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Pharmacological applications of fish components and products in oxidative stress-induced diseases

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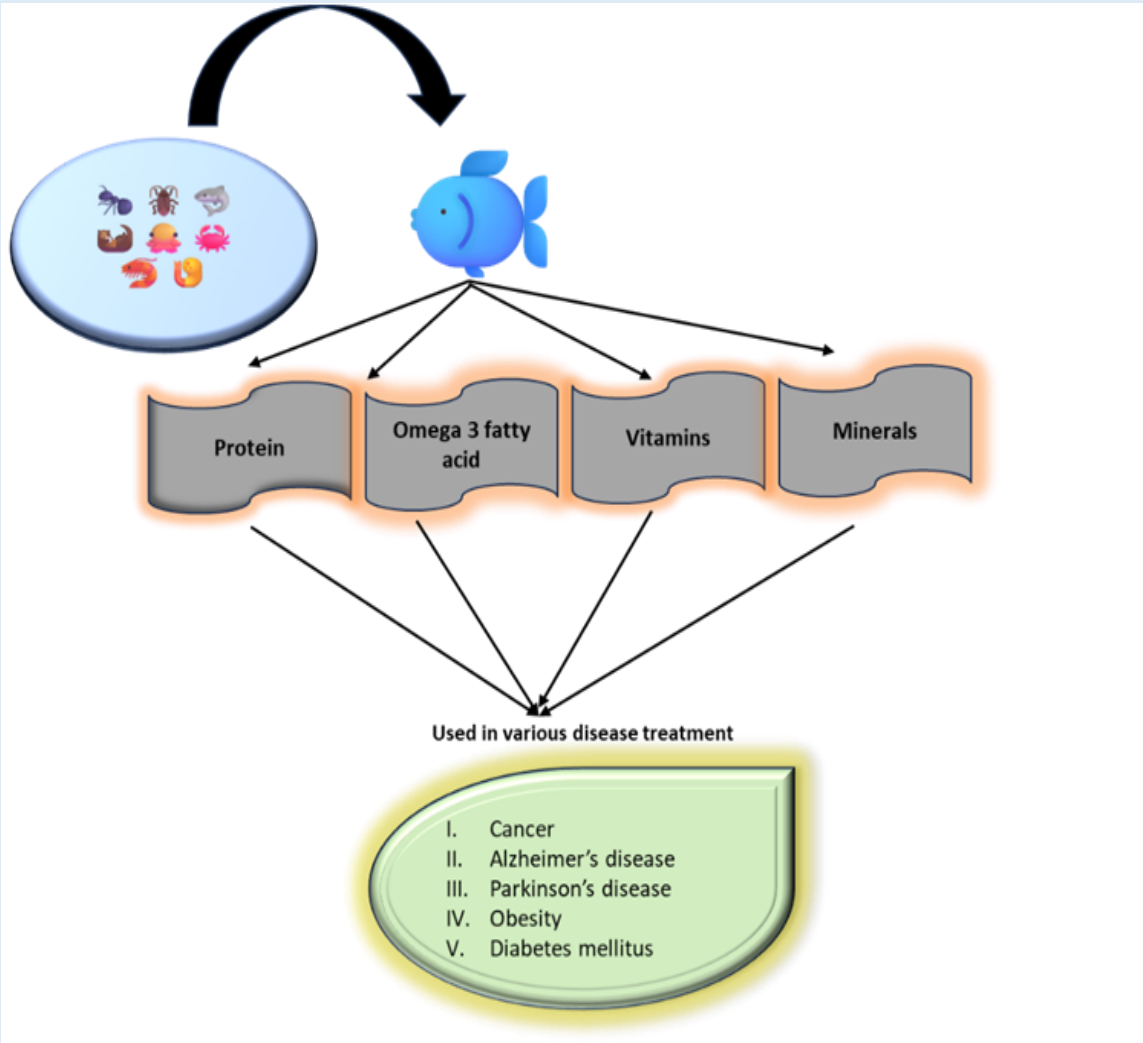
ABSTRACT

As populations expand day by day, global food requisition is also growing. Challenges to fulfill the demand for food will rise by the year 2050. Food acquired from land biomass has become expensive and challenging due to overpopulation, posing life-threatening situations to various animals and organisms due to the overuse of harmful chemical fertilizers and pesticides. Thus, food from marine ecosystems addresses a significant resource for food security. The objectives of the designed manuscript are to present updated and advanced research on functional food and nutraceuticals containing bioactive compounds obtained from fish and their pharmacological aspects. Fish exhibit various valuable bioactive compounds like essential omega-3 fatty acids, vitamins, minerals, and proteins, which offer numerous health benefits and are associated with mitigating various chronic disorders. The findings of this review paper indicate that fish farming may be a good source for functional food and therapeutic compounds for managing chronic diseases. Fish farming using advanced techniques is significantly cost-effective and environmentally friendly, producing more functional food ingredients and therapeutic compounds.

Keywords: Bioactive Compounds, Nutraceutical, Functional food, Cancer, Chronic diseases



Graphical Abstract: Pharmacological applications of fish components and products in oxidative stress-induced diseases

INTRODUCTION

As the world population increases, food and agricultural organizations of the United Nations indicate that the total population will cross 9.7 billion worldwide by 2050, leading to inadequate food resources. Due to food scarcity, billions of people worldwide are starving or malnourished. Various alternative methods have been researched to reduce food scarcity, such as extracting protein from algae, meat from fish, or insect-based substitutes. The findings show that fish are an abundant source of protein, essential oils, minerals, and vitamins, which have various therapeutic values in treating diseases. Currently, the demand for fish is increasing, and it has been reported that approximately 70% of fish are produced through aquaculture [1]. Fish muscles contain high macro and micronutrients, vitamins,

polyunsaturated fatty acids (PUFA) that include omega-6 PUFA, and omega-3 [2].

Presently, people have accepted the role of functional foods as nutraceuticals [3]. The sustained use of functional foods and their products has multiple positive impacts on improving health, disease prevention, treatment, and management of chronic diseases [4, 5]. Protein obtained from fish has a high nutritional value due to the presence of all amino acids. Various studies reported that more fish consumption has reduced the incidence of cardiovascular, cerebrovascular disorders, diabetes, obesity, and neuronal disorders [6]. The marine ecosystem has diverse microfloras that serve as a significant source of therapeutics. The Food and Agriculture Organization reported that approximately 167.2 million metric tons of seafood were consumed worldwide in 2014 [7]. Diverse varieties of fish, including tuna, salmon, mackerel, anchovies, and cod, were used as food. The most crucial objective of this designed paper is to address the present-day scenario behind the consumption of fish as nutraceuticals. In this review, we will explore fish farming as an alternative source of food and therapeutics instead of other available resources for bioactive compounds.

Pharmacological importance of bioactive constituents of fish: Fish are valuable sources of seafood and therapeutics. Epidemiological research has shown a direct correlation between a high dietary intake of fish and the bioactive compounds obtained from it, which minimize the risk of developing acute and chronic diseases. Detailed descriptions of different pharmacological properties are as follows:

Cancer: Cancer is one of the most life-threatening diseases and a significant cause of death worldwide [8]. Recent reports suggest that fish PUFA, like ALA, EPA, and DHA, are essential in removing cancerous cells through apoptosis. Several studies have reported that omega-6 PUFA promote apoptosis, a naturally programmed cell death. It encompasses two main routes: intrinsic and extrinsic routes to carry out the apoptosis (Figure 1). In the intrinsic route, it is induced by various factors like generating free radicals in mitochondria and cytokine depletion. These signals stimulate the mitochondria outer membrane permeabilization (MOMP), which allows the mitochondria to release proteins such as cytochrome c and SMAC [9]. These mitochondrial proteins stimulate Caspase-9 and Caspase-3, 6, 7 (Cleave Asp residues), responsible for cell death. These caspases lead to the deterioration of the enzyme Poly (ADP-ribose) polymerase (PARP), which induces DNA damage in cancerous cells [10]. However, the intrinsic route is linked to membrane cell death receptors, including TRAIL-R, FAS, and TNFR-1. FAS, TRAIL-R, and TNFR-1 bind to their corresponding ligands; they trigger adapter proteins like TRADD and FADD, which form the death-inducing signaling complex (DISC) (Figure 1). DISC triggers caspase-8, 9, inducing apoptosis in cancerous cells [10]. The fish's bioactive compounds, like PUFA (omega 3 and omega 6) and vitamins (A, D, and E), induce apoptosis in cancerous cells through different mechanisms explained in the next section.

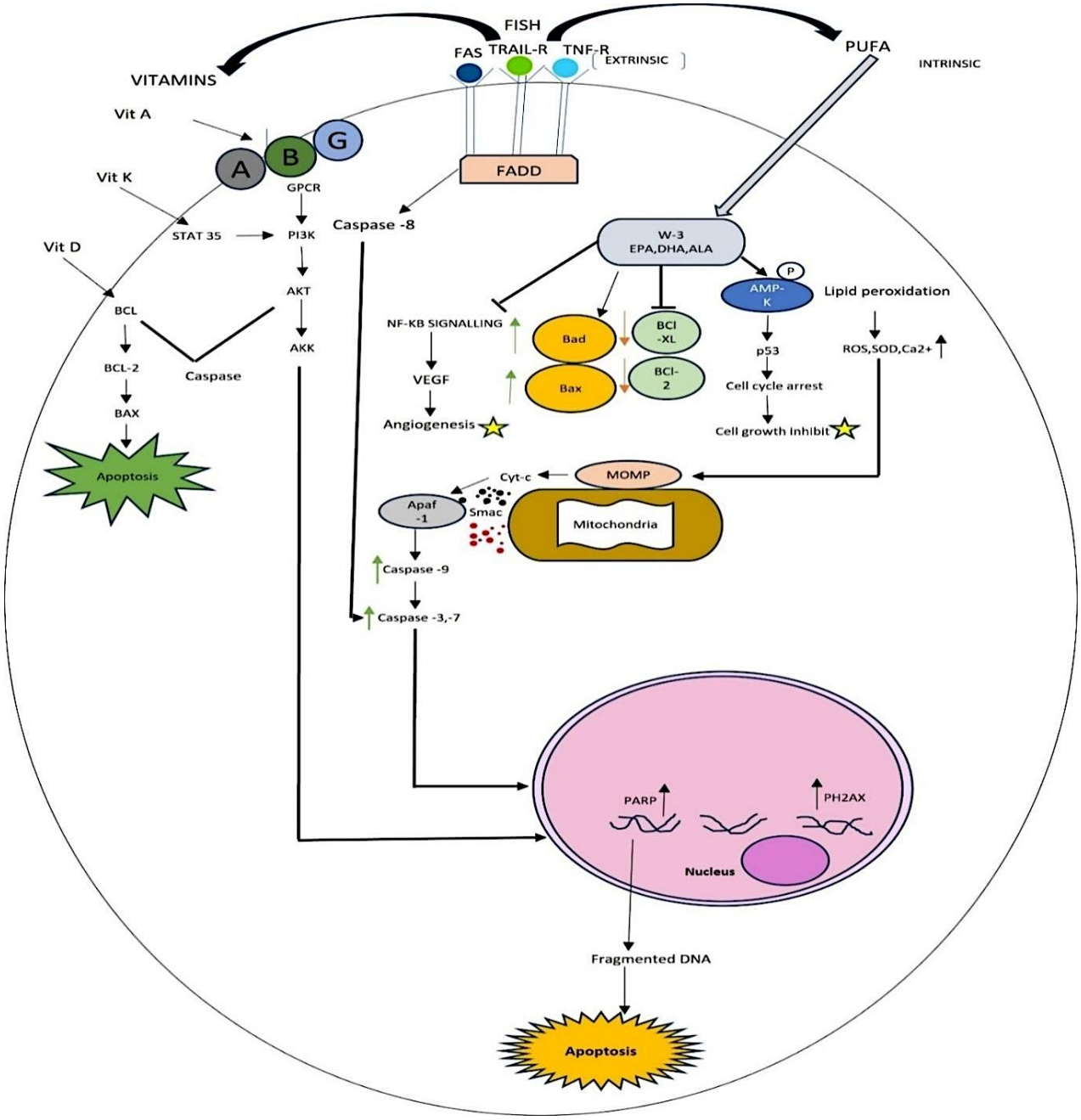


Figure 1. Molecular mechanism of PUFA and vitamins in cancer disease treatment. PUFAs inhibit cancer development by suppressing the expression of anti-apoptotic proteins and inducing the expression of apoptotic proteins by inhibiting angiogenesis. Vitamins A, D, and E induce apoptosis by activating different caspases.

Polyunsaturated fatty acids: Omega-3 PUFAs are exclusively present in fish oil. PUFA consists of an> 18-carbon chain with multiple double bonds. PUFAs are categorized into 2 sub-groups, such as ω−3 fatty acids (ALA, DHA, and EPA) and ω−6 fatty acids (GLA, LA, and AA). Sawada *et al.* [11] reported that omega-3 PUFA are crucial nutrients required for various physiological functions. Our body cannot adequately synthesize this fatty acid, so it must be obtained from the diet. Omega-3 fatty acids possess anticancer properties that can be utilized for various cancer therapies. Reports showed that a component of PUFA, DHA, causes cell growth inhibition

and stops proliferating at G1 or G2/M phase in breast cancer cells [12]. Reports suggested that PUFA, for example, EPA and DHA from fish oil, decrease angiogenesis and can suppress VEGF-stimulated endothelial cell proliferation. Ingestion of omega-3 PUFA may diminish the risk of skin cancer (melanoma), and it has been found that simultaneous consumption of EPA and DHA suppressed almost 80% of skin cancer. In a designed study, when researchers inserted the rodent skin cancer cells into the bloodstream along with EPA, EPA reduced metastasis and inhibited the growth of cancerous cells. The lipoxygenase pathway is necessary for cancer proliferation and is regulated by the EPA [13]. Tan *et al.* [14] have investigated how PUFA, isolated from algal oil, reduces lung cancer by stimulating autophagy. Autophagy is regulated by specific proteins, including JNK, MAPK, and mTOR, which reduce cytokine production and prevent the spread of cancer.

Vitamins: Fish like sardines, mackerel, herring, lake trout, and salmon are highly enriched in water-soluble and fat-soluble vitamins, influencing several metabolic pathways related to vision, bone mineralization, and immune function [15]. Several reports suggest that vitamins A, D, and E also show anticancer properties.

Vitamin A: Vitamin A can be obtained from fatty fish oil, leafy green vegetables, and eggs. It is also known that retinol and β-carotene can be precursors of Vitamin A. Vitamin A suppresses various kinds of cancer, including breast, lung, and colorectal cancer. Vitamin A inhibits the JAK-STAT pathway, which prevents lung cancer and induces apoptosis of cancerous cells (Figure 2) [16].

Vitamin D: Vitamin D can alter the progression and development of cancer by modifying multiple mechanisms in cancer cells, including inhibition of angiogenesis, differentiation, and various signaling pathways, which trigger cancer progression. Vitamin D can reduce cancer development by downregulating the β-catenin pathway, responsible for cancer cell proliferation and metastasis. Vitamin D implements its anticancerous activity by elevating the expression of E-cadherin and catenin (cell adhesion molecule), which causes cell-to-cell adhesion and protects against the spread of cancer and downregulates COX-2 expression. Irimie *et al.* [16] reported that vitamin D deficiency leads to inhibition of prostaglandin synthesis and cancer cell progression, such as colon cancer, breast cancer, ovarian cancer, and prostate cancer.

Vitamin E: It has been reported that vitamin E suppresses various signaling pathways that induce cancer progression, including 5-lipooxygenase-catalysed eicosanoids and COX. Jiang et al. [17] investigated that gamma tocotrienols initiate the mechanism of autophagy of tumor cells by inactivating two pathways, m-TOR and PI3 Kinase. Gamma tocotrienols induce apoptosis in mammary cancer cells through apoptosis facilitated by the endoplasmic reticulum.

Alzheimer's disease: Alzheimer's disease (AD) is a neurological problem that affects about 35 million individuals worldwide, with an estimated 115 million more expected to suffer by 2050 [18]. In this disease, patients suffer from memory loss and face problems associated with thinking and behavior. In PUFA, both EPA and DHA are responsible for minimizing inflammation. DHA manifests for the maintenance of normal brain

structure, whereas EPA displays or improves mental illness. Dominant genetic changes in APP genes, specifically presenilin 1 and 2, cause AD. A specialized protein, apo-lipoprotein E (Apo-E) gene, is also responsible for AD development. Apo-E acts as a lipid transporter in the brain and is also responsible for inhibiting the metabolism of β-amyloid protein. Neurofibrillary tangles (NFTs) and amyloid plaques in the gaps between brain nerve cells are indicators of Alzheimer's disease. NFTs consist of hyperphosphorylation of the tau protein, which is gathered between neurons, whereas amyloid plaques are clusters of amyloid beta proteins on the neuronal periphery. When tau proteins are phosphorylated, they obstruct the movement of mitochondria associated with microtubules, resulting in energy inadequacy in the neuron's communications and causing breakdown of neuronal events [19].

Mechanism of Alzheimer's disease prevention by PUFA:

APP is a transmembrane protein found in neuronal tissues. APP breakage leads to the formation of plaques composed of β-amyloid peptide (Aβ), which triggers neural cell apoptosis and inflammation. Breakage of amyloid precursor protein follows two distinct pathways: amyloidogenic and non-amyloidogenic. These two pathways are facilitated by secretases α, β, and γ. Amyloidogenic pathway is mediated by β and γ secretases, while the non-amyloidogenic pathway is mediated by α and γ secretases, which are responsible for the formation of plaques. DHA plays a crucial role in neurodegenerative disease, retains membranes' fluidity, and influences synaptic signal transmission. EPA is responsible for producing substances that help mitigate inflammation and assist cardiac fitness [20]. N-3 PUFA influences the GRP120 protein present on the membrane and nuclear activin protein (PPARY) that helps in the reduction of pro-inflammatory transcription factors like NF-KB, which is responsible for diminishing the expression of adhesion molecules, cytokines, and chemokines that cause inflammation.

Resolvins like E, D, and protectins like NPD 1 are found in omega-3 PUFA. Resolvin E and D are also called specialized pre-resolvin mediators (SPM). SPM is responsible for the suppression of NF-κB expression, resulting in the inhibition of pro-inflammatory molecules (TNF-α and IFN-γ). Specialized pre-resolvin complex enhances the mechanism of phagocytosis, which is associated with ingestion of apoptotic cells, and is responsible for ameliorating Alzheimer's disease [21]. NPD 1 (protecting) represses the IKK and NF-KB expression and inhibits the IKB signaling pathway (Figure 2).

Several studies reported that BV-2 microglial cells are found in the brain, which are crucial immune cells in the brain. When EPA and DHA are delivered to the BV-2 microglial cell, they suppress substances that trigger inflammation, such as COX-2, NO synthase, and NF-κB. Interestingly, it is noted that EPA and DHA minimize the expression of cell surface proteins CD_{14} and toll-like receptor 4, which induce inflammation. Devore *et al.* [22] stated that intake of multiple varieties of fish and omega-3 PUFA supplements reduces the risk of developing long-term dementia. Recent research has proved that intake of 1600 mg of EPA per day and 700 mg of DHA or 350 mg of DHA and 800 mg of EPA daily for 25 months decreases the concentration of macrophage inflammatory protein [23].

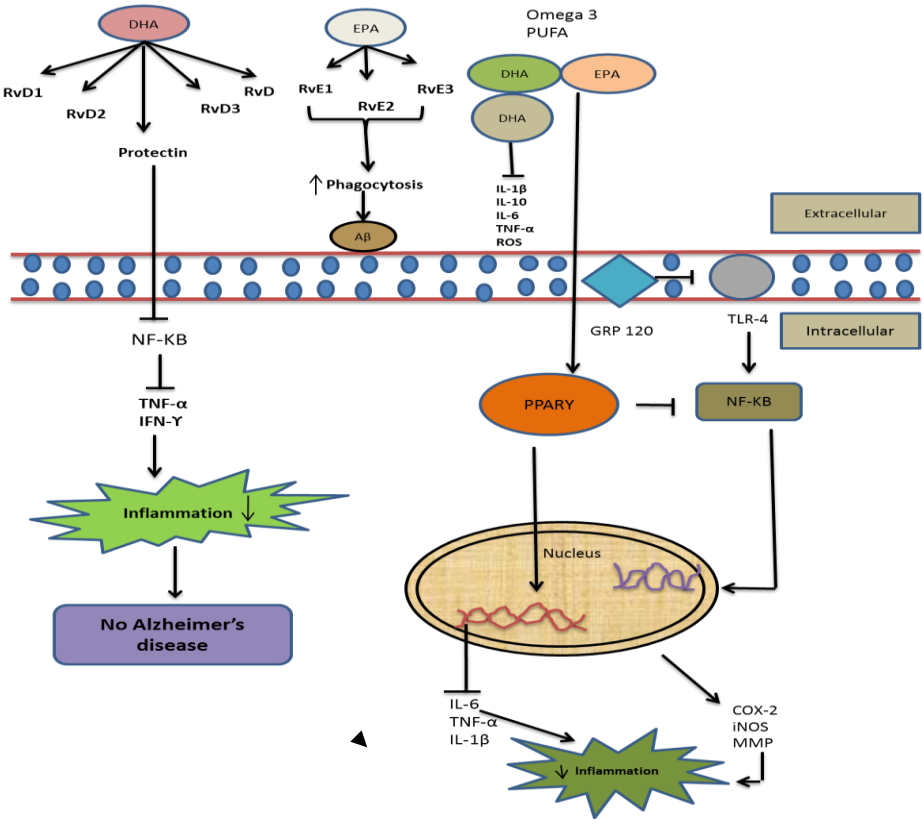


Figure 2. Molecular mechanism of PUFA in Alzheimer's disease treatment. PUFA prevents the onset of Alzheimer's disease by reducing inflammation and promoting clearance of amyloid-β protein.

Obesity: Obesity is a severe disorder in which body fat is exclusively deposited in the adipose tissue. It can lead to multiple health issues, such as diabetes, kidney disorder, non-alcoholic fatty liver disease, dyslipidemia, heart disease, and various other health issues. A study reported that omega-3 PUFA supplements play a beneficial role in preventing metabolic and cardiovascular diseases [24].

Molecular pathway by which EPA and DHA regulate adipose tissue function: N-3 PUFAs are essential nutrients that consist of EPA, DHA, ALA, and DPA and are mainly obtained from marine food, specifically fish. N-3 PUFA significantly reduces obesity, tumors, and cardiovascular disease. N-3 PUFA also exhibit anti-inflammatory and anti-arrhythmia effects. Omega-3 PUFA, especially DHA, inhibit the mTOR signaling pathway associated with obesity. However, DHA is also responsible for improving mitochondrial function. Another mechanism is that PUFA inhibits the lipopolysaccharides (LPS) associated with the LPS binding protein (LBP) on the cell surface. LBP promotes the LPS binding to CD14. CD14 is a soluble protein not present in the intracellular or transmembrane domain of the lipid bilayer; it cannot influence the signal transduction pathway because it is present on the extracellular cell surface. Lipopolysaccharides are associated with the TLR2/TLR4 complex; they trigger the release of the inflammatory molecule IL-6, which enables the synthesis of MYD88 and IRAK-4. The stimulation of NF-KB and TRAF phosphorylates IRAK-1. NF-$_k$B migrates into the nucleus and triggers IL-6 activation. Interestingly, it is noted that EPA and DHA also suppress the NF-$_k$B pathway by GPR120 receptor (G protein coupled receptors). DHA and EPA also reduce the IL-6 gene expression by regulating NF-$_k$B and IRAK-1 pathways (Figure 3). However, this fatty acid stimulates adenosine-monophosphate activated protein kinase (AMPK) and triggers mitochondrial growth, which is crucial for fat burning and providing energy. DHA and

EPA encourage the activation of anti-inflammatory molecules, i.e., adiponectin, which can help regulate metabolism and improve insulin sensitivity, fatty acid oxidation, and anti-atherogenic properties [25]. The experimental findings suggest that the administration of DHA (5mg/g/day) and HFD-EPA (2mg) in obese mice for eight weeks indicates a decrease in adipose tissue and inflammation [26]. In another finding, results showed that there is a decrease in body weight, inflammation, and steatosis when DHA (0.06mg/kg/day) and EPA (0.03mg/kg/day) were given to Mice (C57BL/6J) for 11 weeks [27].

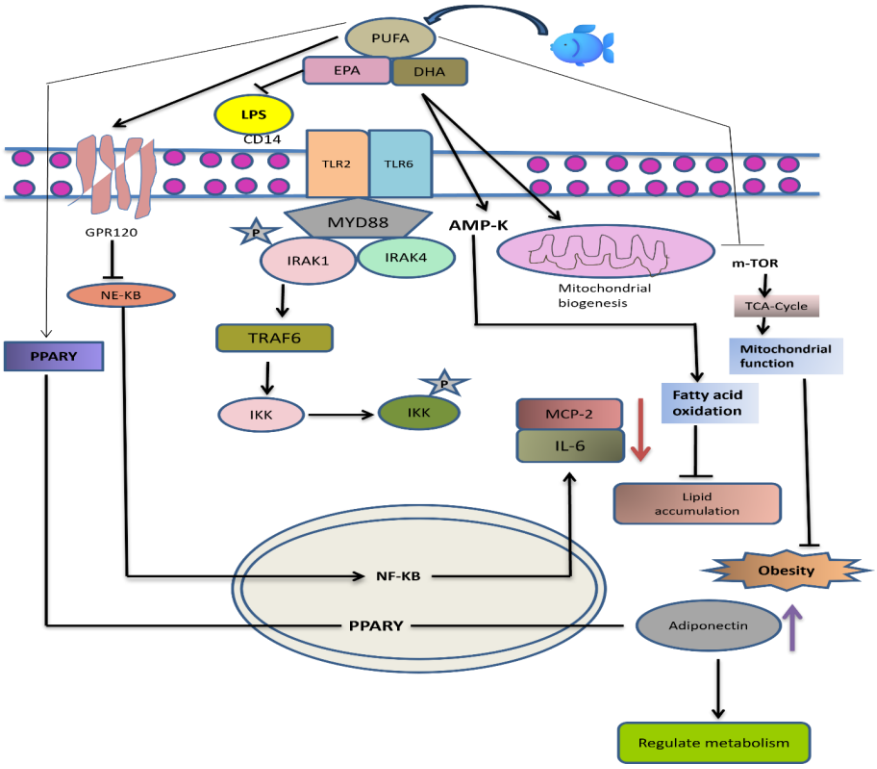


Figure 3. Molecular mechanism of PUFA in the reduction of obesity. PUFA (EPA and DHA) may improve body composition and obesity-related metabolic changes by modulating lipid metabolism; regulating adipokines like leptin and adiponectin; promoting adipogenesis, increasing fat oxidation, and energy expenditure.

Parkinson's disease: Parkinson's disease (PD) is the second most common neurological disorder after Alzheimer's disease. In the substantia nigra (SN), dopaminergic (DA) neurons are deficient in this disorder. In Parkinson's disease, brain cells responsible for dopamine secretion die off, leading to problems associated with movement and behavior. PD is concerned with protein deposition in the neuronal cell called α-synuclein. Hallmarks of PD involve mitochondrial dysfunction, nitric oxide production, ROS generation, inflammation, and misfolded protein aggregation [28]. Main symptoms of PD involve bradykinesia, tremors, depression, sarcopenia, tremors and memory loss. Exact treatment of PD is not understood, but it is observed that fish vitamins play an effective role in treating PD.

Molecular mechanism of fish vitamins against PD

Vitamin C: Vitamin C is pivotal in maintaining a healthy nervous system and is an antioxidant that suppresses lipid peroxidation and oxidative stress [29-30]. Molecular pathways of vitamin C act on PD. PD-associated neurotoxin resulting in aggregation of α-synuclein protein is known as Lewy bodies. These Lewy bodies influence the inflammatory reaction and provoke mitochondrial impairment. Vitamin C attaches to the SVCT-2 transporter

and penetrates inside the cells, preventing α-synuclein aggregation and suppressing inflammation caused by microglia and astrocytes. Interestingly, vitamin C triggers the signaling pathway, including NRF2/KEAP1 [31], suppressing ROS generation and inhibiting dopamine deterioration [32]. Nagayama *et al*. [33] reported that vitamin C increases the absorption of levodopa in PD patients.

Vitamin D: Molecular mechanisms showed that vitamin D can effectively prevent PD, as summarized in Figure 4. Vitamin D penetrates inside the cell and reduces ROS levels, which are associated with PD. Nitric oxide synthase and monoamine oxidase B enzymes, inhibited by vitamin D, are involved in ROS generation. Additionally, vitamin D stimulates the neurotrophic factor of glial and brain-derived neurotrophic factor. These factors prevent nerve cell damage and reduce dopamine deterioration, and vitamin D also suppresses an inflammatory response in neuronal cells [34].

Vitamin E: Figure 4 shows the molecular mechanism by which vitamin E can act on PD. Vitamin E binds to its receptor LRP on the neuronal cell surface and enters the cell. By suppressing GSK-3 signaling and activating estrogen receptor beta/phosphatidylinositol 3-phosphate/AKT (ER beta/PI3K/AKT) signaling, vitamin E can reduce neuroinflammation and, as a result, dopamine degradation [35].

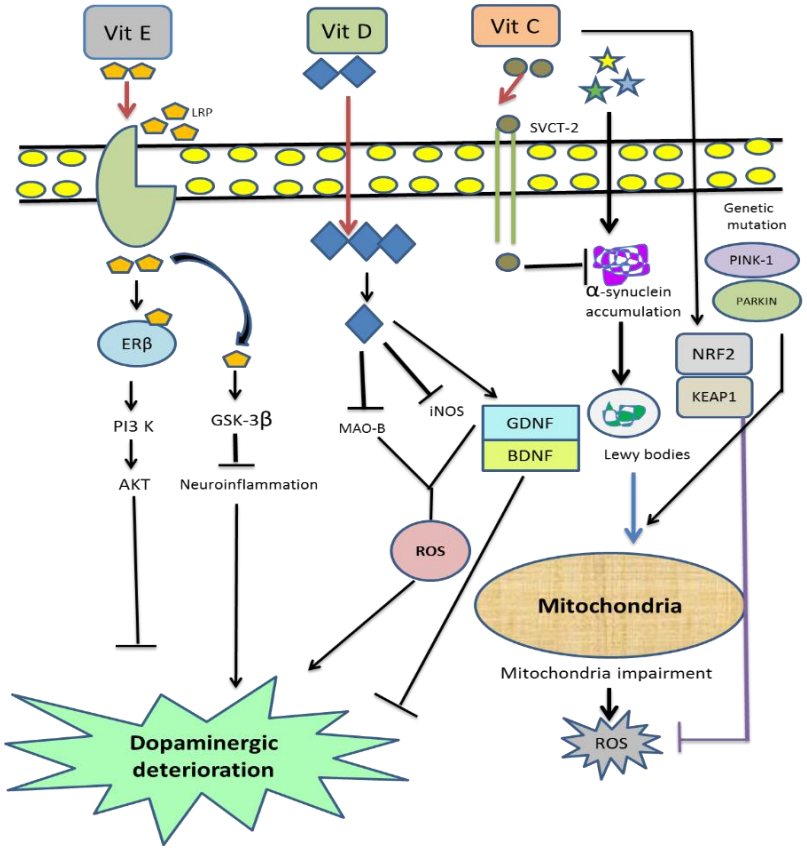


Figure 4. Molecular mechanism of fish vitamins used in Parkinson's disease treatment. Vitamin D inhibits the NO synthase and monoamine oxidase B enzymes involved in ROS generation and suppresses the inflammatory response in neuronal cells. Vitamin E inhibits the dopamine deterioration by ER beta/PI3K/AKT signaling, while vitamin C suppresses ROS generation by regulating the NRF2/KEAP1 pathway and dopamine deterioration.

Diabetes: Diabetes mellitus (DM) is a metabolic disease characterized by elevated glucose levels in the blood above the normal level, which is triggered by various environmental or genetic factors. DM is considered an

endocrine disorder. It occurs when the insulin hormone is deficient. Pathological shift of diabetes involves retinopathy (eye deformities), nephropathy (kidney deformities), and cardiovascular deformities held in the body. DM is categorized into 2 sub-groups, i.e., type 1 and type 2. Type 1 DM patients are treated with insulin replacement therapy, whereas type 2 DM patients are treated with a combination of diet, exercise, and oral medication (Metformin) to reduce blood glucose levels. If blood glucose levels do not return to normal with oral medication, insulin may be injected into the body.

Mechanism by which fish bioactive compounds exhibit anti-diabetic effect: To investigate the potential benefits of biologically active compounds derived from fish in diabetes treatment, investigations were conducted. It has been found that fish protein and peptides have a positive impact on diabetes. Multiple molecular pathways, such as secretion of glucagon-like peptide 1 (GLP-1), decreased activity of dipeptidyl peptidase 4 (DPP-4), antihyperglycemic medications, elevated levels of insulin secretion from pancreatic β-cell through potassium ATP channel, and regulation of GLUT-4 activity, are used to maintain blood glucose concentration. In an experimental study, Jin *et al.* [36] reported that when skin peptides bioactive compounds obtained from Tilapia fish species were administered in STZ-induced diabetes male rats, they showed improvement in mitochondrial dysfunction and activated the BNIP3/Nix signaling pathway that suppresses diabetic neuropathy. In another research finding, it was found that muscle protein hydrolysates isolated from *Capros aper* Boar fish minimize the blood glucose concentration, improve plasma insulin level, increase GLP-1 secretion in GLUTag cells, and suppress DPP-4 activity. Researchers have reported that environmental factors like sanitation and dietary intake are involved in the progression of type 1 diabetes. Omega-3 fatty acids from various sources such as fish, plant oil, and seafood are crucial in managing diabetes.

Cardiovascular disease: Cardiovascular disease (CVD) is regarded as complications that influence the typical structure and functions of blood vessels and the heart, which causes heart failure, hypertension, coronary artery blockage, and hypertension [37-38]. It is considered a major contributor to death all over the world. CVD is correlated with obesity, high blood pressure, and high cholesterol levels. It has been estimated that approximately 17.3 million deaths per year are due to CVD. Omega-3 PUFA plays a significant role in preventing CVD by modifying TLR-4 signaling, and it can mitigate the risk of inflammation, atherosclerosis, and diabetes mellitus Type2.

Role of n-3 PUFA on Atherosclerosis: Atherosclerosis is a disorder associated with cardiovascular disease. It is characterized by the aggregation of plaque inside the arterial walls that leads to a constricted arterial wall. The hardening of the arterial wall impedes blood flow, which causes serious health complications like stroke and heart attacks. Figure 5 shows the mechanism of n-3 PUFA (EPA+DHA), which suppresses the generation of cytokines or pro-inflammatory molecules mediated through two routes.

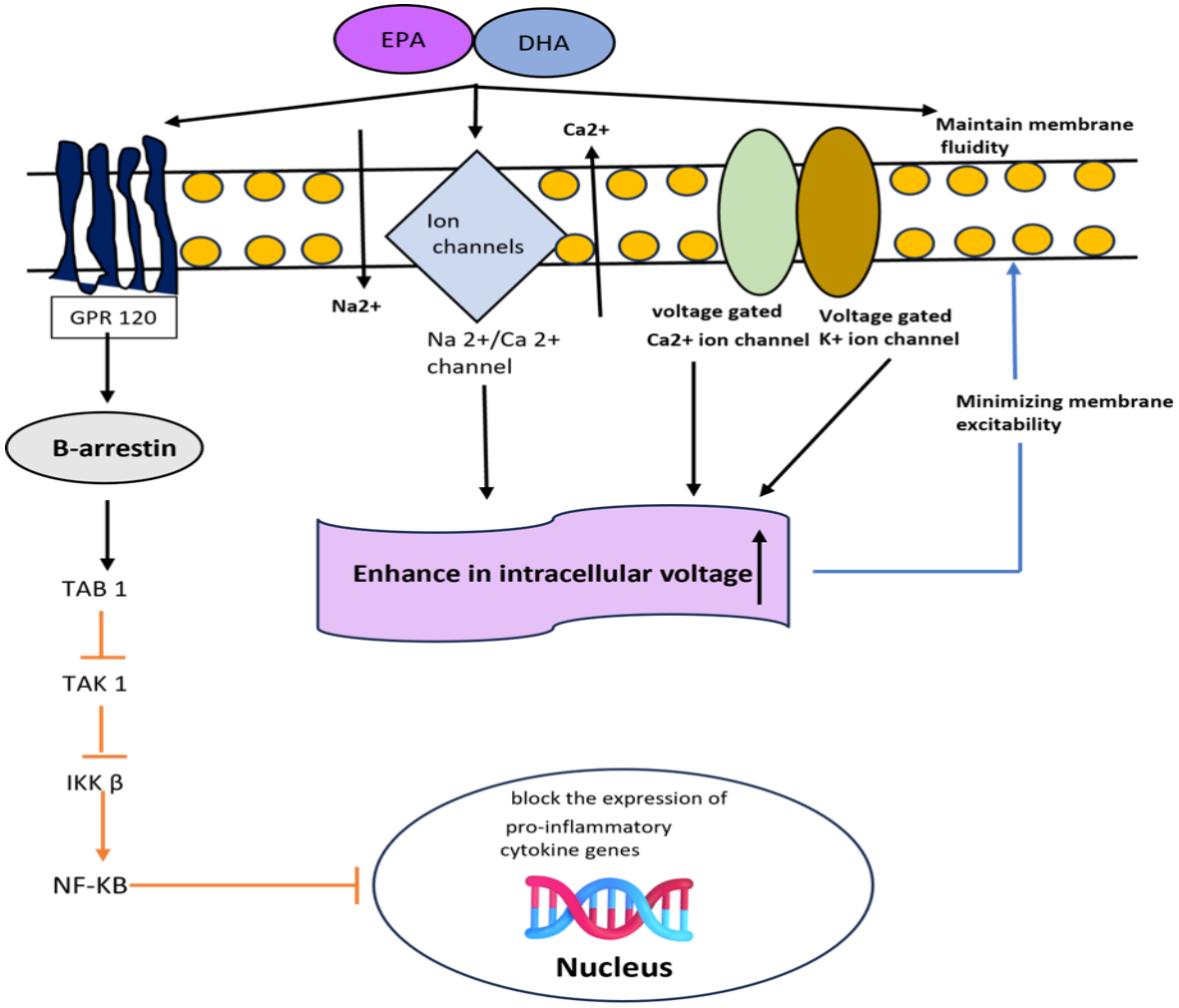


Figure 5. Molecular mechanism of fish PUFA in the treatment of cardiovascular diseases. Omega-3 PUFAs block the expression of pro-inflammatory cytokines genes by modifying NF-κB and PARα/γ, GPR120 signaling.

CONCLUSIONS

In conclusion, fish farming has been explored as one of the crucial food components available worldwide. Fish exhibit various valuable nutraceuticals and functional foods that offer numerous health benefits. Fish has several nutritional and pharmacological bioactive compounds like essential fatty acids, vitamins, minerals, and proteins, of which omega-3 fatty acids are widely used to treat various chronic disorders. These compounds offered anti-inflammatory, neuroprotective, and antioxidant properties. Moreover, recent research demonstrated that consumption of fish results in a reduction in the risk of various chronic disorders like cancer, neurodegenerative disease, obesity, and diabetes. In the coming years, fish farming may be a rapidly growing food security and therapeutic compounds sector.

List of abbreviation: AD: Alzheimer's disease, ALA: Alpha linoleic acid, AMPK: Adenosine monophosphate activated protein kinase, APP: Amyloid precursor protein, BCL-2: B Cell lymphoma 2, BCL-Xl: B cell lymphoma-extra-large, COX-2: Cyclooxygenase 2, CVD: Cardiovascular disease, Cyt c: Cytochrome c, DA: Dopaminergic, DHA: Docosahexanoic acid, DISC: Death inducing signaling

complex, DM: Diabetes mellitus, DPA: Docosapentaenoic acid, DPP-4: Dipeptidyl peptidase 4, EPA: Eicosapentaenoic acid, ER: Estrogen receptor, FADD: FAS associated death domain protein, Fas L: Fas ligand, GDNF: Glial derived neurotropic factor, GLP-1: Glucagon-like peptide 1, GSK: Glycogen synthase kinase, IFN-γ: Interferon gamma, iNOS: Inducible nitric oxide synthase, IRAK: Interleukin-1 receptor associated kinase, JNK: c-Jun N-terminal kinase, KEAP-1: Kelch like ECH associated protein, LBP: LPS binding protein, LPS: Lipopolysaccharides, MAO-B: Monoamine oxidase B, MAPK: p38 mitogen-activated protein kinase, MOMP: Mitochondria outer membrane permeabilization, MyD88: Myeloid differentiation factor 88, NF-κB: Nuclear factor kappa B, NFTs: Neurofibrillary tangles, NHEJ: Non-homologous end joining, NRF2: Nuclear factor erythroid-2 related factor 2, PARP: Poly (ADP-ribose) polymerase, PD: Parkinson's disease, pH2AX: Phospho histone H2AX, PI3: Phosphatidylinositol-3 kinase protein, PPARγ-1: Peroxisome proliferating activated receptor gamma-1, PPAY: Peroxisome proliferator activated receptor gamma, PUFA: Polyunsaturated fatty acids, ROS: Reactive oxygen species, RvD: D series resolving, RvE: R series resolving, Smac: Second mitochondria-derived activator of caspases, SN: Substantia nigra, SOD: Superoxide dismutase, SPM: Specialized pre-resolving mediators, TAB-1: Activity kinase 1 binding protein 1, TAK-1: TGF-β activated kinase 1, TGF-β: Transforming growth factor β, TNFR-1: TNF receptor superfamily member 1A, TNF-α: Tumor necrosis factor alpha, TRADD: TNF associated death domain protein, TRAF: TNF receptor associated factor, TRAIL-R: TNF- related apoptosis inducing ligand receptor.

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REFERENCES

1. Tidwell JH, Allan GL. Fish as food: aquaculture's contribution. Ecological and Economic Impacts and Contributions of Fish Farming and Capture Fisheries. EMBO Rep. 2001; 2(11):958-63. DOI: https://doi.org/10.1093/embo-reports/kve236.
2. Food and Agriculture Organization of the United Nations. The State of World Fisheries and Aquaculture 2016. Rome: Food and Agriculture Organization of the United Nations (2016).
3. Martirosyan D, von Brugger J, Bialow S. Functional Food Science: Differences and Similarities with Food Science. Funct Foods Health Dis. 2021a; 11(9):408-430. DOI: https://www.doi.org/10.31989/ffhd.v11i9.831.
4. Martirosyan D, Kanya H, Nadalet C. Can Functional Foods Reduce the Risk of Disease? Advancement of Functional Food Definition and Steps to Create Functional Food Products. Funct Foods Health Dis. 2021b; 11(5):213-221. DOI: https://www.doi.org/10.31989/ffhd.v11i5.788.
5. Soumya NP, Mini S, Sivan S, Mondal S. Bioactive compounds in Functional Foods and Their Role as Therapeutics. Bioact Compd. Health Dis. 2021; 4(3):24-39. DOI: https://www.doi.org/10.31989/bchd.v4i3.786.
6. Calder PC. n-3 Fatty Acids, Inflammation and Immunity: New Mechanisms to Explain Old Actions. Proc Nutr Soc. 2013; 72(3):326-336. DOI: https://www.doi.org/10.1017/S0029665113001031.
7. Venugopal V. Valorization of Seafood Processing Discards: Bioconversion and Bio-Refinery Approaches. Front Sustain Food Syst. 2021; (5):611835. DOI: https://doi.org/10.3389/fsufs.2021.611835.
8. Teibo JO, Ayinde KS, Olaoba OT, Adelusi TI, Teibo TKA, Bamikunle MV, Jimoh YA et al. Functional Foods' Bioactive Components and Their Chemoprevention Mechanism in Cervical, Breast, and Liver Cancers: A Systematic Review. Funct Foods Health Dis. 2021; 11(11):559-585. DOI: https://www.doi.org/10.31989/ffhd.v11i11.818.

9. Montecillo-Aguado M, Tirado-Rodriguez B, Huerta-Yepez S. The Involvement of Polyunsaturated Fatty Acids in Apoptosis Mechanisms and Their Implications in Cancer. Int J Mol Sci. 2003; 24(14):11691. DOI: https://www.doi.org/10.3390/ijms241411691.
10. Shalini S, Dorstyn L, Dawar S, Kumar S. Old, New and Emerging Functions of Caspases. Cell Death Differ. 2015; (22):526–539. DOI: https://www.doi.org/10.1038/cdd.2014.216.
11. Sawada Y, Saito-Sasaki N, Nakamura M. Omega 3 Fatty Acid and Skin Diseases. Front Immunol. 2021; 11:623052. DOI: https://www.doi.org/10.3389/fimmu.2020.623052.
12. Terme N, Chénais B, Fournière M, Bourgougnon N, Bedoux, G. Algal Derived Functional Lipids and Their Role in Promoting Health. In Recent Advances in Micro and Macroalgal Processing. Gaurav Rajauria; Yvonne V. Yuan. Recent Advances in Micro and Macroalgal Processing: Food and Health Perspectives, Wiley, 2021. DOI: https://www.doi.org/10.1002/9781119542650.ch13ff.
13. Reich R, Royce L, Martin GR. Eicosapentaenoic Acid Reduces the Invasive and Metastatic Activities of Malignant Tumor Cells. Biochem Biophys Res Commun. 1989; 160(2):559-64. DOI: https://www.doi.org/10.1016/0006-291x(89)92469-8.
14. Tan RH, Wang F, Fan CL, Zhang XH, Zhao JS, Zhang JJ, Yang Y, Xi Y, Zou ZQ, Bu SZ. Algal Oil Rich in N-3 Polyunsaturated Fatty Acids Suppresses B16F10 Melanoma Lung Metastasis by Autophagy Induction. Food Funct. 2018; 9(12):6179-6186. DOI: https://www.doi.org/10.1039/c8fo01617h.
15. Andrès E, Lorenzo-Villalba N, Terrade JE, Méndez-Bailon M. Fat-Soluble Vitamins A, D, E, and K: Review of the Literature and Points of Interest for the Clinician. J Clin Med. 2024; 13(13):3641. DOI: https://www.doi.org/10.3390/jcm13133641.
16. Irimie AI, Braicu C, Pasca S, Magdo L, Gulei D, Cojocneanu R, Ciocan C, Olariu A, Coza O, Berindan-Neagoe I. Role of Key Micronutrients from Nutrigenetic and Nutrigenomic Perspectives in Cancer Prevention. Medicina (Kaunas). 2019; 55(6):283. DOI: https://www.doi.org/10.3390/medicina55060283.
17. Jiang Q, Rao X, Kim CY, Freiser H, Zhang Q, Jiang Z, Li G. Gamma-tocotrienol Induces Apoptosis and Autophagy in Prostate Cancer Cells by Increasing Intracellular Dihydrosphingosine and Dihydroceramide. Int J Cancer. 2012; 130(3):685-93. DOI: https://www.doi.org/10.1002/ijc.26054.
18. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The Global Prevalence of Dementia: A Systematic Review and Metaanalysis. Alzheimers Dement. 2013; 9(1):63-75.e2. DOI: https://www.doi.org/10.1016/j.jalz.2012.11.007.
19. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. Lancet. 2006; 368(9533):387-403. DOI: https://www.doi.org/10.1016/S0140-6736(06)69113-7.
20. Shearer GC, Savinova OV, Harris WS. Fish Oil -How Does it Reduce Plasma Triglycerides? Biochim Biophys Acta. 2012; 1821(5):843-51. DOI: https://www.doi.org/10.1016/j.bbalip.2011.10.011.
21. Desale SE, Chinnathambi S. Role of Dietary Fatty Acids in Microglial Polarization in Alzheimer's Disease. J Neuroinflammation. 2020; 17(1):93. DOI: https://www.doi.org/10.1186/s12974-020-01742-3.
22. Devore EE, Grodstein F, van Rooij FJ, Hofman A, Rosner B, Stampfer MJ, Witteman JC, Breteler MM. Dietary Intake of Fish and Omega-3 Fatty Acids in Relation to Long-Term Dementia Risk. Am J Clin Nutr. 2009; 90(1):170-6. DOI: https://www.doi.org/10.3945/ajcn.2008.27037.
23. Lin PY, Cheng C, Satyanarayanan SK, Chiu LT, Chien YC, Chuu CP, Lan TH, Su KP. Omega-3 Fatty Acids and Blood-Based Biomarkers in Alzheimer's Disease and Mild Cognitive Impairment: A Randomized Placebo-Controlled Trial. Brain Behav Immun. 2022; 99:289-298. DOI: https://www.doi.org/10.1016/j.bbi.2021.10.014.
24. Bender N, Portmann M, Heg Z, Hofmann K, Zwahlen M, Egger M. Fish or n3-PUFA Intake and Body Composition: A Systematic Review and Meta-Analysis. Obes Rev. 2014; 15(8):657-65. DOI: https://www.doi.org/10.1111/obr.12189.
25. Kalupahana NS, Claycombe KJ, Moustaid-Moussa N. (n-3) Fatty Acids Alleviate Adipose Tissue Inflammation and Insulin Resistance: Mechanistic Insights. Adv Nutr. 2011; 2(4):304-16. DOI: https://www.doi.org/10.3945/an.111.000505.
26. Soni N, Ross AB, Scheers N, Nookaew I, Gabrielsson BG, Sandberg AS. The Omega-3 Fatty Acids EPA and DHA, as a Part of a Murine High-Fat Diet, Reduced Lipid Accumulation in Brown and White Adipose Tissues. Int J Mol Sci. 2019; 20(23):5895. DOI: https://www.doi.org/10.3390/ijms20235895.
27. Shang T, Liu L, Zhou J, Zhang M, Hu Q, Fang M, Wu Y, Yao P, Gong Z. Protective Effects of Various Ratios of DHA/EPA Supplementation on High-Fat Diet-Induced Liver Damage in Mice. Lipids Health Dis. 2017; 16(1):65. DOI: https://www.doi.org/10.1186/s12944-017-0461-2.
28. Renani PG, Taheri F, Rostami D, Farahani N, Abdolkarimi H, Abdollahi E, Taghizadeh E, Gheibi Hayat SM. Involvement of

Aberrant Regulation of Epigenetic Mechanisms in the Pathogenesis of Parkinson's Disease and Epigenetic-Based Therapies. J Cell Physiol. 2019; 234(11):19307-19319. DOI: https://www.doi.org/10.1002/jcp.28622

29. Singh P, Singh RL, Pathak N, Singh PK, Tripathi M, Mondal S. Phytochemistry and Nutraceutical Properties of *Carica papaya* (Linn.): A Review. Diet Supple Nutra. 2022; 1(9):1-15. DOI: https://www.doi.org/10.31989/dsn.v1i9.99
30. Singh U, Singh P, Singh PK,Shukla S, Singh RL. Evaluation of Antioxidant, Oxidative DNA Damage and Hepatoprotective Activities of Ethanolic Leaf Extract of *Lagenaria Siceraria* Plant Against Acetaminophen Induced Hepatotoxicity. Functional Foods in Health and Disease. 2023; 13(3):117-134. DOI: https://www.doi.org/10.31989/ffhd.v13i2.1072.
31. Zhang N, Zhao W, Hu ZJ, Ge SM, Huo Y, Liu LX, Gao BL. Protective Effects and Mechanisms of High-Dose Vitamin C on Sepsis-Associated Cognitive Impairment in Rats. Sci Rep. 2021; 11(1):14511. DOI: https://www.doi.org/10.1038/s41598-021-93861-x.
32. Wąsik A, Antkiewicz-Michaluk L. The Mechanism of Neuroprotective Action of Natural Compounds. Pharmacol Rep. 2017; 69(5):851-860. DOI: https://www.doi.org/10.1016/j.pharep.2017.03.018.
33. Nagayama H, Hamamoto M, Ueda M, Nito C, Yamaguchi H, Katayama Y. The Effect of Ascorbic Acid on the Pharmacokinetics of Levodopa in Elderly Patients with Parkinson Disease. Clin Neuropharmacol. 2004; 27(6):270-3. DOI: https://www.doi.org/10.1097/01.wnf.0000150865.21759.bc.
34. Bayo-Olugbami A, Nafiu AB, Amin A, Ogundele OM, Lee CC, Owoyele BV. Vitamin D Attenuated 6-OHDA-Induced Behavioural Deficits, Dopamine Dysmetabolism, Oxidative Stress, and Neuro-Inflammation in Mice. Nutr Neurosci. 2022; 25(4):823-834. DOI: https://www.doi.org/10.1080/1028415X.2020.1815331.
35. Zaulkffali AS, Md Razip NN, Syed Alwi SS, Abd Jalil A, Abd Mutalib MS, Gopalsamy B, Chang SK, Zainal Z, Ibrahim NN, Zakaria ZA, Khaza'ai H. Vitamins D and E Stimulate the PI3K-AKT Signalling Pathway in Insulin-Resistant SK-N-SH Neuronal Cells. Nutrients. 2019; 11(10):2525. DOI: https://www.doi.org/10.3390/nu11102525.
36. Jin L, Zheng D, Yang G, Li W, Yang H, Jiang Q, Chen Y, Zhang Y, Xie X. Tilapia Skin Peptides Ameliorate Diabetic Nephropathy in STZ-Induced Diabetic Rats and HG-Induced GMCs by Improving Mitochondrial Dysfunction. Mar Drugs. 2020; 18(7):363. DOI: https://www.doi.org/10.3390/md18070363
37. Martirosyan DM, Lampert T, Lee M. A Comprehensive Review on the Role of Food Bioactive Compounds in Functional Food Science. Functional Food Science. 2022; 3(2): 64-79. DOI: https://www.doi.org/10.31989/ffs.v2i3.906.
38. Williams K, Oo T, Martirosyan DM. Exploring the effectiveness of lactobacillus probiotics in weight management: A literature review. Functional Food Science. 2023; 3(5): 42-54. DOI: https://www.doi.org/10.31989/ffs.v3i5.1115.