecules such as aspirin. Formation of such complexes between PUFAs and other biologically active molecules could help in the synthesis of newly formed derivatives like NPD1 that in turn shows varied biological actions useful to our body. Elucidating the role of enzymes in the pathway, formation of such biologically active complexes is not only interesting but also challenging since such complexes may form the basis of understanding certain less well understood physiological and pathological processes. Furthermore, studies have to be carried out on pro and anticancer, anti-inflammatory association of ω-3 fatty acids. Synthesis of synthetic and stable potent eicosanoids such as LXs, resolvins, and NPD1 would help in amelioration of several inflammatory responses. In view of their diverse actions, PUFAs may lay a strong foundation for the formulation of many pharmaceutical drugs.

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