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Multifaceted Clinical and Therapeutic Potential of Omega-3 Fatty Acids in Humans

Aryadeep Roychoudhury[1]

[1]*Post Graduate Department of Biotechnology, St. Xavier's College (Autonomous), 30, Mother Teresa Sarani, Kolkata-700016, West Bengal, India.*

Correspondence E-mail Id: *aryadeep.rc@gmail.com*

Abstract

Omega-3 (ω-3) and omega-6 (ω-6) fatty acids are polyunsaturated fatty acids (PUFAs), both of which metabolically yield very long chain fatty acids supporting numerous physiological and developmental processes in human body. These are essential fatty acids since they are not synthesized *de novo* in human beings and must be obtained through the diet. The major dietary sources are plant seeds, nuts, fish oils and other sea foods. Omega-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been shown to exert antitumor actions that regulate malignant growth. Several other health benefits have been attributed to long-chain ω-3 PUFAs including protection against cardiac arrhythmia, triglyceride-lowering, and amelioration of inflammatory and neurodegenerative disorders. They act as cardioprotective, vasodilatory, anti-inflammatory, hypolipidemic, anti-diabetic, antiallergic and antimicrobial agents, and are known to efficiently combat bronchial disorders, atherosclerosis, intestinal inflammation and neurocognitive disorders, improving memory and brain function. A variety of these beneficial effects are mediated by omega-3 epoxyeicosanoids, a class of novel ω-3 long chain-PUFA-derived lipid mediators, which are generated via the cytochrome P450 (CYP) epoxygenase pathway. CYP enzymes accept EPA and DHA, the major fish oil, as efficient substrates. The dietary EPA/DHA supplementation in humans causes a profound shift of the endogenous CYP-eicosanoid profile from arachidonic acid (AA)- to EPA- and DHA-derived metabolites. Improper balance between ω-6 fatty acids and ω-3 fatty acids may cause detrimental effects with a lot of diseased conditions. The present article highlights the multifaceted clinical and therapeutic implications of ω-3 fatty acids in the prevention of several diseases and disorders in humans, suggesting their role in maintaining sound health.

Keywords: Omega-3 fatty acids, clinical and therapeutic uses, cancer and tumor, fish oil, cardiovascular diseases, neurocognition.

Introduction

Fatty acids containing more than one carbon double bond are termed polyunsaturated fatty acids (PUFAs). Most of the PUFAs of the ω-3 and ω-6 series are essential compounds that humans must obtain through their diet or supplements because the body does not synthesize them. Omega-3 PUFAs include α-linolenic acid (LNA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), whereas ω-6 PUFAs include linoleic acid (LA) and arachidonic acid (AA). Omega-3 fatty acids are a group of essential fatty acids (EFAs) vital to human health. EFAs are fatty acids that humans and other animals must ingest because the body requires them for good health, but cannot synthesize them. The EFAs help in the formation of healthy cell membranes, proper development and functioning of the brain and nervous system and production of hormone-like substances called eicosanoids, thromboxanes, leukotrienes, and prostaglandins. They are also responsible for regulating blood pressure, oedema, blood viscosity, vasoconstriction, and immune and inflammatory responses. They exhibit pleiotropic biological functions like anti-adhesion, anti-aggregation, vasodilation and antioxidant (Gazem and Chandrashekariah 2014).

The historical evolution of human diet and the modernization of food manufacturing processes in recent decades have led to a dramatically altered dietary ratio of ω-6: ω-3 fatty acids in many countries around the world. The present ratio in Western diets is approximately 15–20:1, while human beings evolved for a long time on a ratio of approximately 1–2:1. This is due to a significant increase in the intake of ω-6 PUFAs and a concomitant decrease in the intake of ω-3 PUFAs, which has led to both an absolute and relative deficiency in the long-chain ω-3 PUFA; this imbalance has been linked to the increased impact of a variety of diseases like cancer, cardiovascular disease, coronary artery disease, rheumatoid arthritis, osteoporosis, bronchial disorders and asthma (Michael-Titus 2009). Omega-3 epoxyeicosanoids display cardioprotective, vasodilatory, anti-inflammatory and anti-allergic properties that contribute to the beneficial effects of ω-3 long chain-PUFAs in the above diseased conditions. The background nutrition as well as genetic and diseased state related factors could limit the response to EPA/DHA-supplementation by reducing the formation and/or enhancing the degradation of ω-3 epoxyeicosanoids. The inhibition of tumor growth by ω-3 PUFAs is via immunoregulation through production of five series leukotrienes, three series prostaglandins and thromboxanes, and resolvins (Simonetto et al. 2019). This review attempts to convey the updated information with respect to the biological activities, disease prevention and nutritional advantages of ω-3-PUFAs in human systems. Thus replacement of saturated fatty acids with ω-PUFAs offers protection against metabolic disorders and diseases, since ω-3 PUFAs have been considered as one of the cornerstones for healthy living and good nutrition.

Common ω-3 fatty acids and their sources

Polyunsaturated fatty acids (PUFAs) are large hydrocarbon molecules with different number of unsaturated bonds. They are fatty acids with two or more double bonds in their carbon

chain. PUFAs can be categorized according to the location of the first double bond relative to the terminal methyl group. The presence of the first double bond in the positions 3, 6 or 9 from the terminal CH_3 group of the hydrocarbon chain classifies them as fatty acids of the ω-series which are of special interest for their health benefits. Omega (ω)-3 and ω-6 PUFAs are characterized by the presence of a double bond, three and six atoms away from the methyl terminus respectively. The ω-3 fatty acids are essential PUFAs, not synthesized in human body due to the lack of delta-12 and delta-15 desaturases, which are enzymes present only in marine algae, marine animals and few plants. The inability of the human body to derive linoleic acid (LA) and arachidonic acid (AA) from compounds such as carbohydrates or proteins points to the fact that they, along with all ω-3 fatty acids, are essential fatty acids. Linolenic acid (LNA) is the parent fatty acid of the ω-3 family with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as the most essential ω-3 fatty acids in human diet. EPA, docosapentaenoic acid **(**DPA) and DHA are often collectively mentioned as very long-chain (ω-3) PUFAs. Despite the essentiality of these fatty acids, they are not produced by the human body, but are acquired through proper nutritional diet and supplements, mediated by the metabolism of LNA using a series of enzymes like desaturases and elongases. Cold-water oily marine fish such as mackerel, salmon, albacore tuna, herring, anchovies, sardines and smelt, in particular, provide sufficient amounts of EPA and DHA, together with fish liver oil/fish eggs, organ meats and human milk. Among the plant sources, ω-3 fatty acids are derived from limited sources like flaxseed or canola oil, corn oil, sunflower oil, walnuts and wheat germ oils. Mono and digalactosyldiacylglycerol galactolipids with a high content of PUFAs, mainly ω-3, are the most widespread non-phosphorous polar lipids in the biosphere and account for 80% of the membrane lipids that are found in green plant tissues. These lipids are also the major constituents of the photosynthetic membranes of higher plants, algae and bacteria. Fish are therefore able to build up large concentrations of ω-3 PUFAs in their tissues by consuming algae and plankton and are therefore the main dietary source of essential ω-3 PUFAs in humans.

Omega-3 fatty acids and therapeutics

Depending on the LA: LNA ratio, humans can convert LNA to EPA and DHA, though the conversion rate is below 5%, which is higher in women than in men, since it is under estrogen control. This conversion involves a cascade of elongation and desaturation processes, catalyzed by specialized enzymes. The LNA and its derivatives, eicosanoids and docosanoids regulate human health and development and have distinct biological activities in cardiovascular disease, diabetes, inflammation, asthma, rheumatoid arthritis, osteoporosis, cancer, and age-related functional decline. The ω-3 fatty acids reduce the level of reactive oxygen species (ROS) and cytokines, and produce anti-inflammatory mediators like resolvins. The body requires a certain level of EPA and DHA for normal functioning. Lower level of EPA especially in adolescents and adults is associated with neurodegenerative diseases, depression, joint and bone conditions, heart problems, dyslexia and dyspraxia. These effects have been linked to EPA and the ratio of EPA/AA determines prostanoid

metabolism and function. Arachidonic acid, the pro-inflammatory precursor is displaced by EPA via regulation of phospholipase A2 and cyclooxygenase enzymes to produce anti-inflammatory products, which inhibit the production of AA from dihomo-γ-LNA.

Cardiovascular diseases, atherosclerosis and Sickle cell disease

In the early 2000s, several Cardiac Societies recommended the intake of 1 g/day of EPA and DHA for cardiovascular disease (CVD) prevention, prevention of sudden cardiac death and secondary CVD prevention. Purified EPA/DHA-supplements have been approved as prescription products for reducing triglyceride concentrations in adults. One of the prime reasons for cardiovascular diseases is the imbalance of pro-inflammatory hormones (e.g., eicosanoids) and pro-resolution hormones (e.g., resolvins). The resolvins are produced in blood from the EPA and DHA, when their daily intake exceeds 3 g/day, depending on the AA/EPA ratio. The lower the starting level of the AA/EPA ratio in the studied population, the lower the dose of ω-3 fatty acids that will be required to demonstrate a therapeutic effect (Sears 2018).

The proresolving lipid mediators involved in atherosclerosis is derived from lipoxygenase-metabolism of ω-3 PUFAs which serve as the substrate for the formation of D-series resolvins (RvD), maresins (MaR), and protectins (PD) from DHA and E-series resolvins (RvE) from EPA, which together with the lipoxins collectively constitute Specialized Proresolving Mediators (SPMs). SPMs exert their actions through specific G-protein-coupled receptors (GPCR), namely, ChemR23 and BLT1 for RvE1, ALX/FPR2 and GPR32 for RvD1 and RvD3, and GPR18 for RvD2. The proresolving lipid mediator resolvin E1 (RvE1) is formed by enzymatic conversion of EPA, and signals resolution of inflammation through its receptor, ChemR23 (Carracedo et al. 2019). Dietary supplementation with ω-3 PUFA increase the substrate for SPM formation and alter systemic cholesterol levels towards a beneficial lipoprotein profile and are locally incorporated into cardiovascular tissues. A possible way to obtain an appropriate resolution of inflammation without immunosuppression would hence be to increase the endogenous production of proresolving mediators. Omega-3 fatty acids also influence vascular function and inhibit vessel proliferation through EPA and DHA. EPA inhibits vascular smooth muscle cell proliferation and DHA has been reported to trigger vascular smooth muscle cell apoptosis, implicating a role in vascular remodeling (Ramos et al. 2004). EPA and DHA also prove to be effective in inhibiting spontaneous or warfarin-induced vascular calcification.

Sickle cell disease (SCD) is characterized by HbS polymerization which directly or indirectly alters the typical lipid bilayer and proteins of the erythrocyte membrane. In addition, the plasma membrane of red blood cells, white blood cells and platelets of patients with SCD has an abnormal fatty acid composition, characterized by decreased levels of DHA and EPA, and a concomitant increase in AA. Omega-3 fatty acids are therefore effective and safe treatment options for patients with SCD. There is evidence that abnormality of membrane fatty acids,

rheological abnormalities of red blood cells, inflammation and haemolysis in patients with SCD are ameliorated by treatment with ω-3 fatty acids (Daak et al. 2018).

As antimicrobial agents

Linolenic acid and its derivatives used singly or in combination act as antimicrobial agents. Increased production of EPA and DHA in the liver of *Vibrio vulnificus*-infected transgenic zebrafish via overexpressing *delta-6 desaturase* and *elongase* genes inhibited bacterial growth and enhanced production of anti-inflammatory cytokines, thereby protecting zebrafish from *V. vulnificus* infection. EPA and DHA can induce the death of the *Plasmodium* species, inhibit viral replication, exert anti-hepatitis C virus activity, and exhibit bactericidal and fungicidal effects, suggesting that ω-3 PUFAs function as endogenous antimicrobial molecules (Chanda et al. 2018). The mechanism by which the ω-3 PUFAs act as antimicrobial agents are as follows:

(i) Fatty acids are reported to alter cell membrane hydrophobicity, cell surface charges and membrane integrity, which lead to electron leakage from bacteria, thereby disrupting electron transport system and ATP production, resulting in cell death. The phospholipid acyl chains regulate the viscosity of the cell membrane, and it is through this viscosity adjustment that impacts are made on the vital functions of the cell membrane, such as the transportation of active solutes, passive permeability of hydrophobic molecules, and protein-to-protein interactions.

(ii) Omega-3 fatty acids exert some of their activity on the cell membrane. In presence of DHA or EPA, cellular distortion and growth inhibition of *Porphyromonas gingivalis* and *Fusobacterium nucleatum* were noted along with down regulation of expression of virulence factors. Blocking the action of enoyl-acyl carrier protein reductase (FabI) in bacteria through exogenous fatty acids like DHA, LNA, etc. negatively affected the fatty acid biosynthetic pathway such as the malfunctioning of phospholipids. DHA is an effective inhibitor against FabI enzyme and *N*-myristoyltransferase of *Plasmodium falciparum, Staphylococcus aureus* and *Staphylococcus pyogenes* thus showing antifungal activity. DHA supplementation also induced antioxidant effect directly proportional to its antimicrobial effect (Chanda et al. 2018).

Neurological treatment

Omega-3 fatty acids are essential for the development of the mammalian nervous system. The principal ω-3 PUFA in the central nervous system (CNS) is DHA, representing 10–20% of the total fatty acid composition, whereas EPA and AA represent less than 1%. After release from membrane phospholipids by phospholipases, DHA and EPA can be metabolized and produce eicosanoids that are anti-inflammatory. Deficiency in ω-3 fatty acids in neural membranes can lead to impaired G-protein-coupled receptor signaling, which have profound effects on neurotransmission. The important role of DHA in neurodevelopment is reflected in the major neurological deficits as seen in Zellweger's syndrome, a peroxisomal disorder

where the biosynthesis of DHA is compromised. Over the last 10–15 years, ω-3 fatty acids, and a possible deficiency of such acids, have been linked to several diseases in neurology and psychiatry, including depression, bipolar disorder, schizophrenia, attention deficit–hyperactive disorder and neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and Huntington's disease (Michael-Titus 2009).

Acute traumatic injury to the central nervous system, viz., brain and spinal cord injury is a serious concern that can result in permanent and major disability. Compression of the spinal cord leading to anoxia is proportional to the severity of the initial injury. Oedema develops at the injury epicenter, spreads rostrocaudally and triggers a complex inflammatory reaction, which starts with the local activation of the microglia, followed by infiltration of neutrophils, systemic macrophages and T-cells. The neuroprotective effect of acute intravenous DHA bolus is further enhanced by combination with a sustained dietary DHA supplementation, in the weeks following injury. Omega-3 PUFAs are not only essential structural compounds in the CNS, but also act as endogenous ligands at a variety of receptors and ion channels, and as substrates of enzymes. Their activity at potassium and sodium channels could be a major factor controlling hyperexcitability after injury. DHA acts as a ligand for the retinoid X receptor (RXR), which can heterodimerize with retinoic acid receptors (RAR) and act as a modulator of gene expression at retinoid-responsive promoters. Omega-3 PUFAs can also activate PPARs (peroxisome proliferator activated receptors) that can bind DNA as a heterodimer with RXR, and exhibit therapeutic value in spinal cord injury. Following trauma, PUFAs like DHA are cleaved from membrane phospholipids to free (unesterified) DHA by phospholipase A2 enzymes. The free DHA can then be converted to neuroactive metabolites such as neuroprotectin D1 (NPD1). The ω-3 PUFAs enhance the expression of neurotrophins, including brain-derived neurotrophic factor (BDNF). Even the ω-3 PUFAs and their metabolites can up-regulate the expression of anti-apoptotic proteins such as the Bcl-2 family, whilst down regulating the apoptotic proteases caspase-3 and 9, and pro-apoptotic signaling proteins including Bax, Bad, Bid and Bik. Overall, these compounds lead to increased neuronal and glial survival, limit the damaging neuroinflammation and protect neurites. EPA and DHA have a complex pharmacodynamics, activating a multitude of targets, including voltage and ligand-gated ion channels, transcription factors and G-protein coupled receptors (Gladman et al. 2011).

Memory improvement

Omega-3 PUFA supplementation increases the expression of synaptophysin, which regulates synaptic density and synaptic vesicle formation. Brain EPA is important for normal serotonin release, as observed from the positive correlation between human plasma ω-3 levels and serotonin metabolite in cerebrospinal fluid. Decrease in ω-3 fatty acids is linked with diminished serotonergic neurotransmission and reduction of serotonin concentration in the frontal cortex. Diet rich with fish tends to restore normal serotonin activity by increasing serotonin transporter proteins. Besides serotonin, fish oil supplementation also stabilizes the endocannabinoid 2-arachidonylglycerol (2-AG), dopamine (DA), neuropeptide Y (NPY), and

CaMKII, silent mating type information regulation 1 (SIRT-1), and brain-derived neurotrophic factor (BDNF). Deficiency in ω-3 fatty acids decreases the activity of vesicular glutamate transporters, together with alteration in glutamate discharge amount. The ω-3 fatty acids can considerably enhance memory by reversing the memory deficits caused due to diminished acetylcholine release. Diets lacking ω-3 PUFA decrease cholinergic neurotransmission by causing a significant loss of DHA in the membrane, altering membrane composition with a drop in muscarinic-receptor binding. DHA also regulates dopamine receptors and dopamine-containing vesicles. Incorporation of ω-3 PUFAs into cell membranes also leads to reorganization of lipid raft formation. Lipid rafts are membrane domains that contain clusters of receptors and proteins involved in signal transduction. Anti-inflammatory mechanism of ω-3 PUFAs is due to the G protein-coupled receptor 120 (GPR120) as ω-3 PUFA receptor/sensor (Oh et al., 2010), suggesting that ω-3 PUFAs can be anti-inflammatory and antioxidant compounds. Eicosanoids derived from ω-3 PUFAs, such as prostacyclin I3 and thromboxane A3, are generally considered anti-inflammatory, antithrombotic, vasodilatory and antineoplastic (Reimers and Ljung 2019). The anti-inflammatory effects of ω-3 PUFAS most probably contribute to their neuroprotective effects in various neuropsychiatric conditions. They also work against depression, schizophrenia, Parkinson's disease and other neurological and psychiatric disorders. Omega-3 fatty acid supplementation at a dosage of 300 mg/day for 15 weeks or 100 mg/day for 30 weeks in diet is recommended in healthy individuals as a safe dosage to prevent cognitive decline, dementia and verbal episodic memory deteriorations, especially in elderly persons (Tareke et al. 2019). It has been suggested that ≥ 180 mg/d of dietary DHA (≈2.7 fish servings/week) is associated with ≈50% reduction in dementia risk (Aarti and Priyanka 2018). Alzheimer's disease (AD) is a neurodegenerative disorder associated with a significant decline in DHA, and accordingly, administration of DHA and its derivatives like 2-hydroxy DHA-(OHDHA) has been proposed as a possible treatment for this pathology. DHA induces lipid modifications paralleled with a reduction in amyloid-beta (Aβ) accumulation and full recovery of cognitive impairment. Omega-3 fatty acids also cause alterations in the subcellular distribution of secretases and reduced Aβ-induced tau protein phosphorylation as well. Furthermore, OHDHA enhanced the survival of neuron-like differentiated cells exposed to different insults such as oligomeric Aβ and N-methyl-D-aspartate-mediated neurotoxicity (Aarti and Priyanka 2018).

Cancer and tumor arrest

Both EPA and DHA regulate apoptosis, affecting tumor cell invasion and proliferation and inhibiting metastasis and angiogenesis. DHA acts as anti-cancer adjuvant, facilitating uptake of anti-cancer drugs, especially in drug-resistant cells. The dietary fish oil EPA or DHA inhibited the genesis of osteolytic lesions in bone, proposing a useful impact of EPA and DHA on breast cancer cell metastasis to bone. DHA-rich diet, when administered to the tumor cells inhibited lung metastasis, which was associated with alterations in the fatty acid composition of tumor cell, damaging tumor cell membrane and reducing the capability to

metastasize. Some targets of DHA consisting of Cyclooxygenase-2 (COX2), NF-kB, mitogen-activated protein kinase (MAPK), peroxisome proliferator activated receptor-γ (PPAR-γ), Akt and B-cell lymphoma/Bcl-2 related X protein (BCL-2/BAX) altogether play a major role in the inhibition of metastasis. Fish oil supplementation significantly suppressed mRNA and protein levels of the cell-surface, CD44 adhesion molecule in the MDA-MB-231 tumors, hence recognizing a novel performance for DHA in tumor cells. There is also evidence that ω-3 PUFAs and especially DHA may have an importance in nutritional therapy of breast cancer as part of both adjuvant and post-excision adjuvant anti-metastatic diet. Combination of genistein (an isoflavonoid from soybean) and DHA led to synergistic suppression of cell invasiveness, inhibition of PGE2 production and COX2 expression in cancer cells.

Mitochondria-generated reactive oxygen species (ROS) influence activation and oxidation of transcription factors such as APEX1, NF-kB, P53, and HIF-1α, and oxidize and suppress signaling molecules like P38 MAPK phosphatase, leading to increased proliferation and survival of cancer cells. It has been shown that *in vitro* administration of DHA enhanced more tumor cell lipid peroxidation and oxidative injury as compared to chemotherapy alone. Though the enhanced anticancer drug absorption or uptake by DHA does not work for all tumor cells, it can make cells more susceptible to oxidative injury made by exogenous factors. DHA appears to be a strong inducer of apoptosis only in cancer cells (e.g., colon cancer cells), but not in normal cells (NCM460 normal human colon mucosal epithelial cell line). The proapoptotic effect of DHA operates via both the intrinsic and extrinsic pathways, being absorbed by mitochondrial membranes, thereby changing their permeability and reducing the mitochondrial membrane potential. The anti-cancer effect of DHA, observed in presence of low doses of chemotherapeutic agents, was performed first by loss of mitochondrial membrane potential and then via caspase-9 activation (Abiri and Vafa 2018).

Cancer anorexia is triggered by proinflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-1, related to the interaction between macrophages and the growing tumor. Omega-3 fatty acids inhibit the production of IL-1 and TNF-α, thereby diminishing the biological activities of cytokines, particularly their anorexigenic effects, delaying tumor appearance, causing reduced tumor growth and attenuating cachexia. Incorporation of EPA and DHA into the tumor membrane phospholipids may alter the membrane function, influencing cytokine activity, decreasing concentrations of vascular endothelial growth factor, and consequently decreasing tumor vascular supply (Ramos et al. 2004).

Combinations of DHA with doxorubicin, irinotecan, cisplatin, melphalan and vincristine showed synergism in the neuroblastoma cell survival, and the DHA or epirubicin, cyclophosphamide and 5-fluoracil combination caused tumor reduction and increased survival of patients with breast cancer. DHA or sulindac sulfate combination reduced tumor growth through the apoptotic receptor (DR5) in the colon xenotransplant. DHA or clioquinol treatment showed PPARα dependent synergy, diminished the NF-κB and survival molecule,

viz., Bcl-2, Akt and p65 production in tumor cells and enhanced the antiproliferative effects of curcumin in breast cancer cells (Márquez-Fernández and Camargo 2019).

Macular degeneration and Stargardt disease

Age-related macular degeneration (AMD) is the leading cause of visual impairment and blindness in the elderly; an estimated 200 million people suffer from AMD worldwide. By the year 2040, the number of these individuals is estimated to increase by 50%. The factors associated with AMD include inflammatory-related proteins, including C-reactive protein, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). Omega-3 PUFAs have a protective role in inflammatory-associated, ischemia-associated, light-associated, oxygen-associated and age-associated pathology of the vascular and neural retinas. Supplementation with ω-3 PUFAs has been found to be beneficial for dry AMD regression when AA/EPA=1–1.5 which can be considered as a potential therapeutic regimen for patients with dry AMD (Prokopiou et al. 2017).

Stargardt disease is a recessively inherited disorder that leads to AMD with an estimated prevalence of 1 in 10,000. The genetic basis of this disease is mutations observed in *ATP-binding cassette 4* (*ABCA4*) gene which encodes a transporter protein located in the rims of photoreceptor outer segment discs in the retina. A key characteristic of the disease is the accumulation of lipofuscin, a lipid-containing fluorophore in the retinal pigment epithelium (RPE) cells, derived from the chemically modified residues of incompletely digested photoreceptor outer segments, as a result of the mutated ABCA4 transporter. The major component of lipofuscin in the mouse is N-retinylidene-N-retinylethanolamine (A2E), a vitamin A–derived pyridinium bisretinoid isomer that is a byproduct of the visual cycle and that may cause RPE damage. In turn, RPE damage may lead to retinal degeneration and eventually central blindness with a poor visual outcome. It has been reported that ω-3 PUFAs protect the eye from retinal damage by reducing inflammation through resolvins that are derived from EPA and DHA. EPA and DHA, 5:1 supplementation and AA/EPA ratio maintained between 1 and 1.5 reduced the accumulation of lipofuscin granules and A2E, and decreased C3 level, limiting a complement-induced inflammatory response consistent with slowing the rate of the Stargardt disease (Prokopiou et al. 2018).

Anti-hyperlipidemia and anti-diabetic effects

Proper maintenance of EPA/DHA ratio can reduce accumulation of body fat by limiting both hypertrophy and hyperplasia of fat cells, indicating antiadipogenic effect against obesity. Omega-3 fatty acids exhibit beneficial effects by lowering serum cholesterol and raising high-density lipoprotein. Long chain ω-3 PUFAs have been shown to have therapeutic effects in patients suffering from non-alcoholic fatty liver disease, which occurs due to lipid accumulation in hepatocytes, commonly encountered in the context of insulin resistance and visceral obesity. LC-ω3 feeding increases adiponectin production, while reducing that of TNF-α and anandamide, thereby inhibiting hepatocyte nSREBP-1c activity. Intracellular LC-

ω3 PUFAs undergo enzymatic and non-enzymatic oxygenation. Oxy-LC-ω3 mediators inhibit the LXR-RXR interaction, the stability of the pSREBP-1c transcript, and activate PPAR-α. This results in the increased activity of fatty acid-oxidative enzymes with a concomitant reduction in lipogenic enzyme activity (Shapiro et al. 2011).

Dietary intake of ω-3 fatty acids reduces the risk of islet autoimmunity (IA) in children with augmented genetic risk of type 1 diabetes. The beneficial effect of ω-3 PUFAs on T cell functions in type I diabetes could be attributed to their suppressive effect and modulation of cytokine secretion, and improvement of intracellular oxidative status. Higher consumption of long chain fatty acids and fish also reduces the risk of type 2 diabetes mellitus (Gazem and Chandrashekariah 2014).

Anti-inflammatory effects

Omega-3 fatty acids reduce the risk of rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and asthma. Omega-3 PUFAs are the precursors of biological lipid mediators, termed as eicosanoids, which play an important role in the regulation of inflammation. Increasing the ratio of ω-3 to ω-6 fatty acids in diet favors the production of EPA in the body. Omega-3 PUFAs regulate macrophage inflammation negatively by deacetylating NF-kB, which acts through activation of adenosine monophosphate-activated protein kinase/sirtuin and regulation of T1 (AMPK/SIRT1) pathway, demonstrating the anti-inflammatory potential of ω-3 PUFAs (Gazem and Chandrashekariah 2014).

Conclusion and future perspectives

Omega-3 fatty acids play vital role in disease prevention and health promotion due to their action against hyperlipidemia, obesity, diabetes, inflammation, cancer and heart diseases. It is essential to increase the dietary uptake of PUFAs, or to enhance the ratio of ω-3 to ω-6 fatty acids in the diet to avoid many chronic diseases and inflammatory disorders. Although several ongoing clinical trials assess the potential of ω-3 PUFAs in cancer prevention, researchers do not seem to be translating the profoundly beneficial results seen in the laboratory to the bedside. The researchers also need to explore some additional novel ways of ω-3 PUFA supplementation. Ongoing and future clinical trials using intravenous ω-3 PUFA infusions in cancer therapy are eagerly awaited. The use of ω-3 PUFAs as a therapeutic option in the treatment of neurological and psychiatric disorders is still in its infancy, but their therapeutic potential, favorable safety profile, ease of administration and low treatment costs are promising. In order to resolve atherosclerotic inflammation, it is important to consider both the immune response and the structural cells of the vascular wall, with greater emphasis on the EPA-derived lipid mediator, RvE1 through its receptor ChemR23. Omega-3 PUFAs can also be included in the list of potential antimicrobial agents, since they have less effect on evolving antimicrobial resistance and are safe for human use, though more clinical studies are necessary to support this role. However, the high instability of **ω**-3-PUFAs to oxidative deterioration, lower bioavailability at the target tissues and their reduced bioactivity

are collective impediments for achieving their maximum therapeutic potential. Due to the exceptionally unsaturated nature of ω-3-PUFAs, they are susceptible to oxidation and promptly deliver hydro-peroxides-off flavors and odors-which result in poor patient compliance. Therefore, different types of nano-encapsulated ω-3-PUFA formulations have been reported. These nano formulations can be manipulated according to specific requirement (Ahmad et al. 2020). More studies need to be performed to evaluate the *in vitro* or *in vivo* effects of nano encapsulated ω-3-PUFAs and monitor their efficiency in controlling the progression, recurrence and disorder of the disease. Moreover, the optimum loading, along with targeting and releasing capacity of such nanomedicines need to be optimized. At present, ω-3 PUFAs appear to be more useful in long-term preventive approaches rather than treatment of acute episodes.

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