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# Fish Oils

## DESCRIPTION

Fish oils, also known as marine oils, are lipids found in fish, particularly cold water fish, and other marine life such as phytoplankton. These oils are rich sources of long-chain polyunsaturated fatty acids (LCPUFA) of the n-3 (omega-3) type. The two most studied fish oils are the 20 carbon eicosapentaenoic acid (EPA; C20:5n-3) and the 22-carbon docosahexaenoic acid (DHA; C22:6n-3). EPA contains five double bonds and DHA, six double bonds. These double bonds are all in the cis configuration. DHA is a vital component of the phospholipids of human cellular membranes, especially those in the brain and retina.

Both EPA and DHA are found naturally in the form of triacylglycerols or TAGs. The docosahexaenate in the triacylglycerols of fish oil appears to be primarily in the sn-2 position (the middle carbon) of glycerol whereas there is more random distribution of eicosapantaenoate over all three positions of glycerol.

In September 2004, the Food and Drug Administration (FDA) announced the following qualified health claim for EPA and DHA omega-3 fatty acids: "Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. One serving of (name of food, typically an oily fish, such as salmon, tuna and herring) provides (x) grams of EPA and DHA fatty acids." In 2000, the FDA announced a similar qualified health claim for dietary supplements containing EPA and DHA omega-3 fatty acids and the reduced risk of coronary heart disease (CHD). The FDA recommended that consumers not exceed more than a total of 3 grams per day of EPA and DHA omega-3 fatty acids, with no more than 2 grams from a nutritional supplement.

## ACTIONS AND PHARMACOLOGY

### ACTIONS

Supplemental fish oils have triglyceride-lowering activity. They may also have anti-inflammatory, anti-thrombotic and immunomodulatory actions.

### MECHANISM OF ACTION

EPA and DHA have several actions in a number of body systems. EPA and DHA lower elevated triglyceride levels. In the cardiovascular system, EPA and DHA have anti-arrhythmic properties. EPA and DHA have anti-inflammatory

and immune-modulating properties and are beneficial for the musculoskeletal, gastrointestinal and immune systems. EPA and DHA are also important for maintenance of normal blood flow as they lower fibrinogen levels and prevent platelets from sticking to each other. DHA is vital for normal brain development for the fetus and infant and for the maintenance of normal brain function throughout life. DHA appears to be a major determinant of membrane fluidity in brain cells, and this could play a major role in the maintenance of normal cognition and mood.

The triglyceride-lowering effect of EPA and DHA appears to result from the combined effects of inhibition of lipogenesis and stimulation of fatty acid oxidation in liver. EPA and DHA inhibit the transcription of genes coding for lipogenesis enzymes and increase the transcription of the regulatory enzymes of fatty acid oxidation. Stimulation of fatty acid oxidation is through activation of PPAR (peroxisome proliferator-activated receptor)- alpha. Inhibition of lipogenesis is through down-regulation of SREBP (sterol regulatory element binding protein) -1c messenger RNA.

Several mechanisms are believed to account for the anti-inflammatory activity of EPA and DHA. The two competitively inhibit the conversion of arachidonic acid to the pro-inflammatory eicosanoids PG (prostaglandin)$E_2$ and LT(leukotiene)$B_4$, thus reducing their synthesis. EPA and DHA also inhibit the synthesis of the inflammatory cytokines TNF (tumor necrosis factor)-alpha and IL(interleukin)-1 beta in both healthy volunteers and rheumatoid arthritis patients. EPA and DHA inhibit the 5-LOX (lipoxygenase) pathway responsible for the conversion of arachidonic acid to inflammatory leukotrienes in neutrophils and monocytes and can suppress phospholipase C-mediated signal transduction, also involved in inflammatory events. EPA and DHA may possess disease-modifying activity. Incorporation of EPA and DHA into articular cartilage chondrocyte membranes results in a dose-dependent reduction in the expression and activity of the proteoglycan-degrading enzymes known as aggrecanases. This similarly results in decreased expression of interleukin IL-1 alpha and TNF-alpha as well as COX (cyclooxygenase) -2, but not COX-1.

EPA and DHA have both similar and dissimilar physiologic roles. EPA appears to be more important in those roles where the eicosanoids are involved, whereas DHA seems to play its most important roles in the membranes of CNS cells and in the PPAR system. EPA is the precursor to series-3 prostaglandins (PG), the series-5 leukotrienes (LT) and the series-3 thromboxanes (TX). Specifically, EPA is the precursor of $TXA_3$ and $LTB_5$, eicosanoids, which reduce platelet aggregation and increase vasodilation. This could account in part for those fish oil effects that may lead to reduced clotting activity and decreased blood pressure.

Fish oils appear to have mood-stabilizing properties when used in the treatment of bipolar disorder. Overactive cell-signaling pathways may be involved in the pathophysiology of bipolar disorder. EPA and DHA may dampen signal transduction associated with phosphatidylinositol and arachidonic acid. These LCPUFAs, especially DHA, are incorporated into the phospholipids of the membranes of cells involved in cell-signaling pathways.

The mechanism by which fish oils appear to prevent cardiac arrhythmia is unclear but also may have something to do with the incorporation of these LCPUFAs into the cell membranes of the heart.

Fish oils may have cancer chemopreventive effects, but clinical chemoprevention studies are needed to determine if this is the case. *In vitro* and animal studies have shown EPA and DHA to suppress neoplastic transformation, inhibit cancer growth, enhance apoptosis or programmed cell death and to have anti-angiogenic activity. A common mechanism underlying all of the above activity could be the role of the LCPUFAs in modulating eicosanoid production and activity. Fats other than from fish sources are known risk factors for cancer as well as cardiovascular disease. Those fats may direct the eicosanoid pathways toward situations in which cancer cells can flourish, whereas the opposite may be the case for the fish oils.

### PHARMACOKINETICS

Different forms of fish oil are commercially available. The natural forms of EPA and DHA, as found in fish and phytoplankton, exist in the form of triacylglycerols (TAGs). These are the forms most commonly available at present. More concentrated forms of EPA and DHA are the EPA and DHA ethyl esters and free (i.e. unesterified) EPA and DHA. The pharmacokinetics of these forms is similar.

EPA- and DHA-laden triacylglycerols, following ingestion, undergo hydrolysis via lipases to form monoglycerides and free fatty acids. In the enterocytes, reacylation takes place reforming TAGs, which are then assembled with phospholipids, cholesterol and apoproteins into chylomicrons. The chylomicrons are released into the lymphatics from whence they are transported to the systemic circulation. In the circulation, the chylomicrons are degraded by lipoprotein lipase, and EPA and DHA are transported by the circulation to various tissues of the body where they are used mainly for the synthesis of phospholipids. These phospholipids are incorporated into the cell membranes of red blood cells, platelets and CNS cells, among others. EPA and DHA are mainly found in the phospholipid components of the cell membranes. DHA is taken up by the brain in preference to other fatty acids. DHA can partially retroconvert to EPA, and EPA may partially convert to DHA.

Enteral absorption of EPA and DHA is at least as good from semi-synthetic ethyl esters as it is from the natural forms.

**INDICATIONS AND USAGE**

Fish oils may primarily be indicated to lower triglyceride levels in those with hypertriglyceridemia. Another important indication may be to prevent death in those who have suffered myocardial infarctions. Fish oils are used to decrease clotting tendencies of the blood. They may also be indicated for lowering blood pressure, for preventing restenosis following coronary angioplasty, for alleviating some of the symptoms of rheumatoid arthritis and for ulcerative colitis. The claim that they can help prevent relapse in Crohn's disease is questioned by recent research. They may help stabilize mood in bipolar disorder and may have beneficial effects in IgA nephropathy. There is evidence they may help prevent rejection in renal transplant patients, and they are used in enteral feeding of various patient categories.

There is some evidence that fish oils have neuroprotective properties and may be useful in very mild, early stages of Alzheimer's disease. They may also be beneficial for eye health.

There is very little evidence in support of an indication for use in angina and no convincing evidence to support claimed indications for asthma, hay fever and psoriasis. There is insufficient data to make any judgment about possible use of fish oil in cancer.

**RESEARCH SUMMARY**

A meta-analysis of several studies to determine the effect of fish oil supplementation on serum triglyceride levels consistently shows a significant triglyceride-lowering effect. Doses of fish oil in the studies ranged from 0.5 grams to 25 grams daily with an average intake of about 6 grams daily. These numbers refer to the amount of EPA and DHA received. The average ratio of EPA to DHA in these studies was about 1.5, and the studies lasted from two weeks to two years. The triglyceride-lowering effect was dose-related. Overall, cholesterol levels did not change. Some of the studies reported an increase in LDL cholesterol and some showed an increase in HDL cholesterol.

A double-blind, placebo-controlled study was performed to determine the triglyceride-lowering effect of EPA and DHA by themselves. In this seven-week study, 234 healthy men were randomly given the following: EPA, in the ethyl ester at a dose of 3.8 grams daily, the ethyl ester of DHA at 3.6 grams daily or corn oil at 4 grams daily. Triglycerides decreased by 21% in the EPA group and by 26% in the DHA group when compared to placebo. Some retroconversion from DHA to EPA was noted, but no significant conversion of EPA to DHA was observed. A slight, but significant, increase in HDL-cholesterol was seen in the DHA group, and a slight, but significant, decrease of total cholesterol and apolipoprotein A1 was noted in the EPA group.

Another study looked at the effect on serum lipids of fish oil supplements by themselves and in combination with fish oils and garlic powder. Fifty men with moderately elevated cholesterol were assigned to one of four treatment groups and followed for 12 weeks. The fish oil used in this study was a natural triacylglycerol, and those receiving fish oil took 12 grams containing 30% of a mixture of EPA and DHA in a 1.5 ratio for a total of 2.16 grams of EPA and 1.44 grams of DHA daily. One group received fish oil and garlic powder, another group received fish oil and a placebo powder, a third group received powder and a placebo oil, and the remaining group was given a placebo oil and a placebo powder.

The fish oil group registered a 3.73% lowering of serum triglycerides, no significant change in total cholesterol and an 8.5% increase in LDL-cholesterol. No significant changes were noted in this group in the ratios of total cholesterol over HDL-cholesterol and LDL-cholesterol over HDL-cholesterol. The fish oil and garlic powder group were found to have a 34.3% lowering of triglycerides, a 12% lowering of total cholesterol, a 9.5% decrease in LDL cholesterol, a 16% decrease in the total cholesterol over HDL-cholesterol ratio and a 19% decrease in the LDL-cholesterol over HDL-cholesterol ratio. The garlic group showed no change in the serum triglyceride value, and 11.5% decrease in total cholesterol, a 14% decrease in LDL cholesterol, a 12.5% decrease in the total cholesterol to HDL-cholesterol ratio and a 15% decrease in the LDL-cholesterol ratio. No change in HDL-cholesterol was observed in the fish oil group. A slight non-significant increase in HDL-cholesterol was noted in the garlic group.

The GISSI-Prevenzione study examined the effect of dietary fish oil and vitamin E supplementation on mortality and morbidity in over 11,000 subjects who had suffered a myocardial infarction within three months of entering the trial. The subjects (85% men, 51% younger than 60) were randomly assigned to one of four groups. One group, consisting of 2,836 subjects, received 1 gram of fish oil daily containing 850 to 882 milligrams of EPA and DHA in the form of the ethyl esters and in a ratio of EPA to DHA of 1 to 2. A second group, consisting of 2,830 subjects, received 300 milligrams of vitamin E in the form of synthetic D alpha-tocopherol. A third group of 2,830 subjects received both the fish oils and vitamin E, while the fourth group of 2,828 acted as the control. The trial lasted for 42 months.

The primary combined endpoint was death, non-fatal myocardial infarction and stroke. Treatment with fish oil, but not vitamin E, significantly lowered the risk of the primary

endpoint. The effect of the combined treatment was similar to that of fish oil alone. Although vitamin E did show a trend toward a reduction in mortality, the trend did not show significance. No adverse effects were reported except for some mild gastrointestinal symptoms. The dose of fish oil used in the trial lowered serum triglycerides by 3.4%.

The most significant result of this trial was the reduction in risk for overall and sudden cardiac death. It is believed that the reduction of sudden cardiac death was due to the anti-arrhythmic effect of the LCPUFAs. The study suggests that up to 20 lives per 1,000 post-MI patients could be saved by consuming daily doses of less than 1 gram of EPA and DHA.

Meta-analysis of 17 controlled studies with fish oil indicates that supplementation with 3 or more grams of fish oil daily can lead to clinically relevant systolic and diastolic blood pressure reductions in individuals with untreated hypertension but not in normotensives. The EPA plus DHA doses used in these trials ranged from 1 to 15 grams with an EPA to DHA ratio of about 1.5.

A meta-analysis of the effect of fish oils following coronary angioplasty indicated that subjects who had undergone successful angioplasty had a significantly lower rate (13.9%) of restenosis when given 4 to 5 grams daily of mixtures of EPA and DHA for three months to one year following the angioplasty.

In contrast to these positive findings, one meta-analysis conducted a few years ago failed to find a clear effect of long-chain and shorter-chain omega-3 fats on total mortality, combined cardiovascular events or cancer. These researchers went so far as to say that "clinically important harm could not be excluded" based on their analysis of the data reviewed. More recently, however, the GISSI group, using new data, found that the omega-3 fatty acids "can provide a small beneficial advantage in terms of mortality and admission to hospital for cardiovascular reasons in patients with heart failure in a context of usual care." An editorial accompanying this study's publication concluded that "supplementation with n-3 polyunsaturated fatty acids should join the short list of evidence-based life-prolonging therapies for heart failure."

Another recent review cited three large controlled, randomized trials involving 32,000 participants in which supplementation with DHA and EPA resulted in significant reductions in cardiovascular events. These findings, they concluded, show that intake of fish oils should be increased, especially among those at risk of cardiovascular disease. They recommended consuming both DHA and EPA in a combined dose of about 500 mg for those without disease and 1,000 mg in those with known coronary artery disease. They further recommended that those with hypertriglyceridemia take 3 to 4 grams of DHA/EPA daily, a dosage that they say can reduce triglyceride levels by 25 to 50%. They further suggested that blood levels of DHA and EPA could one day be used to identify patients with insufficient levels and to individualize treatment protocols.

And yet another recent review of the data related to omega-3 fatty acids and their use in coronary heart disease concluded that the relevant studies demonstrate a definite benefit. The American Heart Association currently recommends about 1 gram of fish oils per day for those with known coronary artery disease. And people with no known heart disease, it suggests, should eat oily fish at least twice a week. Because of possible mercury and other contaminants in some fish and fish oils, the FDA has cautioned pregnant women to avoid any probable contaminated source. Daily ingestion of at least 3 grams of EPA and DHA mixtures for a period of 12 weeks or longer has been found to reduce the number of tender joints and amount of morning stiffness in subjects with rheumatoid arthritis. Those with rheumatoid arthritis consuming these supplements have been reported to lower or discontinue use of nonsteroidal anti-inflammatory drugs or disease-modifying anti-rheumatic drugs. The supplements appeared to be well tolerated in these individuals, and no serious toxicity was reported.

A one-year double-blind trial of subjects with Crohn's disease randomized these subjects into two groups. One group received a mixture of 2.7 grams of EPA and DHA daily. The fish oil was in the form of enterically coated free fatty acids and provided 1.8 grams of EPA and 0.9 grams of DHA daily. It was noted that the subjects taking the fish oil supplement had a significantly reduced relapse rate. No significant adverse effects were reported. More recently, however, two randomized, placebo-controlled studies conducted at 98 centers in Canada, Europe, the U.S. and Israel found that the omega-3 fatty acids are not effective for the prevention of relapse in Crohn's disease. Rate of relapse was similar in both fatty acid and placebo groups at one year.

Supplementation of fish oils in subjects with ulcerative colitis has shown some encouraging trends. In one study, six patients with active ulcerative colitis were given 3 to 4 grams of a mixture of EPA and DHA daily in the form of natural triacylglycerols for a period of 12 weeks. Significant results were reported regarding the subjects' symptoms and histological appearance of the rectal mucosa by the end of the 12 weeks.

A few open studies with few subjects have suggested that fish oil supplements positively affect the clinical course of psoriasis. The best study to date, a double-blind, placebo-controlled, multi-center trial of 155 subjects with moderate-to-severe psoriasis showed no clinically important difference

between subjects receiving 5 grams daily of EPA and DHA in ethyl ester form and the placebo group over a four-month period.

A four-month, double-blind, placebo-controlled study of 30 subjects with bipolar disorder compared the effects of fish oil supplements with placebo. Fourteen subjects received 9.6 grams daily of fish oil consisting of 6.2 grams of EPA and 3.4 grams of DHA, and 16 subjects received olive oil as a placebo. This study showed improvement in the short-term course of the disorder with fish oil supplementation. Among those taking fish oils, longer periods of remission were observed in nearly every outcome category, and the results were statistically significant. Mild gastrointestinal side effects were reported in the fish oil group.

The author of a recent review article concluded that omega-3 shows positive results as an adjunctive treatment for depressive—but not manic—symptoms in bipolar disorder. The author cautioned that the data are few and called for larger, well-designed studies to further investigate. With respect to other depressive disorders, there is some evidence that fish oils may be of some benefit, although a recent review concluded that no meaningful determinations can be made at this time based on available research results. More study is clearly warranted.

There is evidence that fish oils have some neuroprotective properties that could be significant. EPA has shown some efficacy in ameliorating such neurodegenerative disorders as Huntington's disease, multiple sclerosis and others. (See EPA.) The fish oils also show some evidence of being able to impede very mild, early manifestations of Alzheimer's disease. Again, more research is needed and warranted.

Increased consumption of EPA and DHA may reduce the risk of age-related macular degeneration by about 70% according to some recent research.

Immunoglobulin (Ig) A nephropathy is the most common glomerular disease worldwide. Beneficial effects with fish oil supplements have been reported in two studies, while two other studies showed no beneficial effects. In the largest and longest study to date, daily supplementation with fish oil showed protection against progressive renal disease. This blinded, placebo-controlled trial included 51 subjects who received a daily mixture of EPA and DHA at 1.87 grams and 1.36 grams, respectively. The study lasted two years, and the placebo group used olive oil as the control. It was concluded that fish oil retarded the rate of renal function loss.

There is some epidemiological and animal data suggesting that fish oils may have some anticancer effects. There are no data, however, to directly establish any efficacy for fish oil supplements in any cancer.

## CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

### CONTRAINDICATIONS

Known hypersensitivity to a fish oil-containing product.

### PRECAUTIONS

Fish oil supplements should be used by children, pregnant women and nursing mothers only if recommended and monitored by a physician. Because of the possible anti-thrombotic effect of fish oil supplements, hemophiliacs and those taking warfarin (Coumadin) should exercise caution in their use. Fish oil supplements should be stopped before any surgical procedure. Conflicting results have been reported regarding the effects of fish oil supplements on glycemic control in those with glucose intolerance including type 2 diabetics. Some early studies indicated that fish oil supplements might have detrimental effects in those groups. Recently, better designed studies have not reported these adverse effects. There is no evidence that fish oil supplements have detrimental effects on glucose tolerance, insulin secretion or insulin resistance in non-diabetic subjects. Diabetics should discuss the use of these supplements with their physicians and note if the supplements affect their glycemic control. Diabetics who take fish oil supplements should be monitored by their physicians.

### ADVERSE REACTIONS

There have been no reports of serious adverse events in those taking fish oil supplements, even up to 15 grams daily for prolonged periods of time. Those side effects that have been reported include mild gastrointestinal upsets such as dyspepsia, nausea and diarrhea, halitosis, eructation and "fishy" smelling breath, skin and even urine. The blood-thinning effects can cause occasional nosebleeds and easy bruising. Diabetics may experience worsening of glycemic control.

## INTERACTIONS

Interactions may occur between fish oil supplements and aspirin and other non-steroidal anti-inflammatory drugs and herbs such as garlic (*Allium sativum*) and ginkgo (*Ginkgo biloba*). Such interactions might be manifested by increased susceptibility to bruising, nosebleeds, hemoptysis, hematemesis, hematuria and blood in the stool. Most who take fish oil supplements and the above drugs or herbs do not suffer from these problems, and, if they occur, they are rare. If they do occur, the dose should be lowered or discontinued.

## OVERDOSAGE

Not reported.

## DOSAGE AND ADMINISTRATION

There are several forms of fish oil supplements. The most common form is natural fish oil, usually produced from the body of cold-water fish. These fish oils are, typically, 30% EPA and DHA with a ratio of EPA to DHA of 1.5. A typical 1 gram softgel capsule of fish oil contains 180 milligrams of

EPA and 120 milligrams of DHA. Natural EPA and DHA are chemically triacylglycerols. Natural fish oil capsules containing 50% EPA and DHA in a 1.5 ratio are now available. Some natural fish oil supplements contain EPA and DHA in a higher ratio, i.e. higher EPA. There are also fish oil supplements with a lower ratio, i.e. higher DHA.

A more concentrated form of fish oil is the semi-synthetic ethyl ester product containing 85% EPA/DHA. One such product contains 490 milligrams of EPA ethyl ester and 350 milligrams of DHA ethyl ester per 1 gram capsule.

Enteric coated EPA and DHA as the free fatty acids are also available. These capsules are more concentrated in EPA and DHA. Emulsions of fish oils are now available that can be used as constituents for salad dressings and other foods. Functional foods, including bars containing fish oil, are becoming available. Infant formulas containing DHA are available in Europe and Japan. Certain enteral supplements contain EPA and DHA as well as other immune-modulating nutrients such as L-arginine, L-glutamine and RNA.

Recommended fish oil products must contain antioxidants such as tocopherol to protect against their oxidation. Further, fish oil products that contain high quantities of vitamin A and D, which could be toxic, should not be used.

The usual oral dose of fish oil for use in hypertriglyceridemia is about 5 grams of combined EPA/DHA daily. The values expressed in this section refer to the amounts of EPA plus DHA. The actual weight of the capsule is typically much higher. Labels should be checked in order to determine the actual EPA/DHA content. The daily intake should be taken in divided doses; the supplements are best tolerated with meals. The usual dose for hypertensives who have not previously been treated is about 3 grams of EPA/DHA daily. About 3 grams daily is also the usual dose for those with rheumatoid arthritis, Crohn's disease and ulcerative colitis. Those who have had successful angioplasty and are trying to prevent restenosis might use 4 to 5 grams daily. Based on the GISSI-Prevenzione trial, a dose of 1 gram daily of EPA and DHA might have protective value for those who have had an MI.

In 2005, the FDA approved a highly concentrated omega-3 polyunsaturated fatty acid preparation (*Lovaza*) as an adjunct to diet for treatment of very high plasma triglyceride concentrations. The product is a combination of the ethyl esters of EPA and DHA. The recommended daily dosage for *Lovaza* is 4 grams once daily or 2 grams twice a day, taken with meals.

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# Flaxseed Lignans

**DESCRIPTION**

Lignans are phenylpropanoid dimers widely distributed in the plant kingdom. Flaxseed (*Linum usitatissimum* L.) is one of the richest sources of dietary lignans. Plant lignans comprise one of the two main groups of phytoestrogens, the other group being the isoflavonoids.

The major flax lignan is secoisolariciresinol diglucoside (SDG). Flaxseed is the richest food source of SDG. Flaxseed also contains much smaller amounts of matairesinol, lariciresinol and pinoresinol. The plant lignans are converted by the intestinal microflora in the proximal or upper part of the large intestine to enterodiol (END) and enterolactone (ENL). END and ENL are not themselves plant lignans and are called mammalian lignans or enterolignans. Plant lignans are precursors of mammalian lignans. It is thought that many of the possible biological actions of SDG are due to its conversion to END and ENL.

SDG is a dibenzylbutyrolactone. This is one of the two major structural types of plant lignans. The spruce lignan 7-hydroxymatairesinol also possesses this type of chemical structure. (See Spruce Lignans.) The other major chemical type is the tetrahydrofuran type that can be found in the sesame seed lignans sesamin and sesaminol. (See Sesame Seed Lignans.) The biphenolic nature of SDG resembles many of the substances known to exert estrogenic action or to block estrogen receptor sites. Lignans have been observed in some epidemiological studies to be correlated with