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Advances in therapeutic applications of fish oil: A review

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ABSTRACT

Fish oil is oil that is extracted from fish tissue and contains numerous essential fatty acids. It is considered as a functional food because of its functional component mainly polyunsaturated fatty acids, which has positive impact on human health when consumed in a sufficient quantity. Fish oil offers more benefits over the direct consumption of fish. The prevalence of non-communicable diseases has increased worldwide over the past few years. Several experimental investigations on in vivo and in vitro model proved that fish oil possess several health benefits including anti-obesity, anti-cancer, cardioprotective, anti-inflammatory, neuroprotective, hepatoprotective, and immunostimulatory properties. In this concern, fish oil has a potential therapeutic efficacy as nutraceutical agent depending on their dose and duration. Fish oil enriched with essential fatty acids can regulate various signaling pathways involving different transcriptional factors which can control many physiological functions. Therefore, this review focuses on some molecular mechanisms through which fish oil may protect from various life threatening diseases namely dyslipidemia, diabetes, cardiovascular disorder, kidney disorder, cancer and many more.

Introduction

Throughout the history of human civilization, seafood is considered as a human food resource. In Paleolithic times, when man was enjoying different species of fish, crustaceans and molluscs, preservation technique including smoking and drying were originate thus allowing wide application of this food [1]. It was found that, despite eating a diet high in fat, the Greenland Inuit had a low mortality rate from coronary heart disease, which led to the establishment of the link between omega 3 fatty acids and cardiovascular disease. In the 1970s, the Danish researchers Bang and Dyerberg speculated that this may be because of the large amount of omega 3 fatty acids in the Inuit diet, which primarily comprised of fish, seal, and whale [2]. Ingestion of fish becomes trendy in daily meals. Fish is considered as an affordable source of countless healthful nutrients exclusively rich in protein as well as fat, which play a valuable role in human diet. Fish provides micronutrients comprising selenium, iodine, potassium, vitamin D and B-vitamins [3]. Fish proteins are excellent source of lysine as well as sulphur containing amino acid namely methionine and cysteine which are absent in plant protein [4]. Fish protein is primarily important for muscular tissue growth and repair, as well as increase immunity power. Because of its high content of essential fatty acids, it is extremely prescribed in the diet. Fatty acids are the body's prime source of energy, and are categorized depending on the length of carbon chain and the degree of unsaturation. They consist of a hydrocarbon chain and a terminal carboxylic group. Dietary fatty acids, especially long-chain polyunsaturated fatty acids, are chemical molecules necessary for mammalian growth and development, including human growth and development [5]. The fish oil industry dates back to the 1770s in the United Kingdom, when cod liver oils were initially promoted as a remedy for rheumatism treatment [6]. The oil obtained from fish tissue is known as fish oil. The oil obtained from fish contain triglycerides, phospholipids, fatty acids, wax esters, sterols, other minor compounds like glyceryl esters, glycolipids, hydrocarbons like squalene, sulpholipids etc., Other lipids operate as energy reservoirs, while phospholipids and sterols are structural components in cell membrane. Fish oil has a more varied fatty acid profile with a focus on monounsaturated fatty acids (MUFA) along with polyunsaturated fatty acids (PUFA). PUFAs are classified as per the positioning of first double bond in their chemical structure. Omega-6 and omega-3 fatty acids are the key donors to polyunsaturated fatty acids, with the former being higher in freshwater fish and the latter being the predominant contributor in marine fish. The beneficial omega-3 fatty acids are α-linolenic

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acid (18:3, ALA), Eicosa Pentaenoic Acid (20:5, EPA) and Docosa Hexaenoic Acid (22:6, DHA) [7]. Furthermore, fish oil normally consist some vitamin A and D which are crucial for growth and development of children. By 1800s, fish oil was used to the treatment of rickets for its vitamin D content. The principal types of omega-3 s in fish oil are EPA and DHA, while the type found in plant sources is mainly ALA. The major types of omega-6 s present in fish oil Conjugated linoleic acid (CLA), while arachidonic acid found in meat, eggs and dairy products [8]. The ratio of omega-3 to omega-6 fatty acids varies from 1.3 to 21.2, according to the European Food Safety Authority (EFSA). As a result, increasing fish consumption in the diet may greatly contribute to enhanced omega-3 fatty acid intake and optimised EPA and DHA usage for the betterment of many physiological activities [9].

Sources and requirement of fish oil

Lipids are key macronutrient in human diet. Sources of fish oil includes oily fish such as sardines, tuna, mackerel, herring, bluefish, anchovies, trout, mullet, and salmon, fish liver oils such as cod liver oil, other seafood such as oysters and shrimp etc. [11,12]. Various marine fish available in different states of India such as Silver Pomfret, Black Pomfret, Hilsa, Prawn (Sea Tiger, White, Brown, Karikari, Flower), Surmai, Bangda/ Indian Mackerel, Pedvey, Snail, Crab, Indian Salmon, Bombay duck, Tapra, Topse, Ruli, Ribon, various types of Croker, Pabda are also nutritionally good as well as cost effective [10]. Fish consumption should be limited to 1 to 4 servings per week, based on the report of World Health Organization (WHO) [13]. Nevertheless, if people will not consume 1–2 servings of fish each week, fish oil supplements can help people have received adequate omega-3 s. For people who don't have any cardiovascular problem, the American Heart Association recommends eating oily fish at least twice a week, or about 500 mg of EPA/DHA per day [14]. The type of omega-3s present in fish oil shows higher nutritional advantages than the omega-3 s present in different plant origin. Fish oils are used as healthy additives and ingredients in many value-added food compounds or health-food capsules. Fish oils differ in their composition of fatty acid based on the species of origin as well as seasonal variations.

However, some reviews on the nutritional effects of fish oil were outdated. Therefore, aim of this review to systematically summarize the current literature regarding the nutritional profits of fish oil intake underlying the corresponding biological activities from PubMed, Google Scholar, and Scopus on the basis of their uniqueness.

Positive impact of fish oil on human health

Fish is considered as a functional food when it comes to the principle of diminished risk, improved function and elementary nutrition, and its validity. In the diet, fatty fish consists nutrients which are beneficial to physiological as well as psychological health, and fish oil can diminish the possibilities of various health problems namely cardiovascular illness [15], cancer, diabetes [16], mental disorders, kidney disorder, obesity, bone diseases [17], and severe inflammation.

Fish oil and obesity

The word obesity (it comes from the Latin ob-esum, which means on account of having been eaten) is a colloquial term that indicates the same as fatness but with moderately abusive connotations. Due to an imbalance between energy intake and expenditure, obesity has become an epidemic on a global scale and plays a significant role in the burden of chronic illness and disability. According to WHO, Overweight or obese people make up over 39 % of the world's population, with about 13 % of adults falling into this category. ICMR-INDIAB study 2015, reported that prevalence rates of obesity and central obesity in India may range from 11.8 % to 31.3 % and 16.9 % to 36.3 % respectively [18]. Presently, over one billion persons in world are overweight, with at least 300 million of them being clinically obese [19]. Most body fat is kept in adipose tissue, which is made up of adipocytes, vascular endothelial cells, fibroblasts along with numerous immune cells like macrophages. Adipocytes release free fatty acids, which help maintain energy balance and lipid homeostasis and accumulating triglycerides concerning variations in energy needs [20]. Adipose tissue is an endocrine organ that secretes hormones such as adiponectin, adipsin, leptin and cytokines known as adipocytokines like tumor necrosis factor-α (TNF-α), interleukin (IL)−6. White adipose tissue also secretes lipoproteins lipase, apolipoprotein, and cholesterol ester transfer protein as crucial modulators of lipoprotein metabolism. There are three forms of adipose tissue have been found such as white adipose tissue, brown adipose tissue and beige ("brite") adipose tissue. Brown adipose tissue is essential for thermogenesis, while white adipose tissue is responsible for energy repository as triglycerides [21]. Adiponectin exerts its effects through AdipoR1 and AdipoR2 receptors. AdipoR1 increased fatty acid oxidation by stimulating Adenosine monophosphate-activated protein kinase (AMPK) activity in skeletal muscle, whereas AdipoR2 engaged in activation of PPARs thereby increasing glucose uptake in the liver [22]. Obesity leads to adipose tissue dysfunction results various metabolic syndrome like insulin resistance. Fish oil exerts anti-obesity function through elevated adipocyte death [23], changed lipid degradation and energy loss, and enhanced plasma adiponectin levels [24]. Fish oil elevates fatty acid oxidation in the hepatic tissue, adipose tissue and skeletal muscle; thereby prevent lipid deposition in liver and muscle. Gene involved in cholesterol homeostasis namely apoE, that is directly regulated by LXRs (Lipid X receptors). This apolipoprotein is a high-affinity ligand of the Low density lipoprotein receptor and needed for hepatic uptake of chylomicron remnants, very low density lipoproteins and some subtypes of High density lipoprotein (HDL) [25]. Lipid X receptors are ligand activated transcription factor under nuclear receptor family. Activation of LXRs enhanced lipogenesis thereby increase in the functioning of lipogenic elements including Sterol-regulatory element binding protein 1c (SREBP-1c) and Carbohydrate-response element binding protein (ChREBP) [26]. Sterol regulatory element-binding protein-1c controls a number of genes participating fatty acid and triglyceride synthesis such as acetyl CoA carboxylase (ACC), fatty acid synthase (FAS), and stearoyl CoA desaturase (SCD) [27]. Carbohydrate response element binding protein is known as carbohydrate sensitive transcription factor, that can stimulates action of lipogenic genes and enhance liver's ability to convert excess carbs to fat [28]. Fish oil supplementation prevents sucrose induced hepatic triglyceride accumulation by reducing the activity of ChREBP, SREBP-1c, LXR, Liver pyruvate kinase, ACC1, FAS, and SCD1 in liver [29]. Peroxisome proliferator activated receptor-α is a transcription factor that belongs to the steroid hormone receptor family. It promotes β-oxidation of fatty acid as well as suppress SREBP-1c promoter via inhibition of lipid X receptor signaling [30]. Fish derived omega-3 PUFAs are important biomolecules that can regulate fat metabolism of liver by down-regulating activity of SREBP-1c, preventing lipogenesis and upregulation of peroxisome proliferator activated receptors (PPARs), promoting oxidation of fatty acid [31]. Dietary consumption of fish oil and chitosan have a considerable impact of anti-obesity effects on the down regulation of metabolism of liver fat by inhibiting lipid X receptor-α and promoting Peroxisome Proliferator Activated Receptor-α (PPAR-α) mediated downstream lipogenesis inhibition, which can improve production and aggregation of hepatic fat in the high fat induced rats [32]. Researchers hypothesised that mice given DHA-rich fish oil plus fenofibrate experienced greater increases in adiponectin sensitivity than mice given DHA-rich fish oil alone [33]. In obese children and adolescents, fish oil supplement may diminish systolic blood pressure, serum triglycerides, and Body mass index (BMI) [34]. Dysregulation in adipokines generation and secretion from organ fat related to agonist function of leptin and opponent role of adiponectin. The major function of leptin is to support calorie equilibrium by controlling dietary consumption and energy expenditure [35]. Supplementation of EPA increase blood leptin levels and play a significant role to lose weight [36]. Obesity may result to interpenetration of the enlarged adipocytes by macrophages and enhanced levels of proinflammatory cytokines. In adipocytes, TNF-α suppress genes that are responsible for storing non-esterified fatty acids and absorbing glucose. It also affects the expression of several adipocyte secreted factors, such as interleukin-6 and monocyte chemoattractant protein (MCP)−1 [37]. Tapra fish which is found in seacoast region of West Bengal, the tapra fish oil contain numerous essential fatty acids. Furthermore, in comparison to the control group, tapra fish oil treatment for obese mice dramatically reduced body weight, BMI, serum total cholesterol, triglycerides, low-density lipoprotein, and very low-density lipoprotein levels while also increase in high density lipoprotein levels. The obese animal treated with tapra fish oil also showed a decline in TNF-α [38]. Hence, these fish oil might be used as an anti-obese food supplement. In this review, possible mechanisms of obesity are first discussed in order to better understand how fish oil can alleviate obesity (Fig. 1).

Fish oil and diabetes

Diabetes mellitus is the most terrible, non-communicable metabolic disorder characterized by the abnormalities in insulin secretion and insulin resistance of significant target tissues [39]. Significance of insulin as an anabolic hormone leads to metabolic dysfunctions of proteins, lipids, and carbohydrates.Type-1, type-2 and gestational diabetes mellitus are the different types of diabetes mellitus according to American Diabetic Association [40]. Type 1 diabetes is primarily brought on by the autoimmune death of the pancreatic β cells via a humoral (B cell) and T-cell mediated inflammatory response (insulitis) [41]. In type-2 diabetes, the body can able to produce insulin but is unable to respond to its effect known as insulin resistance [42]. The International Diabetes Federation (IDF) has been tracking diabetes prevalence at the local, national, and international levels. 285 million people were thought to have diabetes in 2009, this number rose to 366 million in 2011, 382 million in 2013, 415 million in 2015 and 425 million in 2017 [43].

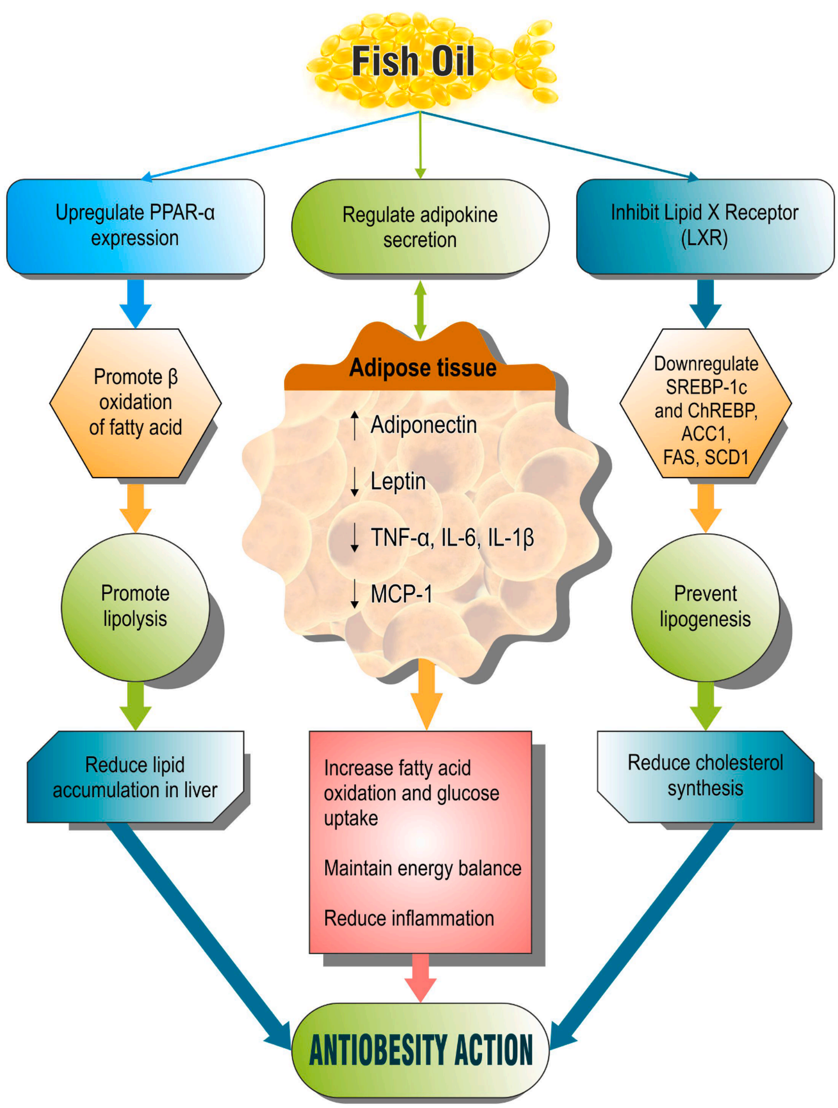

Fig. 1. Projected prospective anti-obesity health attributes of fish oil. Fish oil can mitigate adipogenesis by several biochemical pathways, such as accelerates lipolysis and suppresses lipogenesis via reducing triglyceride accumulation, regulating adipokines (leptin, adiponectin), increasing fatty acid oxidation and glucose uptake, as well as inhibits Inflammasome activation via downregulating the expression of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) and regulatory cellular mediators (MCP-1, Toll Like Receptor-4, Nuclear factor-κB, c-Jun N-terminal kinase). Abbreviations: PPAR-α, Peroxisome proliferator-activated receptor; LXR, Lipid X receptor; TNF-α, Tumor necrosis factor-α; IL, Interleukin; MCP-1, Monocyte chemoattractant protein-1; SREBP-1c, Sterol-regulatory element binding protein 1c; ChREBP, Carbohydrate-response element binding protein; ACC, Acetyl-CoA carboxylase; FAS, Fatty acid synthase; SCD, Stearoyl CoA desaturase.

Dyslipidemia is the most common feature of diabetes. Abnormal functioning of adipose tissue brought on by obesity is interrelated to insulin resistance in the liver and skeletal muscle [44]. Through glycogenolysis and gluconeogenesis liver maintains normal glucose level while fasting. After feeding, pancreas receives more glucose, which increases the release of insulin. The main effect of insulin on liver is to stop it from producing glucose in liver. Insulin also promote glucose uptake in muscle and fat tissue, mediated by enriching of the glucose transporter (GLUT)−4 from storage vesicles to the plasma membrane. A 12 transmembrane protein called GLUT-4 allows peripheral blood glucose to pass the plasma membrane and enter cells when insulin binds to membrane receptors [45]. GLUT-4 is involved in insulin-stimulated glucose absorption in white adipose tissue. Through the PI3K/Akt signaling pathway, GLUT-4 is essential to maintain glucose homeostasis. Activation of PI3K/Akt are critical steps in insulin-mediated action, with Akt acting as a mediator in the glucose uptake signal pathway, which is regulated by insulin in adipose, muscle, and heart tissues [46]. There are numerous mechanisms by which fish oil can protect from severity of diabetes mellitus (Fig. 2). In muscle, omega-3 fatty acids preserved levels of total GLUT-4, phosphatidylinositol 3-kinase activity and insulin receptor substrate-1 tyrosine phosphorylation [47]. Fish oil supplementation enhanced insulin sensitivity by activating insulin signaling mechanisms (insulin receptor, Akt, insulin receptor substrate-1, and p38 MAP kinase) and migration of GLUT-4 from cytoplasm to plasmatic membrane [48]. Adiponectin is an adipocyte-derived insulin-sensitizing protein. Peroxisome proliferator-activated receptor-γ stimulates adiponectin, which could enhance insulin sensitivity [49]. In obesity, decreased adiponectin and increased inflammatory cytokines, connected with increased fatty acids that can promote resistance of insulin in hepatic tissue and skeletal muscle [50]. Administration of fish oil for long period enhances plasma level of adiponectin thereby increasing insulin sensitivity [51]. Omega-3 fatty acids from fish also exert anti-diabetic response by lowering fasting glucose, diminishing level of Glycated hemoglobin, improving function of pancreatic-β cells and raising PPAR-γ activity [52]. An imbalance between generation and clearance of reactive oxygen species (ROS) is known as oxidative injury, which can lead to imbalance of redox homeostasis. Due to increased metabolic and mechanical demands results lipid peroxidation as well as formation of free radical which affects insulin receptor function and contribute to insulin resistance [53]. Zhang et al. reported that in diabetic mice which were induced by injection of alloxan, high-dose Tilapia Collagen Peptide and metformin were found to lower blood glucose levels by 31.8 and 30.3 percent, respectively. Tilapia Collagen Peptide (TCP) demonstrated notable effects on antioxidant enzymes, for example superoxide dismutase (SOD), catalase (CAT) and malondialdehyde (MDA). High-dose TCP treatment for diabetic mice resulted in an increase in SOD and CAT activity of 23 % and 59.2 %, and decline in MDA level of 39.1 % [54]. Antioxidant enzymes namely catalase, superoxide dismutase maintain endogenous antioxidant defense system and reduce the risk of insulin resistance. This data shows that mice treated with fish oil were close to normal levels in non-diabetic mice because fish oil has strong antioxidant capacity. A study revealed that the hypoglycemic potentiality of fish oil high in MUFAs obtained from hybrid catfish (Pangasius larnaudii × Pangasianodon hypophthalmus) on glycemic control are responsible for at least the depletion of plasma adipokine dysregulation and the enhancement of insulin sensitivity via the maintenance of normal insulin signaling and the inhibition of pro-inflammatory signaling in addition to the improvement of AMPK activation in the skeletal muscle in type-2 diabetic rats that were fed by a high fat diet with Streptozotocin treatment [55]. DHA have the capacity to modulate and regulate oxidative stress by rising liver SOD and total antioxidant capacity levels and upregulate the glucagon-like peptide-1 receptor expression in the cytoplasm of pancreatic islet cells [56]. Intake of fish oil prevents lipid accumulation, reduces fasting glucose level, as well as normalises glycemic or insulin responses to intraperitoneal glucose tolerance test in comparison to high fat/ high sucrose diet through restoring insulin-sensitive Erk activation in epididymal tissue [57]. Fish oil and/or pioglitazone prevent β-cell dysfunctioning by enhancing the insulin sensitivity and reducing pancreatic islet hypergrowth that is repressed by ER stress [58]. In pregnant rats fed a high-fat diet, fish oil had a long-term positive effect, avoiding insulin resistance in adult offspring [59].

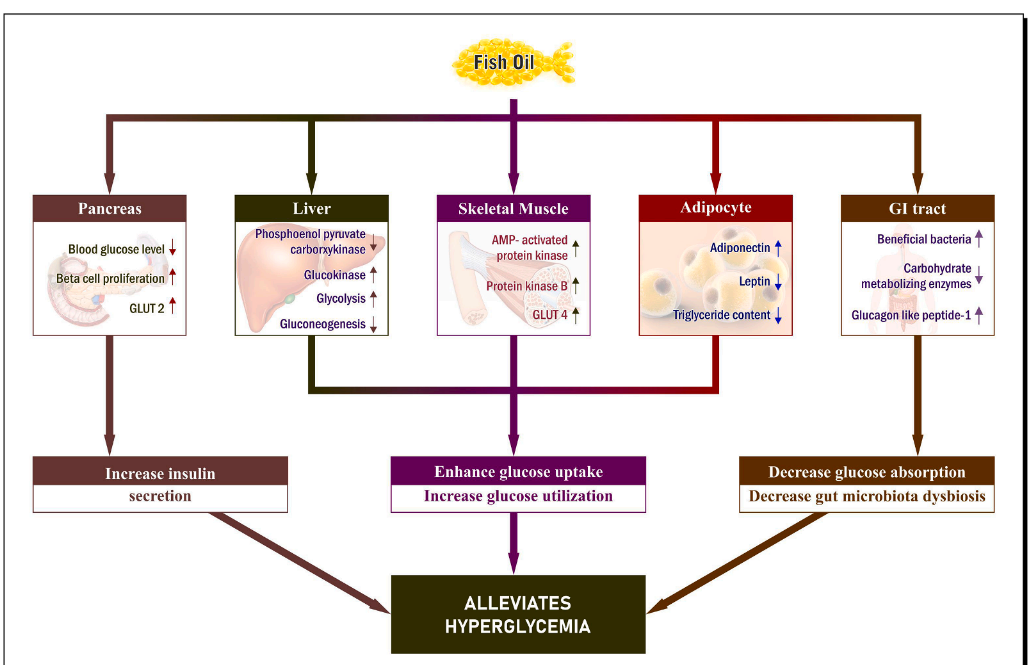

Fig. 2. Biological mechanisms underlying hypoglycemic effects of fish oil. Fish oil can target various organs to control diabetes. Fish oil can stimulate insulin sensitivity in pancreas, increased expression as well as translocation of GLUT-4, promote glycolysis and inhibit gluconeogenesis in liver, enhanced glucose uptake in skeletal muscle and reduced glucose absorption through the inhibition of digestive enzymes such as α-glucosidase and α-amylase in intestine. Abbreviations: GLUT, Glucose transporter; AMP, Adenosine monophosphate.

Fish oil and cancer

Cancer is a heterogeneous set of illnesses that can begin in practically from any organ or tissues of the body. It occur when a clump of aberrant cells proliferate uncontrollably by flouting the normal norms of cell division, cross their normal borders to invade surrounding body parts, and/or spread to other organs. Based on estimation, 9.6 million people die from cancer each year and 18.1 million new cases have been documented alone in 2018, worldwide [60]. Cancer is a serious issue for public health and the second prime cause of death around the world, following cardiovascular diseases [61]. Men are more likely to develop lung, prostate, colorectal, stomach and liver cancer than women, who are more likely to develop breast, colorectal, lung, cervical and thyroid cancers [62]. Today one of the most popular areas of research is ethno pharmacological properties of natural products and their derivative compounds from plants and animals. Natural compounds obtained from medicinal plants, marine fish and microbial origin are the most successful source for developing new drugs with therapeutic potential against cancer and as a potential replacement to resistance displayed by cancer cells at multidrug [63]. Many researchers investigated various mechanisms of fish oil, which exerts anticancer properties. Fish oil has traditionally used five different mechanisms to activate its anti-tumor potentiality (Fig. 3). These mechanisms include prevention of carcinoma cell growth development by programmed cell death, overproduction of free radicals or reactive oxygen species which causes decrease antioxidant status, alteration of estrogen metabolism, and inhibition of pro-inflammatory eicosanoids [64]. Suppression of neoplastic transformation, inhibition of cell cycle [65], increase cell death [66], and antiangiogenicity are some of the mechanisms hypothesised for their anticancer effects [67].

Fish oil reduces inflammatory eicosanoid biosynthesis

One of the possible pathways is the suppression of eicosanoids produced from arachidonic acid results in modify immune system's reaction to cancer cells and can modulate how they proliferate, metastasize, and develop blood vessels. One of the major functions of PUFAs is related to their enzymatic transformation into eicosanoids. Major PUFA found in cell membranes is arachidonic acid; majority of eicosanoids produced will be of the 2-series prostanoids (prostaglandins and thromboxanes) and the 4-series leukotrienes (LT), in the products. In general, arachidonic acid derived eicosanoids show pro-inflammatory property [68], although prostaglandin (PG) E2 also has anti-inflammatory properties [69] whereas EPA-derived eicosanoids have anti-inflammatory effects. Prostaglandin E2, leukotriene B4, thromboxane A2, and 12-hydroxyeicosatetraenoic acid are examples of eicosanoids that have been positively associated with cancer [70]. Supplementation of fish oil suppresses COX-2 expression and increases lipid peroxidation in the tumor thereby diminished tumour cell differentiation and promotes cell death [71]. A collection of transcription factors known as PPARs are activated by omega-3 PUFAs, and the subsequent upgradation of transcription factors may play a crucial function in the early stages of life as well as in the prevention and therapy of a number of disorders, including metabolic, cardiovascular, neuromuscular pathologies, inflammatory disorders [72] and cancer [73]. To further understand their mechanism of action, EPA and DHA in fish oil in tumor inhibition have been tested against variety of cancer cell lines and animal models. Recent study

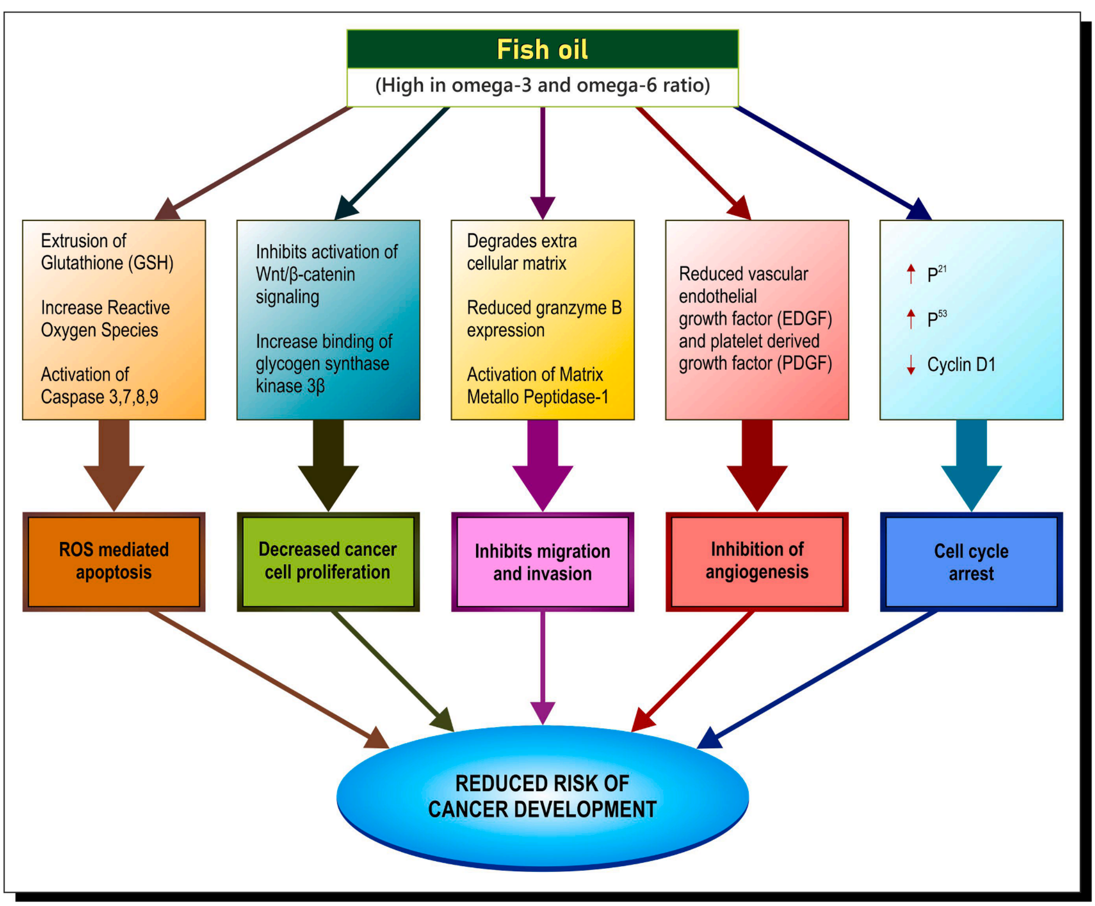

Fig. 3. Cellular and molecular mechanisms involved in anticancer activity of fish oil. Polyunsaturated fatty acids present in fish oil can reduce carcinogenicity via different pathways such as induction of ROS mediated apoptosis through the depletion of GSH that favors ROS-induced oxidative damage, disruption of plasma membrane integrity, enhance lipid peroxidation and cytotoxicity. Fish oil can inhibit cell proliferation; decrease angiogenesis as well as metastasis thereby promote apoptosis and necrosis-like mechanism by the inhibition of cell cycle that prevents invasiveness and migration.

proved that commercial fish oil combined with signal transduction inhibitors reduces the expression of p-Src and COX-2 in breast cancer cell lines, which in turn reduces cell migration [74]. The n-3 fatty acid named EPA from fish oil possess a comparatively higher anti-progressive effect on non-small cell lung cancer A549 cells that express COX-2 and in associated xenograft tissue than that of COX-2 deficient H1299 cells and tumors [75]. Fish oil combined with imiquinod serve as inducers of IL-10 and inhibitors of IL-6, TNF-α as well as exhibited higher concentration dependent immunomodulation human skin carcinoma cell lines [76].

Fish oil promotes apoptosis and decrease cancer cell differentiation

Apoptosis is the process of programmed cell death, core controller of normal tissue equilibrium. Intrinsic mitochondrial mediated cell death mechanism and the extrinsic receptor-mediated cell death mechanism are usually the two major apoptotic pathways that initiate apoptosis. Several cytotoxic stresses such as DNA damage, growth factor withdrawal, and γ-radiation, mitochondria-mediated apoptosis is triggered. The Bcl-2 family of proteins has a big contribution in caspase activation during intrinsic apoptosis. Tumor cells can develop apoptosis resistance by overexpressing antiapoptotic proteins like Bcl-2 or downregulating proapoptotic proteins like BAX. The tumor inhibitory gene P53 controls the function of Bcl-2 and BAX [77]. Treatment with fish oil (FO), rich in n-3 polyunsaturated fatty acids, reduced cell differentiation and promoted cell death in tumour cell by upregulating p53, Bcl-2, caspase-7, caspase-3 expression and downregulating PARP-1 expression [78]. Wnts are secreted glycoprotein that ties up with Frizzled family seven-pass transmembrane receptors. The binding sends a signal to a complex containing proteins adenomatous polyposis coli, Axin, and glycogen synthase kinase-3β. The Wnt/β-catenin pathway prevents the phosphorylation-dependent degradation through stabilization of the transcription coactivator β-catenin. Irregularity of Wnt signaling results in the buildup of β-catenin that subsequently forms a complex with the transcription factor (T cell factor /lymphoid enhancing factor) and promotes the transcription of target genes which regulate cell survival, proliferation, and metastasis. Omega-3 PUFAs inhibit cell growth and increase cell death through the blockage of the Wnt/ β-catenin signal transduction pathways [79]. DHA influence glutathione (GSH) extrusion that can results generation of free radical and activation of caspase, are involved in ROS mediated cell death [80]. Several investigation shows that certain polyunsaturated fatty acids (PUFAs) has been demonstrated to enhance lipid peroxidation [81] and the generation of lipid hydro peroxides and other fat breakdown byproducts which may harmful to cancerous cells [82]. PGE2 inhibits apoptosis and promotes angiogenesis, which are both important in tumour formation. PGE2 stimulate the activity of p38 mitogen activated protein kinase, which enhances COX-2 expression [83]. COX-2 deregulation causes a rise in the amount of its main metabolic product, prostaglandin E2, whose pleiotropic effects appear to affect the majority of the hallmarks of cancer. Fish oil supplementation resulted in lower tumour weight, higher tumour cell apoptosis, less ex vivo tumour cell proliferation, more lipid peroxides in the tumour, less cyclooxygenase-2 expression in tumour cell, and less prostaglandin E2 in the plasma than rats fed regular food or rats supplemented with coconut oil [71].

Fish oil control angiogenesis and cancer cell invasion

Angiogenesis is the process by which cancer cells can form new blood vessel. To meet their metabolic needs, rapidly developing cancer cells require more blood arteries. As a result, tumour growth is dependent on angiogenesis. The angiogenic process begins with the breakdown of the subendothelial basement membrane and surrounding extracellular matrix [84]. The extracellular matrix supports angiogenesis by providing structural support as well as molecular signals that are required for all stages of blood vessel creation, including vascular sprouting, lumen formation, vessel maturation, and vessel stabilisation [85]. Matrix metalloproteinases (MMPs) are a family of Zn^{2+}-dependent endopeptidases, extracellular matrix degrading enzymes that direct cell development, proliferation, angiogenesis, and motility, among other things. MMP-2 and MMP-9 overexpression is linked to pro-oncogenic occurrences like neovascularisation, tumour cell proliferation, and metastasis for the reason that it can disintegrate the extracellular matrix, basement membranes, and adhesion molecules (including vascular cell adhesion molecules and intercellular adhesion molecules) and become aggressive [86]. Angiogenesis is stimulated or inhibited by numerous cytokines and growth factors. One of the most researched angiogenic growth factors is vascular endothelial growth factor (VEGF). Accelerated vascular permeability, stimulation of endothelial cell differentiation and motility, and promotion of endothelial cell survival have all been linked to VEGF [87]. Several reports demonstrated that in VEGF-stimulated human umbilical vein endothelial cells, conjugated eicosapentaenoic acid, which is made by alkalinizing eicosapentaenoic acid, decreased tube formation by inhibiting secretion and mRNA expression of MMP2 and MMP9 [88]. For vascular smooth muscle cells, platelet-derived growth factors show mitogenic and chemoattractant characteristics. Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are primarily seen in oily fish, have powerful anti-angiogenic effects, inhibiting the production of a variety of key angiogenic mediators such as Vascular Endothelial Growth Factor (VEGF), Platelet-Derived Growth Factor (PDGF), Platelet-Derived Endothelial Cell Growth Factor (PDECGF), cyclooxygenase 2, prostaglandin-E2, nitric oxide, Nuclear Factor κB, matrix metalloproteinase and beta-catenin [89].

Fish oil arrest cell cycle

Unchecked cell division is thought to be main result of cancer caused by aberrant cell cycle protein activity. Cyclin-dependent kinase (CDK) is a crucial enzyme that controls cell cycle progression. The retinoblastoma protein is phosphorylated and rendered inactive by a holoenzyme called cyclin D1, which is a regulatory subunit, allowing the cell cycle to move from G1 to S phase. It is well recognised that the long chain polyunsaturated fatty acid, docosahexaenoic acid (DHA), is one of the primary bioactive components in fatty fish. On in vitro study, DHA has the capacity to inhibit G1 cyclin/CDKs and can prevent starved HT-29 cells from entering S-phase when stimulated with serum [90]. Proinflammatory cytokines may undergo post-translational changes as a result of NO, which might promote and initiate tumour. The most important source of DHA is marine fish oil. DHA decreased the expression of the prostaglandin family of genes, as well as cyclooxygenase 2 and many cell cycle-related genes, while increasing the expression of apoptosis-related caspases 5, 8, 9, and 10. The suppression of iNOS by DHA contributes to the differentiation of colonic cells, also up-regulate cyclin-dependent kinase inhibitors p21 and p27 [91]. The cyclin-dependent kinase inhibitors p21 and p27 can control cell proliferation, cell motility, and apoptosis [92]. In melanoma models, DHA has the ability to inhibit tumour and cell expansion as well as the potential for metastasis. It was seen in SK-Mel-110 cells treated with DHA can substantially increase p27 in the absence of FBS [93]. Total fish lipids extracted from *Labeo rohita* exhibit anticancer effects that interrupt cell cycles in the G0/G1 phase of human prostate cancer (PC-3) cells, increasing their cytotoxicity [94].

Fish oil and cardiovascular diseases

The category of illnesses known as cardiovascular diseases (CVD) affects heart and blood arteries. These include coronary artery disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism. The major cause of death worldwide and likely the main inducer of mortality in 2020 are Ischemic heart diseases [95]. American Heart Association Committee reported two portions of fish per seven days should be consumed to maintain a healthy heart [96].

Since 1970s, scientists have paid close attention to the link between fish ingestion and a decreased probability of cardiovascular disease. Fish oil was primarily used for its cardiovascular benefits. Several studies have confirmed that cardio-protective components present in fish oil are EPA and DHA (Fig. 4). Strokes are caused by blood clotting or a blood vessel that has burst. The risk of stroke and heart attack is enhanced by atherosclerosis. Consumption of fish oil will enhance the stability of plaque and thus help to reduce the risk of thrombotic stroke [97]. Plaque rupture is a sudden event that exposes the plaque contents to the vascular lumen's extremely pro-thrombotic environment. As a result, thrombosis develops, potentially leading to a myocardial infarction, stroke, or other vascular catastrophe. Certain matrix metalloproteinases (MMPs) and cysteine proteases appear to aid in the disintegration, thinning, and weakening of the fibrous cap. Plaque rupture is primarily an inflammatory process, and the characteristics of an atherosclerotic plaque that render it susceptible to rupture are a thin fibrous cap and an increase in inflammatory cells including macrophages, T cells, and mast cells [98]. Marine n-3 fatty acids may help to stabilize atherosclerotic plaques by reducing inflammatory and immunological cell infiltration for example, monocyte, macrophages, and lymphocytes. Oily fish's n-3 polyunsaturated fatty acids guard against cardiovascular diseases that can enhance atherosclerotic plaque stability [99]. Many scientists demonstrated that supplementation with fish oil change the membrane fatty acid composition as well as increase the amount of ATP produced by vascular endothelial cells and reduce plasma nor-adrenaline, both of which may mitigate the rise in blood pressure that comes with getting older [100]. Commercial bluefin tuna from Italy may be regarded as a functional food with potential health advantages for the treatment and protection of cardiovascular diseases [101]. Daily supplementation of fish oil encourages alteration of membrane fatty acid construction as well as cardio-protection which carry for a long period of feeding, in addition to a marked elongation of life span following cardiovascular stroke in experimental rats [102]. Fish oil promote β-oxidation of fatty acid that may lead to decrease transport of non-esterified fatty acids to the liver as well as reduce triglyceride synthesis thereby it can be used for treatment of cardiovascular diseases [103]. Lipid peroxidation, endothelial dysfunction and reduced nitric oxide bioavailability results oxidative stress influenced endogenous DNA destruction [104] and it could acts as a main factor for progression of atherosclerotic condition [105]. Fish oil can enhance endogenous nitric oxide synthase expression thereby increase in level of antioxidant enzyme and reduce risk of oxidative injury in vascular endothelial cells by upregulated level of nuclear factor erythroid 2-related factor-2 mediated antioxidant

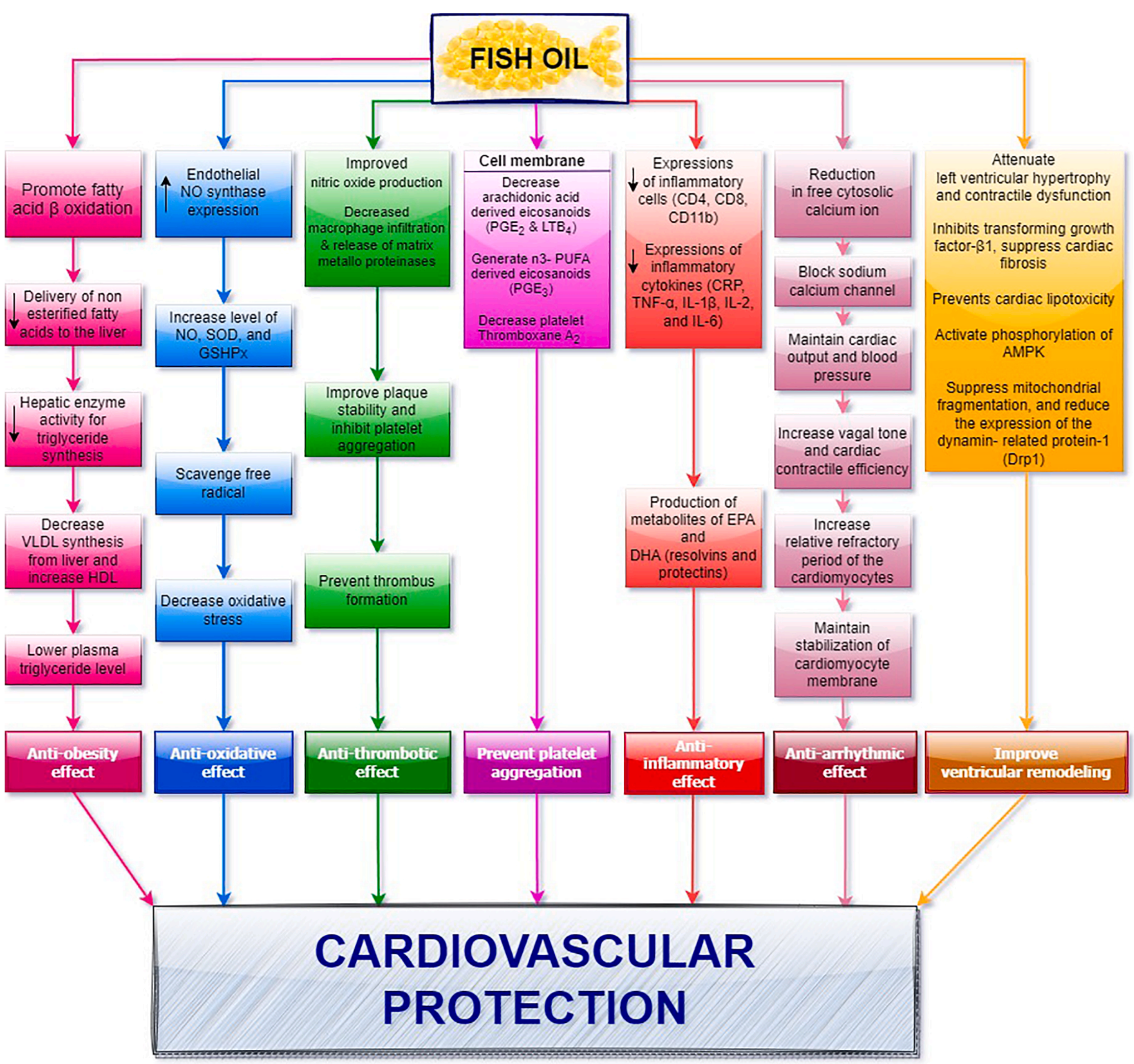

Fig. 4. Possible molecular mechanisms for cardio protective effects of fish oil. Abbreviations: VLDL, Very low density lipoprotein; HDL, High density lipoprotein, NO, Nitric oxide; SOD, Superoxide dismutase; GSHPx, Glutathione peroxidase; PG, Prostaglandin; LT, Leukotriene; PUFA, Polyunsaturated fatty acids; CD, Cluster of differentiation; CRP, C-reactive protein; TNF-α, Tumor necrosis factor- α; IL, Interleukin; EPA, Eicosapentaenoic acid; DHA, Docosahexaenoic acid; AMPK, AMP-activated protein kinase; Drp1, dynamin- related protein-1.

response [106]. Many scientists also demonstrated that omega-3 rich fish oil fat emulsion pre-treatment greater aldehydes via lipid peroxidation, which triggers inflammatory signaling pathway. Therefore enhance myocardiac antioxidant capacity and alleviate MI/RI in experimental animal and TBHP oxidative injury in H9C2 cells [107]. Therefore their result illustrated that omega-3 rich fish oil upgraded the retardation of deterioration and overproduction of free radicals and attenuate myocardial oxidative destruction through activation of the nuclear factor erythroid 2-related factor-2 signaling pathway. Thromboxane A2, a potent aggregatory agent and vasoconstrictor, causes platelet accumulation that is a prior occurrence in the advancement of thrombosis. Supplementing with long-chain polyunsaturated fatty acids enriched fish oil helps to lessen platelet aggregation by suppressing thromboxane A2 [108]. Omaga-3 fatty acids also decreased production of eicosanoids from arachidonic acid such as prostaglandin E2 and leukotriene B4, thus inhibit platelet aggregation [109]. Fish oils or n-3 (omega-3) fatty acids derived from seafood origin have been demonstrated to reduce amount of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) [110], thereby enhanced production of metabolites of EPA and DHA namely resolvins and protectins. Regular intake of fish help to minimize the incidence of ventricular fibrillation induced cardiovascular morbidity and mortality [111]. Cardiac ventricular dysfunction, which leads to heart failure, is frequently caused by ventricular interstitial fibrosis and remodeling. This condition is the last common pathway across a range of heart conditions. According to recent research, fish oil may enhance ventricular remodeling [112].

Researchers published that the ingestion of two fish meals per week would decline cardiovascular death estimate, approximately by 30–40 % [113]. Habitual use of fish oil is correlated with a 13 % less possibility of all cause death, a 16 % less possibility of CVD death, and a 7 % less possibility of CVD occurrences among the common people in UK [114]. However the n-3:n-6 PUFAs ratio is very important on CVD events. A high susceptibility of coronary plaques was linked to a poor ratio of eicosapentaenoic acid to arachidonic acid and a low amount of EPA in the serum [115]. Although because there is a limit to the enzymes' ability to convert ALA to longer chain fatty acids, people will probably need to eat a diet rich in EPA and DHA to keep their levels at the optimal level [116]. Additionally, the most popular dietary sources of omega-3 PUFA such as salmon, sardines, trout, oysters, and herring—have relatively low mercury content. Mercury is found in fish muscle but not in the oil because it is protein-bound and water soluble. Fish oil supplements should therefore have very little mercury in them [117].

Fish oil and mental health

The brain is the most significant and complicated part of human body, responsible for perception, mind, emotions, feeling, eyesight, respiration, body temperature regulation, control food intake and many other bodily functions. In an average adult brain, it composed of 60 % fat. Fish oil contains omega-3 fatty acids, which are crucial for neuronal growth for both brain development [118] and function [119]. Lipids which are present in brain are composed of sphingolipids, glycerophospholipids and cholesterol. The principal long chain n-3 PUFA is docosahexaenoic acid comprising 10 to 20 % of total fatty acid content in adult human brains. On the other hand, α-linolenic acid, eicosapentaenoic acid and docosapentaenoic acid make up less than 1 % of total fatty acid content [120]. Possible mechanisms of fish oil to prevent brain disorders via maintaining neuronal and synaptic plasticity, regulates neurotransmitters level (dopamine, serotonin, norepinephrine, endocannabinoid), regulates Hypothalamic Pituitary Adrenal (HPA) axis, producing anti-inflammatory metabolites (maresins, protectins, resolvins), controlling membrane or intracellular receptors or signal transductors (GPR 120, PPAR-γ, TLR-4), maintain microglia phagocytosis and neuroendocrine exocytosis (Fig. 5). The majority of DHA accumulates in the brain throughout brain development, which occurs from the start of the 3rd trimester of pregnancy to the 2nd year after birth in humans [121] and from the 7th day of pregnancy to the 21st day after birth in rats [122]. However, with age the brain's DHA levels reduce [123] and in the mental disorder like Alzheimer disease [124]. DHA deficiency in brain is linked to decreased memory power and apprehension in rats [125]. Reduced intake of fish ingestion is linked to a higher risk of mental illness, including Alzheimer's disorder [126] or age-related cognitive impairment [127]. Fish oil is beneficial for easing symptoms of distress, unhappiness, nervousness, impatience, cognitive tiredness, tension, suicidal tendencies and nerve illnesses because it contains ω- 3 fatty acids. Fish oil rich in DHA, facilitates improved nerve cell communication. Low serotonin levels in the brain have been linked to low DHA levels that are again connected with an increased tendency to suicidal depression, and violence. DHA is most important for maintaining and growing the brain of learning memory performance [128]. Fish oil supplements have the potential to directly improve the brain's EPA/DHA concentration as well as exert positive impacts on neuron. Administration of fish oil increased cognitive function in both healthy participants [129] and Alzheimer's disease or people with cognitive impairment [130]. Few randomized controlled trials showed that eating

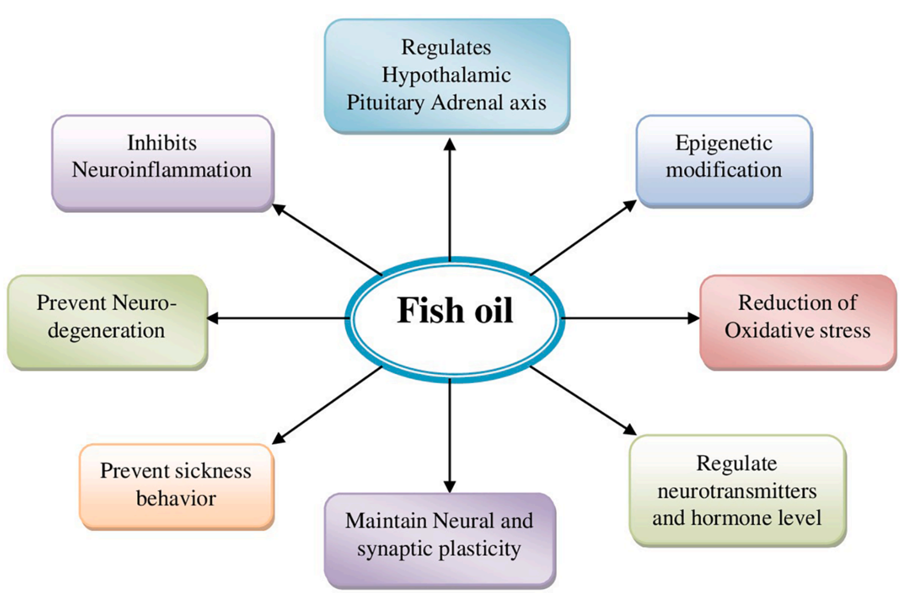

Fig. 5. Multifunctional role of fish oil in the maintainance of brain function.

a balanced diet supplemented with fish oil, can improve mental health in people with depression [131] and fish oil supplementation might reduce the mean depression score during pregnancy [132]. Additionally, Five weeks of fish oil supplementation improves anti-inflammatory brain fat, remedy for glucose intolerance, hampers food intake, mitigates depressive behaviours, and reduces brain gliosis markers in obese mice [133]. There is also evidenced data from meta-analysis suggests that there is no association of consumption of long-chain PUFA with the risk of dementia [134]. Another study shows a positive effect on Alzheimer's disease [135].

Fish oil and kidney disorders

The kidney is an important part that is crucial to human health as well as gradual maturation. Kidney performs many excretory and regulating functions to maintain homeostasis. Kidney disease is explained as a heterogeneous category of illnesses affecting structure and function of kidney. According to the level of glomerular filtration rate, kidney disease is mainly classified as Acute Kidney Injury and Chronic Kidney Disease (CKD). Internationally estimated widespread presence of Chronic Kidney Disease is 11–13 %, and 4.902 to 7.083 million individual with end stage renal failure requiring kidney replacement therapy are thought to exist [136]. It has been estimated that 956,200 deaths occur worldwide due to CKD in 2013 [137]. Chronic Kidney Disease is a major worldwide health issue, particularly in low and middle income nations. A variety of drugs, synthetic substances and heavy minerals can alter kidney structure and function. One of the important functions of kidney is to reabsorbing ions and molecules which in turn depend on the structural stability of Brush Border Membrane (BBM) and availability of ATP, which is provided by several metabolic mechanisms. Dietary PUFAs have the capacity to pass the blood brain barrier via passive transport and facilitators according to the esterification forms. Fish oil enriches with omega-3 fatty acids changes membrane fatty acid composition and hastens the repair and/or restoration of damaged structures, e.g. mitochondria, peroxisomes and increases the tricarboxylic acid cycle and BBM activity, thereby increases the activity of the glucose uptake enzymes. The most crucial function of fish oil is to activate internal antioxidant defence system and protect against free radical injury [138]. Fish oil help to reduced damage to proximal tubular membrane, improved mitochondrial functioning, enhanced lysosomal integrity and reduced oxidative stress [139].

Fish oil and non-alcoholic fatty liver diseases

Non-alcoholic fatty liver disease (NAFLD) is a degenerative condition in which fat build up in the hepatocytes with little or no alcohol use. Non-alcoholic fatty liver disease may be categorized into Non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). Nonalcoholic fatty liver disease is the most frequent hepatic manifestation internationally and is highly linked to obesity and type-2 diabetes [140]. The occurrence of NAFLD is greater in the Mideast (32 %) and South America (30 %), intermediate in Europe (24 %), Asia (27 %) and North America (24%) and lower in Africa (13 %). The incidence of it has climbed from 15 % to 25 % between 2005 and 2010, which has resulted in a sharp rise in the international concern [141]. Animal models are often used to examine NAFLD, and it has been found that fatty liver growth is only correlated with dietary fat intake and weight gain. Non-alcoholic steatohepatitis caused by excess dietary intake of carbohydrate and fat, lead to fatty acids released from the adipose tissue into the blood. De novo lipogenesis is a multi-enzyme process that can transform carbohydrates into fatty acids. In the liver fatty acids can either be oxidised by mitochondria or changed back into triglycerides for VLDL export. In order to produce the cytological phenotype recently known as NASH, Fatty acids enhance the production of lipotoxic molecules (such as diacylglycerols, ceramides, lysophosphatidyl choline) that interfere ER stress, cellular disturbance, liver tissue damage, infection, and cell death [142]. By inhibiting genes participate in carbohydrate utilisation and fat synthesis, such as l-pyruvate kinase, fatty acid synthase, and acetyl-CoA carboxylase, omega-3 fatty acids are effective suppressors of liver glycolysis and de novo synthesis of fatty acids. Supplementation of polyunsaturated fatty acids, upgrades hepatocellular steatosis in obese models by interchanging the gene expression of important enzymes i.e., suppression of the function of carbohydrate regulatory element binding protein, one of the controller of glycolytic, and adipogenic genes, such as l-pyruvate kinase and fatty acid synthase [143,144]. Several reports established that intake of n-3 PUFAs inhibits SREBP-1 activation and adipogenic genes functioning thereby upgrading glycemic efficiency, insulin levels and insulin sensitivity as well as lessen the oxidative injury, and exerting an anti-inflammatory outcome [145]. Consumption of fish oil protects liver against western style diet induced NAFLD via improving liver metabolism and alleviating hepatic inflammation [146].

Fish oil and inflammatory diseases

Inflammation is a way by which immune system of the body reacts to an injury or pathogen attack. Although inflammation is a typical reaction, when it happens inappropriately, it can result in pro-inflammatory mediator production, leukocyte sequestration to an abnormal locations, increased expression of endothelial and leukocyte binding proteins, appearance of soluble forms of adhesion molecules in the circulation, and acute injury to host cells. Greater quantities of TNF-α, IL-1β, and IL-6 which are extremely damaging and are characterized in numerous pathological responses, that take place in endotoxic disturbance, in acute respiratory distress syndrome, several metabolic disorders and in chronic inflammatory diseases like rheumatoid arthritis and inflammatory bowel disorder [147]. The disorders crohn's disease and ulcerative colitis are grouped under the umbrella term of inflammatory bowel disease, which is defined as a persistent inflammation of the gastrointestinal (GI) tract. Fish oil inhibits leukotriene from accumulating in the colon in ulcerative colitis. There are numerous anti-inflammatory and immune-modulating properties of dietary omega-3 fatty acids that may be relevant to atherosclerosis and myocardial infarction, stroke and sudden death. Fish oil might promote expression, release and plasma content of anti-inflammatory hormone adiponectin in adipose tissue through activation of PPAR-γ [148]. Adiponectin is a hormone and adipokine protein exclusively derived from adipose tissues that have anti-inflammatory and anti-atherogenic effects. Peroxisome Activated Proliferator Receptors (α, β or δ, and γ) are ligand-activated transcription factors that are participate in metabolism of lipid and lipoprotein, carbohydrate homeostasis, cellular differentiation and it appears that they also regulate inflammatory response. Peroxisome Activated Proliferator Receptor-γ discourages NF-κB transcriptional activity and inflammatory response in many cardiac cells, mainly epithelial cells [149]. A number of inflammatory genes, such as IL-1β, IL-6, IL-8, COX-2, nitric oxide synthase, MMP, VCAM-1, and acute phase proteins, have been demonstrated to be inhibited by activators of both PPAR-α and PPAR-γ. PPARγ activators can repress the expression of pro-inflammatory cytokines such as interleukin-2, interferon (IFN)-γ and tumor necrosis factor-α in human as well as animal lymphocytes [150]. Additionally, PPARγ ligands reduce the release of IL-12 in dendritic cells triggered by CD40 [151]. Higher intakes of oily fish, which is substantial in long chain EPA and DHA, causes a reduction in the generation of inflammatory eicosanoids derived from Arachidonic Acid (2 series prostaglandins and thromboxanes, 4 series leukotrienes) and increase in the quantity of anti-inflammatory eicosanoids derived from EPA (3 series prostaglandins and thromboxanes, 5 series leukotrienes). Thereby fish oil can modulate the genetic information of adhesion molecules and might be used as an agent to control endotoxemia or systemic inflammatory response syndrome [152]. Cyclooxygenase (COX) is a crucial component in the inflammatory prostaglandin (PG) production system that is a significant producer of reactive species and disrupts redox balance. Dietary fish oil (omega-3 PUFAs) competes with the inflammatory eicosanoids and displaces arachidonic acid from cell membrane. Fish oil has a capacity to reduced nitric oxide production by suppressing iNOS production [153]. For those who are infected with chronic inflammatory diseases, regular consumption of fish oil in the form of supplements, tablets, pills and capsules is very helpful.

Fish oil and bone health

Skeletal system is made up of cartilage and bones, and it performs two vital tasks. The first is a morphological role that includes supporting and safeguarding major inner organs like bone marrow and even the muscular interconnections for motion and secondly, crucial metabolic role where the skeleton acts as a reserve of calcium and phosphate ions that help to buffer variations in hydrogen ion concentration and are hence necessary for such regulation of serum homeostasis. Bone is a dynamic organ that undergoes remodeling throughout life. Bone remodeling is a continuing process where the skeleton's mature bone tissue is eliminated (a process known as bone resorption mediated by osteoclasts) and new bone tissue is formed (a process known as bone formation mediated by osteoblasts) to maintain homeostasis as well as gives bone its normal structure in the body. Bone related disorders such as osteoporosis, osteoarthritis, Paget disorder, osteomalacia etc. are significant contributors to prevalence and death in the United States.

Effect of fish oil on osteoporosis

Common bone condition called osteoporosis characterised by loss of bone mass leading to bone fragility and increase in fracture incidence. Around 200 millions of people suffer osteoporosis related long term consequences, over 9 million fractures have been documented per annum [154]. It is more prevalent in older women, some man are also at high risk having family history of fracture and age greater than 65 years. Impairment of bone architecture results in drop of bone mineral strength and greater chances of fractures. Bone mineral density is the amount of minerals in bone. Alteration of remodeling can cause estrogen deprivation, elevated parathyroid hormone level, stimulation of pro-inflammatory cytokines, surges of growth hormone, and changes in serum calcium levels [155]. Various inflammatory cytokines cause osteoblastic and stromal cells to produce COX-2, which boosts the production of the osteoclastogenic component, PGE2 [156]. Extreme levels of PGE2 can effectively cause bone resorption [157]. Fish oil can lower PGE2 levels in cultures of bone organs [158]. TNF-α, IL-1β, and IL-6 are pro-inflammatory cytokines that encourage bone resorption and increased with aging [159]. Concentrated fish oil can inhibit osteoclastogenic factor, receptor activator of NF-κB ligand that is needed to pre-osteoclasts differentiation to mature osteoclasts. Concentrated fish oil can limit osteoclast development and activation, which would reduce bone resorption and reduce bone loss in old mice [160]. Regulation of p38 mitogen activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK) pathway have a significant impact on osteoclastogenesis [161]. The p38 MAPK can arrest bone loss in postmenopausal women with osteoporosis [162]. Fish oil protects bone loss in postmenopausal mice [163] and rats [164] with ovariectomies compared to diets with corn oil [165]. An earlier study showed that a high intake of omega-3 rich fatty fish more than three portions per week was linked to the maintenance of femoral neck bone mineral density in elderly [166]. Fish and fish oil also contain vitamin D in the form of D_3 (cholecalciferol). Low bone mineral density, rickets, osteomalacia, and osteopenia are linked to vitamin-D. Deficiency of vitamin D along with inadequate calcium intake resulting rapid bone loss in every susceptible elderly population. Supplementation of fish oil improves bone mineral density in prednisolone induced osteoporosis rats [167].

Effect of fish oil on osteoarthritis

The most prevalent kind of arthritis, Osteoarthritis (OA) is slowly progressing degenerative joint illness marked by cartilage degradation, subchondral bone alterations, osteophyte growth, muscle weakning, and tissue inflammation of the synovium and tendon [168]. With 18 % of women and 9.6 % of men greater than 60 years of age affected globally [169], OA is a prominent risk factor of persistent pain and stiffness in the older adults and the main reasons for knee and hip replacement, resulting in higher expenses and a heavier load on the health-care system [170]. Several factors are related to the progression of osteoarthritis including nutritional imbalances, chronic inflammation [171], obesity, ageing and oxidative stress [172]. Reactive oxygen species can mediate intracellular signaling and gene activation of cytokine in chondrocytes. The production of ROS by chondrocytes can lead to deterioration of the cartilage matrix [173]. Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are abundant in fish oil, which act as effective intermediates for such enzymes that breakdown arachidonic acid and its byproducts [174]. Deep sea fish oil can modulate oxidative stress by improving glutathione level and reduce MDA level in dogs [175]. Pro-inflammatory mediators promote the breakdown of cartilage matrix and deterioration of the articular cartilage, ending in fewer collagen and proteoglycans in cartilage. It has been demonstrated that IL-1β and TNF-α reduce the expression of collagen and proteoglycans while increasing the expression of Matrix Metallo Proteinases (MMPs), thereby eventually loss of joint function [176]. Several non-steroidal anti-inflammatory drugs have demonstrated efficacy for the treating of osteoarthritis. However, they have some adverse effects like stomach pain, heart burn, ulcers, renal toxicity, and cardiovascular risk [177]. Some scientists reported that krill oil could attenuate cartilage degeneration in monosodium iodoacetate induced osteoarthritic animals by the suppression of action of pro-inflammatory cytokines (IL-1β, TNF-α) and inflammatory factors [178].

Effect of fish oil on rheumatoid arthritis

A musculoskeletal illness called arthritis causes muscle pain, swelling, tightness and limited mobility. Rheumatoid arthritis is a systemic persistent autoimmune illness caused by erosional synovitis (joint inflammation) than osteoarthritis. This is a systemic condition that causes symmetrical inflammation, extra-articular participation of many organs and perhaps gradual joint destruction [179]. The discharge of harmful substances into the synovium is related to inflammation of the joint tissues which accelerate destruction of cartilage and bone within the joint [180]. Fish oil reduced synovitis and increased IL-13 when compared to corn oil supplementation [181]. In the pathogenesis of Rheumatoid arthritis, Nitric oxide, superoxide radicals, hydrogen peroxide, and hydroxyl radicals are examples of highly transitory reactive species known as reactive oxygen species that can lead to start cell injury (to proteins, lipids, etc.) in joint tissues. TNF-α, PDGF and IL-1 are all produced in the rheumatoid synovium and important mediators of inflammation, fibroblast proliferation and cartilage destruction [182]. IL-6 plays an active contribution in the promotion of the acute-phase protein expression, maturation of hematopoietic precursor cells, and synovial fibroblast multiplication [183]. Senftleber et al. [184] stated that marine oil or fish oil is effective for arthritis patients to alleviate pain. Oral administration of ω−3 polyunsaturated fatty acids lead to amelioration of early morning stiffness, tender joint count, pain scale, left grip toughness, ritchie articular index and also significantly decreased leukotriene B4 level in rheumatoid arthritis sufferers [185].

Fish oil and immunity

Immune system is a multiplex network of organs (thymus, bone marrow, and lymph node), cells (white blood cells) and proteins (antibodies) that protect the host against infectious agent. Fish oil has the capacity to boost human immunity. Oil obtained from fish stimulates systemic immune system through enhancing IgG and IgM productivity by spleen lymphocytes. Inflammation also drastically affects immune system. Leukotriene B_4 is a potent inducer of type 1 allergy. Fish oil may effective to alleviate type 1 allergic reaction by suppressing LTB_4 [186].

Fatty acids are the important origin of calorie and morphological constituents of cell walls. Fatty acids also act as reactive modulators of protein complexes, affecting the placement and effectiveness of target proteins within the cell [187]. Fish oil can alter composition of fatty acid of immune cells. Fish oil maintains cell membrane fluidity and initiates immunological reaction by exposing T-lymphocytes to antigen upon the surface of cells [188]. Cell signaling pathways are influenced by physical properties of the membrane thereby expression and transduction of intracellular signaling mechanisms would be modified [189]. Substantial amounts of PUFA are found in fish tissue and cell surfaces, especially those of phagocytic cells (macrophages, neutrophils). Fish oil declines the quantity of arachidonic acid in the membrane surface of monocytes/macrophages [190], thereby fewer substrates accessible for biosynthesis of inflammatory cytokines from arachidonic acid [191]. Fish oil enriched with total parenteral nutrition reduces post operative stress [192]. Aging is interrelated to a delayed immunologic reaction that increased risk of infectious, autoimmune and chronic degenerative diseases. Supplementation of fish oil in older person with exercise is helpful in maintaining immunity balance [193]. Hansen et al. [194] proved that maternal supplementation of fish oil may prevent the risk of asthma in offspring.

Fish oil and altered gut microbiota

Gastrointestinal tract is the primary zone for cross talk between the microorganisms and host. The normal gut microbiota exerts key role on host nutrient metabolism, maintenance of structural integrity of gut mucosal epithelium, metabolism of xenobiotics and drugs, maturation of mucosal immune system, and protection against disease producing agents [195]. Endogenous gastrointestinal microorganisms show beneficial influence on human nutrition and may influence resistance to numerous diseases such as dyslipidemia, insulin resistance, cardiovascular disorders, cancer, inflammatory bowel disease, autoimmune disorders etc. [196]. Fish oil with greater concentration of PUFAs was reported to change gastrointestinal microbiome status [197]. Omega-3 PUFAs acts as a prebiotics, can able to restore gut eubiosis (balance of microbial community). Fatty acids present in fish oil also have antimicrobial activity. The antibacterial properties of fatty acids depend on the presence, number, positioning, and configuration of double bonds as well as length of the carbon chain. Saturated fatty acids show less antibacterial activity than unsaturated fatty acids with equal carbon chain length [198]. Lipopolysaccharides (LPS), primarily present in the outer membrane of Gram-negative bacteria, act as a triggering factor of metabolic endotoxemia [199]. Omega-3 fatty acids increase generation and release of intestinal alkaline phosphatase, that promotes alters in the composition of gastrointestinal microbiota leading to lowers lipopolysaccharide formation and gastrointestinal permeability and thereby, diminishes risk of chronic inflammatory responses and metabolic endotoxemia. Omega-3 PUFA enriched fish oil have a capacity to increase anti-inflammatory and/or LPS-inhibitory bacteria such as *Bifidobacteria*, and to depletion of pro-inflammatory and/or LPS-producing bacteria like *Enterobacteria* [200]. The most prevalent short-chain fatty acids present in gastrointestinal lumen known as acetic acid, propionic acid and butyric acid which are final products of gut microbial fermentation of dietary fibers. Butyrate is a primary source of calorie to the colorectal epithelium and as a critical controller of gene regulation, inflammatory processes, maturation, and death in host cells [201]. Administration of omega-3 PUFAs may enhance the gastrointestinal health by altering the microorganisms to create the anti-inflammatory compounds like short-chain fatty acids [202].

Fish oil and eye disorders

The primary factor in severe vision loss in the elderly is age-related macular degeneration (AMD). Significantly, DHA is the major retinal photoreceptor abundant in the retinal outer segments, and a deficit in it may cause AMD to develop. In addition, oxygenic, inflammatory, and age-related retinal damage, which are major pathogenic factors in the development of AMD, may be prevented by long-chain omega-3 fatty acids. A systematic meta-analysis showed that high dietary intakes of fish and omega-3 fatty acids are linked to a 38 % lower risk of developing both early and late AMD [203]. Dry eye is hypothesized to result from abnormalities in the tear film, which can be caused by aqueous deficiency or tear film evaporation. Evaporation may be slowed down by essential fatty acids, which may improve the tear film's lipid layer [204]. Fatty acids that are absorbed into cell membrane phospholipids produce the main lipid mediators that are produced during inflammation. In addition to regulating gene expression, cell communication, and survival pathways, DHA, its precursor EPA, and their metabolites have the ability to affect immunological and inflammatory processes implicated in the development of retinal vascular and neural cell illness. By creating pro-resolving specialized pro-resolving mediators (NPD1, ResD1, and ResE1) in the retina against neovascularization and suppressing the main proinflammatory cytokine TNF-α, dietary n-3 fatty acids (EPA+DHA) also shielded animals from hyperoxia-/hypoxia-induced pathological retinal angiogenesis [205]. TNF-α is a key player in the development of this disease since it has been demonstrated to upregulate VEGF in retinal and retinal pigment epithelium cells and to cause an inflammatory reaction that alters the retinal vasculature. In fact, a pilot clinical study found that supplementing AMD patients with n-3 fatty acids (1052 mg fish oil containing 400 mg EPA + 200 mg DHA) daily for three months while they received an intravitreal injection of an anti-VEGF significantly reduced vitreal VEGF levels compared to patients who did not take fish oil [206]. After taking a moderate daily dose of both forms of long-chain ω−3 EFAs for three months, people suffering from dry eye disease (DED) noted diminished tear osmolarity and enhanced tear stability. Omega-3 EFAs in a predominantly phospholipid form (krill oil) supplementation may offer advantages over fish oil supplements in addition to improving DED symptoms and lowering basal tear levels of interleukin 17A [207]. Significant improvements in tear osmolarity, omega-3 index levels, tear break-up time, MMP-9, and Ocular Surface Disease Index symptom scores can be attributed to oral consumption of re-esterified omega-3 fatty acids [208].

Fish oil and skin diseases

Lipids are crucial for maintaining the structure and functionality of the skin. Ceramides, cholesterol, and free fatty acids make up the majority of stratum corneum, which encourages cell permeability. Cholesterol, which is derived from the keratinocytes of the epidermis, encourages cornification of the stratum corneum in the last phases of epidermal differentiation [209]. The incorporation of PUFA (Omega-3 fatty acids) in epidermal phospholipids and the epidermis was facilitated by dietary fish oil. Eicosapentaenoic acid and docosahexaenoic acid are conjugated with epidermal phospholipids to create 15-hydroxyeicosapentaenoic acid (15-HEPE) and 17-hydroxydocosahexaenoic acid (17-HDoHE). Leukotriene appeared to be inhibited by these components [210]. In a dose-dependent manner, oral administration of high levels of omega-3 fatty acids decreased the production of IL-4, IL-5, and IL-13 as well as the mRNA expression of their genes in activated MC/9 mast cells and bone marrow-derived mast cells, thereby significantly reducing the severity of dermatitis and the thickening of epidermis/dermis in an NC/Nga murine atopic model [211]. Atopic dermatitis, psoriasis, acne vulgaris, systemic lupus erythematosus, non-melanoma skin cancer, and melanoma all improved with fish oil treatment. Their benefits include enhancing the permeability, maturation, and differentiation of the stratum corneum, inhibiting pro-inflammatory cytokines (tumour necrosis factor-α, interferon-γ, and interleukin-12), inhibiting lipoxygenase, and promoting apoptosis in melanoma cells in addition to the permeability, maturation, and differentiation of the stratum corneum [212]. Overproduction of sebum, altered follicular keratinization, follicular colonisation with *Cutibacterium acnes* (previously *Propionibacterium acnes*), and inflammation that activates both innate and acquired immunity are the four main pathogenic factors that interact to cause acne. The pathogenesis of acne is also thought to be influenced by a number of other variables, such as genetics, neuroendocrine systems, and food. Jung et al. investigated into how Koreans' eating habits affected their acne. They observed that acne patients eat less fish and more junk food when compared to healthy people [213]. *C. acnes* enhance the expression of TLRs on keratinocytes as well as macrophages, which causes keratinocyte hyperproliferation and the onset of an inflammatory response. By triggering keratinocyte TLR-2 and TLR-4, *C. acnes* activates NF-κB and MAPK pathways and causes the synthesis of IL-1, IL-6, IL-8, TNF-α, human β-defensin-2, granulocyte-macrophage colony-stimulating factor (GM-CSF), matrix metalloproteinase, and other cytokines and growth factors [214]. DHA and EPA may lessen the inflammatory response in acne sufferers by reducing the activation of TLR-signaling pathways [215].

Fish oil and preterm birth and low birth weight

Less than 2500 g of body weight at birth is considered low birth weight (LBW). It is a leading cause of newborn mortality and accounts for roughly 15.5 % of all births globally. Most remarkably, developing nations give birth to 95.6 % of all LBW babies. Preterm birth (births occurring before 37 weeks of gestation) or intrauterine growth restriction (IUGR) are the main causes of it. Fish oils can target premature cervical ripening, which is a factor in early preterm delivery, by acting as competitive antagonists of series two prostaglandins. Pregnant women can safely and well tolerate these oils. According to analysis of randomized trial, fish oils have potential as a population-based approach to prevent premature delivery [216]. Muthayya et al. [217] demonstrated that the birth weight of low-fish-eating pregnant women in India was positively correlated with their fish intake during the third trimester. Marine n-3 fatty acids could help reduce the preterm birth and its related consequences by delaying the timing of spontaneous delivery [218]. So far, research has consistently shown that taking n-3 long chain polyunsaturated fatty acid (LCPUFA) supplements throughout pregnancy results in a 2 day increase in the mean gestational duration and a 40–50 % decrease in early preterm births (less than 34 weeks gestation) [219]. Due to the difficulties in ruling out the possibility of lingering confounding environmental influences, a causal relationship between higher n-3 LCPUFA consumption (from fish) during pregnancy and longer gestational length cannot be inferred. Further study in this field will focus on optimising the timing and dosage of n-3 LCPUFA supplementation.

Future directions

The current evaluation makes it clear that fish oil is a valuable and successful area of study with a promising future. Fish oil contains fatty acids that help enhance skin barrier function, prevent UV-induced inflammation and hyperpigmentation, lessen dry skin and dermatitis-induced itch, and speed up skin wound healing. Although various fish oil formulations and PUFAs are created for testing in cell- and animal-based investigations, clinical trials for skin application are still limited. Fish oil should also have potentiality on postmenopausal women but still this area was remains conflict. Omega-3 fats might lower the menopausal problems therefore researchers need to be much focus the exact mechanism between menopause and fish oil. Due to the rising prevalence of multiple diseases and high costs, as well as significant drawbacks in traditional treatment, including greater prices and increased toxic effects of current drugs, researchers have been severely challenged to come up with and develop an innovative, eco-friendly, bioactive, and cost-effective approach in a cleaner and more efficient way. According to this possibility, fish oil will transform the way that numerous diseases are treated within the next ten years. In order to better understand the applications and toxicological aspect of the potential benefits of fish oil, clinical trials on various models should be conducted. Adverse effects must be taken into account while giving omega-3 polyunsaturated fats. Future studies needed to focus on the development of side-effect-free, potent antioxidants from fish oil.

Conclusion

From the last decades, fish oil focuses much attention to the medical science; some physicians also suggest to intake fish oil because of its functional component. Fish is necessary to maintain both for our physical and mental health. The oil obtained from fish is emerging sources of omega-3 fatty acids like EPA and DHA, can protect against the adverse impact of chronic diseases. The dietary ratio of ω−3 and ω−6 fatty acids balance need to maintain against different health related issues. Several experimental studies showed that regular dietary intake of fish or fish oil can reduce possibility of numerous life threatening health problems. In the review, we also focus the marine fish which is available in different costal region of India and their health promoting effects. Generally, supplements of fish oil (capsules, pills, soft gels etc.) are safe for human consumption. This study has reviewed the current scenario of various non-communicable diseases, pathophysiology of these diseases and the mechanism of action through which fish oil can minimize severity of several diseases like obesity, diabetes mellitus, cardiovascular diseases, cancer, kidney disorders, neurological diseases, inflammatory bowel disorder, non-alcoholic fatty liver diseases, bone diseases and many more. Herein, we also reviewed the fish derived nutritional supplements can modulate gut microbiome, inducing colonization of beneficial bacteria. Fish oil also has immune boosting capacity, needs much in infancy and elderly stage. So, prospective research on fish oil and the exploration of its nutritional value may be aided by the findings of this review. We can conclude that more awareness should be require to the large segment of population about the dosage, duration, importance and adverse effects of fish oil for the betterment of society.

CRediT authorship contribution statement

Pipika Das: Conceptualization, Writing – original draft. **Ananya Dutta:** Formal analysis, Resources, Software. **Titli Panchali:** Formal analysis, Resources, Software. **Amina Khatun:** Conceptualization. **Riya Kar:** Conceptualization, Formal analysis, Software. **Tridip Kumar Das:** Conceptualization, Resources. **Manisha Phoujdar:** Conceptualization, Formal analysis. **Sudipta Chakrabarti:** Investigation, Project administration. **Kuntal Ghosh:** Investigation, Project administration. **Shrabani Pradhan:** Conceptualization, Funding acquisition, Investigation, Project administration, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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