Opti EPA/DHA Plus SPM

Specialised Pro-resolving Mediators

Available in **60 & 120 enteric softgel capsules**

Opti EPA/DHA Plus SPM is a high strength fish oil, standardised to total pro-resolving mediators (PRMs), which are important for the anti-inflammatory action of fish oils. This fish oil also contains concentrated omega-3 fatty acids EPA, DHA and DPA to help support cardiovascular health and function. The components of Opti EPA/DHA Plus SPM also help support healthy blood lipids and cognitive function. In addition, they help support eye health and maintain healthy foetal brain and CNS development during pregnancy.

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kd-pür™

- Highly concentrated omega-3 fatty acids with 312 mg EPA, 208 mg DHA, and 9.75 mg DPA, with the added benefit of 45.5 mcg standardised total pro-resolving mediators (PRMs).
- Specialised pro-resolving mediators are naturally produced by the conversion of certain components of omega-3 fatty acids and are important for the relief of inflammation.
- Sustainable wild caught fish oil from the oceans off the coasts of Peru and Chile.
- Uses only small, cold-water, oily fish species such as anchovy, sardine, mackerel and herring.
- Independently tested to meet purity standards set by the Global Organisation for EPA and DHA Omega-3 (GOED) and is therefore extremely low in contaminants such as heavy metals.
- Enteripure™ softgel capsules offer targeted delivery using a technology that embeds only natural ingredients into the softgel casing to prevent them from breaking down in the stomach, ensuring no fishy aftertaste with minimal excipients.
- Supports cardiovascular system health, maintenance of healthy blood lipids and helps reduce inflammation in the body.
- Supports brain health and cognitive function as well as eye health.
- Helps support healthy foetal CNS/brain development.

Active Ingredients

Each enteric softgel capsule contains:

Concentrated fish omega-3 triglycerides (Kd-pür™)	650 mg
Equiv. Eicosapentaenoic acid (EPA)	312 mg
Equiv. Docosahexaenoic acid (DHA)	208 mg
Equiv. Docosapentaenoic acid (DPA)	9.75 mg

Features & Benefits

Omega-3 fatty acids, which are found abundantly in fish oil, exert pleiotropic cardiometabolic effects with a diverse range of actions. This is mainly attributed to the EPA component of fish oil, however, it is the DHA component of fish oil that is typically associated with maintaining cognitive function. DHA is also primarily responsible for eye health maintenance and supportive of healthy foetal brain development. In general, consumption of fish oil supplements helps maintain nutrient levels in the general population as well as in breast-feeding women.

The potency of fish oil can be determined by the concentration of its active components EPA and DHA. What is less known is that other components in fish oil also determine its effect on certain systems within the body. Fish oil has a presence of resolvins and protectins (SPMs), which are families of local lipid mediators generated from the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) during self-limited resolution of inflammation. Docosapentaenoic acid (DPA) is an intermediate fatty species between EPA and DHA and emerging evidence points to its role in cardiovascular and cognitive health as well as other benefits.

CLINICAL EVIDENCE

Inflammation

Fish oil is a good source of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) which compete with arachidonic acid (AA) for access to enzymes cyclooxygenase and lipoxygenase, thereby affecting the production of pro-inflammatory cytokines and blood clotting factors.[1]

EPA and DHA increase the synthesis of series 3 prostanoids and series 5 leukotrienes, but reduce the synthesis of AA derivatives series 2 eicosanoids, including pro-inflammatory prostaglandin E2.[1] Omega-3 fatty acids reduce the production of series 2 eicosanoid thromboxane A2 which causes platelet aggregation and vasoconstriction and can increase undesirable clot formation.[9]

For decades, it was thought that EPA and DHA from fish oil only helped relieve inflammation by competing with pro-inflammatory omega-6 fatty acids. This isn't the whole story. In fact, fish oil may help to relieve inflammation by providing the raw material to build specialised pro-resolving mediators (SPMs), which are the end result of a multi-step conversion process.

Specialised pro-resolving mediators (SPM—lipoxins, resolvins, protectins, and maresins) are produced via the enzymatic conversion of essential fatty acids, including the omega-3 fatty acids docosahexaenoic acid and n-3 docosapentaenoic acid. These mediators exert potent leukocyte directed actions and control vascular inflammation.

SPMs naturally occur in human tissues (mainly immune and endothelial cells), fluids and exudates including the brain, cerebrospinal fluid, adipose cells, synovial fluid, lymph nodes, plasma, serum and breast milk. [2-9]

E-series resolvins (RvE1-RvE3) are produced from EPA via the intermediate 18-hydroxyeicosapentaenoic acid (18-HEPE), whereas D-series resolvins (RvD1-RvD6) are produced from DHA, via the intermediate 17-hydroxydocosahexaenoic acid (17-HDHA) and from n-3 docosapentanoic acid [DPA]). DHA and DPA are also precursors of protectins and maresins. Those that are DHA derived are produced via the intermediates 17-hydroperoxydocosahexaenoic acid (17-HpDHA) and 14-hydroxydocosahexaenoic acid (14-HDHA).[6,11] Lipoxins are produced from the omega-6 fatty acid, arachidonic acid.

Locally synthesised at different stages and concentrations of the inflammatory process in a cell-specific manner, SPMs utilise specific mechanisms in target tissues to promote the resolution of inflammation and tissue repair without inhibiting immunological activity ('immunoresolvent'). Specifically, they help activate the resolution phase, signal to and recruit certain immune cells and inflammatory mediators, repair damage and the clearance of pathogens and prevent further pathological inflammation without immunosuppression.[2,5,8,10]

Unfortunately, the complex conversion process (as seen in Figure 1) to these SPMs is slow and inefficient, even in the healthiest individuals. Normal genetic variation means that some people will convert even more slowly than average.[12-19] Conditions such as obesity, diabetes and metabolic syndrome slow this conversion even further.

A more targeted approach would be to supplement with fish oils standardised to pro-resolving mediators (PRMs), which immediately convert to SPMs, and may help resolve inflammation in a timely manner.

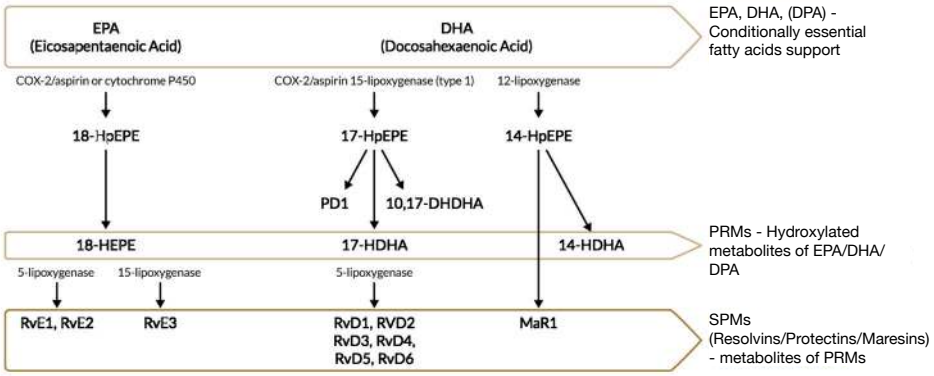

Figure 1: Conversion of omega-3 fatty acids to SPMs is a complex and convoluted process.

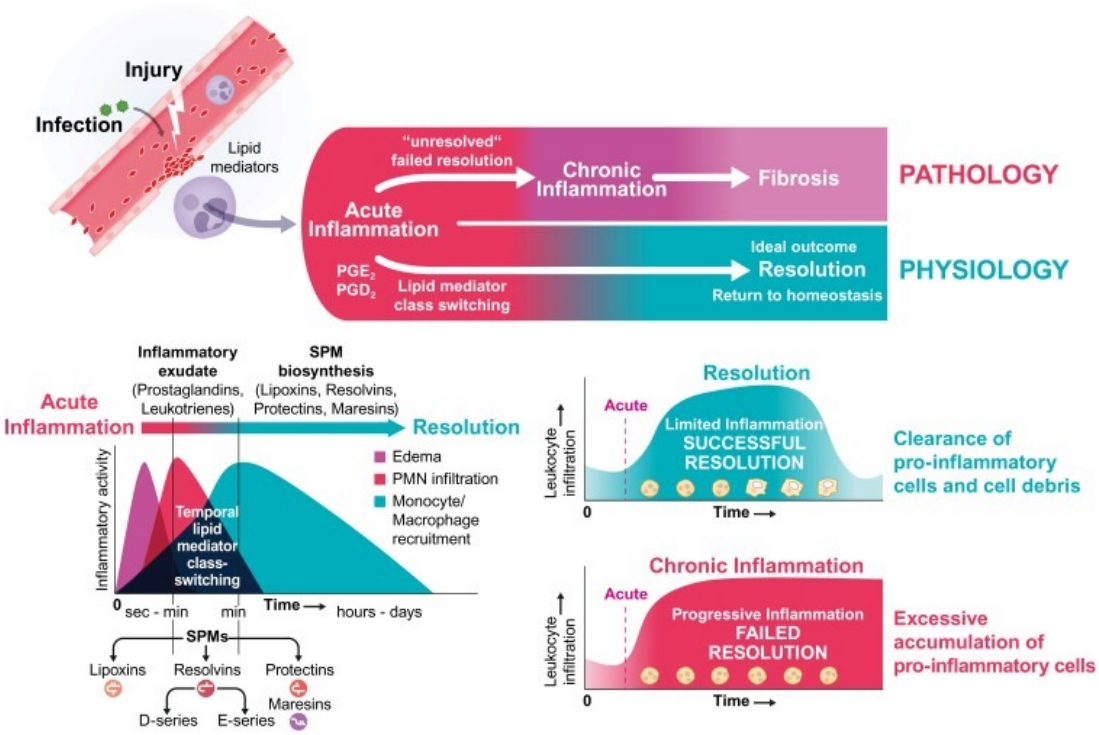

Figure 2: Complete resolution versus failed resolution of acute inflammation. **Notes:** The endogenous specialised pro-resolving mediators (SPMs) control key actions of resolution, including leukocyte trafficking, MΦ reprogramming and MΦ phagocytosis/efferocytosis. **Abbreviations:** MΦ, macrophage; PGD2, prostaglandin D2; PGE2, prostaglandin E2; PMN, polymorphonuclear leukocytes; SPM, specialised pro-resolving mediator.[103]

DHA and DPA

DHA is also essential in the therapeutic action of fish oils. Increased levels of DHA help keep cell membranes fluid and functional, improving cell receptor activity and cellular signalling, especially in the brain.[20]

DHA is highly concentrated in the brain and retina where it is essential for brain development and synaptic function, cognition, mood and emotions, retinal cone and rod structure, and visual acuity.[20,21]

Omega-3 fatty acids modulate lipid metabolism by down-regulating the expression of genes involved in hepatic cholesterol synthesis, reducing the activity of mitochondrial tricarboxylate carrier and cytosolic lipogenic enzymes, to result in reduced plasma levels of low-density lipoprotein (LDL) cholesterol and triglycerides.[22]

DHA also modulates gene expression and the production of proteins involved in signal transduction processes.

Most fish oils contain less than 2% DPA by weight, roughly one-third to one-fifth of the EPA or DHA content. The levels of DPA in human milk are higher than those of EPA and comparable to those of DHA, implicating it as potentially important in human development.[23]

Further, DPA shares structural similarities with EPA and DHA. As an "elongated version of EPA", DPA has two extra carbons in the chain and the same number of double bonds as EPA. Biochemically it is a direct elongation product of EPA. The similarity of DPA to EPA and DHA may explain some of its overlapping biological functions with these more well-known fatty acids.[23]

Cardiovascular Support

EPA and DHA help maintain cardiovascular health by modulating the endocannabinoid system, lowering plasma triglycerides, increasing levels of high-density lipoproteins (HDLs), regulating heartbeat, lowering blood pressure, and through anti-inflammatory, antiatherosclerotic and antithrombotic effects.[28-31]

It is well known that chronic inflammation is a primary factor in cardiovascular disease (CVD) risk and onset.[32,8,33.34] Whilst evidence points to EPA and DHA supplementation for cardiovascular health and disease, sometimes there is a lack of therapeutic benefit observed by other clinical evidence. This is suggested to be driven by suboptimal SPM levels diminishing the body's capacity to effectively resolve inflammation.[32,34] Along with the mechanistic properties of EPA, DHA and SPMs that maintain vascular homeostasis, their importance in cardiovascular health and function is highlighted by low SPM levels in several CVD population groups and elevated levels at the onset of CV events (myocardial infarction, cardiorespiratory failure).[35,2,5,34,36]

Omega-3 fatty acids are also associated with increased endothelial-derived nitric oxide, helping to relax blood vessels, and reduce blood pressure and arterial damage.[22] Additionally, DHA may act at the cellular membrane level, influencing ionic exchange and aiding contraction and relaxation in the heart muscle.[26] In one study, high DHA fish oil led to increases in mitochondrial superoxide dismutase, an antioxidant enzyme.[25] DHA has also been found to reduce fasting blood levels of C-reactive protein, interleukin-6, and tumour necrosis factor alpha.[28]

Epidemiological trials have demonstrated that higher levels of DPA in human blood are positively correlated with lower blood triglycerides, cholesterol, inflammation, and overall risk of coronary heart diseases and acute myocardial infarction.[39-44] For example, in a large epidemiological investigation of older adults, higher circulating levels of DPA were associated with lower total mortality, including death from coronary heart disease.[45]

In a case-controlled study, which involved 73 patients with acute myocardial infarction and 84 matched controls, serum DPA levels were significantly higher in healthy individuals than in the affected group.[43] Further, a study in Australian men showed that the levels of DPA in blood platelets showed a strong negative correlation with mean platelet volume, a risk factor for acute myocardial infarction.[46] In the Edinburgh Artery Study, a cross-sectional survey of more than 1,500 people, DPA was the only LC omega-3 that reduced the likelihood of developing atherosclerosis, suggesting that it may have a protective effect.[47]

Another study in Australian men indicated that blood levels of DPA are influenced by diet, and its consumption has been positively linked to less carotid atherosclerosis.[48] Although these studies do not imply causation, they highlight the link between DPA and better cardiovascular health.

Cognitive Health

DHA makes up 30–40% of PUFAs within the grey matter of the cerebral cortex.[20] Here, DHA modulates signal transduction molecules and is involved in cell membrane fluidity and receptor affinity.

Epidemiological research has noted that populations with high blood levels and dietary intakes of DHA typically have lower rates of cognitive impairment and Alzheimer's disease. DHA is believed to help reduce the risks of dementia in older individuals by improving cerebral blood flow, reducing inflammation, and mitigating amyloid plaque formation.[1]

Both EPA and DHA also help inhibit the conversion of arachidonic acid to series 2 eicosanoids, helping reduce levels of pro-inflammatory cytokines, T-cell proliferation, and leukocyte migration, all of which can help protect against dementia.[1] Unresolved inflammation ('neuroinflammation') is a central pathophysiological process in central nervous system (CNS) dysfunctionality including cognitive impairment and neurodegenerative disease onset and progression.[49-52] As stated above, EPA and DHA are essential for normal CNS structural and functional processes including learning, memory, neurogenesis and synaptic plasticity. With SPMs these omega-3s are also essential for modulating and resolving CNS neuroinflammation and neural repair.[49-54] Impaired age-associated cognitive function is largely attributed to reduced brain phospholipid DHA and EPA concentrations and more recently, lower SPM levels in healthy older vs younger populations.[51] Similarly lower SPM concentrations have also been observed in neurodegenerative diseases and correlate with cognitive impairment in these conditions.[55]

DPA has also been linked to better mental health and cognitive function. Observational studies show that DPA levels in patients with depression were lower than in healthy people.[56,57]

Pregnancy Consumption and Benefit to Offspring

Consumption of omega-3 fatty acids (or any polyunsaturated fatty acid) is known to cross the placental barrier[58,59] via FATP transporters (particularly FATP4)[60] to regulate nervous system development.[61] Unlike adults, the foetus in not capable of inherently synthesising sufficient omega-3 fatty acids and thus parental provision is mandatory[61] and supplemental DHA has been confirmed (in primates) to be approximately 8-22 times more effective at increasing neural DHA stores in offspring than the parent omega-3 fatty acid (ALA).[62] It should be noted that arachidonic acid (omega-6 counterpart to EPA) is also vital for cognitive development, but seems to be less responsive to the diet, suggestive of better regulation.[63]

Docosahexaenoic acid (DHA) plays a critical role in the neural development of the foetus during pregnancy. The foetus depends on parental provision of DHA, either through supplementation or the diet. It is for these reasons that supplemental fish oil is thought to increase cognitive development in unborn children, but it is unknown if the omega 3:6 ratio plays any role here, as arachidonic acid is also critical.

One meta-analysis (38 trials reviewed with 53 intervention arms) has been conducted assessing cognitive and visual development of offspring of mothers who consumed omega-3 fatty acids during pregnancy[64] noted n-3 PUFA supplementation improves childhood psychomotor and visual development.

EPA, DHA and SPM levels are also closely involved in menstrual cyclicity, fertility, pregnancy, labour, foetal growth and development.[24-26,65,36,37]

While acute inflammation plays a central role in ovulation, menstruation, blastocyst implantation, placental vasculature, pregnancy maintenance and labour, chronic unresolved inflammation in reproductive tissues is associated with severe menstrual blood loss, endometriosis progression, gestational diabetes mellitus, foetal growth restriction, preeclampsia preterm labour and suboptimal foetal outcomes.[37,66,68,69]

Maintaining a healthy inflammatory balance is therefore necessary for reproductive, pregnancy and foetal health, and this requires optimal levels of EPA, DHA and SPMs, however low intake is common in pregnancy and women of reproductive age.[65,66] Present in high concentrations in the placenta and breastmilk, particularly in the first month of lactation, maternal EPA, DHA and SPM levels also significantly influences offspring omega-3 status and subsequently their growth, development and health outcomes.[4,66,67,70] Additionally, low blood levels of DPA during pregnancy were linked to a higher prevalence of postpartum depression.[71]

Lactation

Dietary DHA intake is critical during the first three months of life, where it correlates greatly with neural DHA levels (as assessed by autopsy reports)[63,72,73] and it therefore supports cognitive development.[79] Due to this importance it is a mandatory additive to baby formulation[34] and provision to preterm infants is highly recommended.[81] DHA is also a component of breast milk (and thus provided during breast feeding)[75] of which the concentration of DHA in breast milk is correlated with the mother's diet.[76-79]

Supplemental ALA (from flaxseed or plant sources of omega-3) is ineffective in raising breast milk concentrations of DHA, despite an increase in breast milk concentrations of ALA.[79]

However, supplementation with EPA and DHA during pregnancy[81,82] and/or lactation[64,65] has been very effective in increasing their breast milk concentrations, with some manner of dose-dependence and highest levels being reached after 2 weeks of supplementation.[81-86]

Breast milk DHA concentrations also reflect dietary DHA concentrations. Both fish intake and supplementation can elevate levels of breast milk DHA.[100]

Eye health

Omega-3 fatty acids, particularly DHA, are known to be highly involved as modulators of retinal capillary integrity, neovascularisation and inflammation[66] related to their protectins and resolvins.[85]

DHA plays an important role as a structural membrane lipid, particularly in nerve tissue and the retina, and can also act as a precursor to certain eicosanoids. There is a well established role of DHA in retinal function. In fact, a cause and effect relationship has been confirmed between the consumption of DHA and the maintenance of normal vision.

Deficiency of alpha linolenic acid, the parent fatty acid of the longer chain omega-3 polyunsaturated fatty acids, including DHA, results in adverse clinical symptoms including, neurological abnormalities and poor growth. Evidence for the essentiality of omega-3 fatty acids in humans can be drawn from case reports of patients receiving parenteral nutrition with intravenous lipids devoid of such fatty acids. Biochemical changes of omega-3 fatty acids deficiency include a decrease in plasma and tissue DHA concentrations.

DHA is the major structural lipid in brain tissue and the central nervous system and the membrane lipids of brain grey matter and the retina contain very high concentrations of DHA. Biophysical and biochemical properties of DHA affect photoreceptor membrane function by altering permeability, fluidity, thickness, and lipid phase properties.[95,96]

Side Effects

Fish oils are generally well tolerated at normal therapeutic doses. Fishy reflux, fishy aftertaste, mild gastrointestinal discomfort, nausea, and loose stools have been reported with the use of fish oil supplements.[97,98] Bioclinic Naturals Opti EPA/DHA Plus SPM uses Enteripure™ softgel technology, which may help to reduce the incidence of these effects.

Precautions and contraindications

Caution and monitoring are recommended in patients prior to surgery as there is a theoretical increased risk of bleeding.[97,98] A large scale review that included 52 clinical studies concluded that fish oil supplements do not increase the bleeding risk during or after surgery, and that there does not appear to be a need for discontinuation of fish oil supplements prior to surgery or other invasive procedures.[102]

Caution and monitoring is recommended in patients with bleeding disorders.[97,98]

Individuals with bleeding disorders should take fish oil supplements under medical supervision due to a theoretical increased risk of bleeding.[97,98]

Fish oils have immunomodulatory effects.[97] Caution is advised in high-risk patients taking immunosuppressant drugs. Dosage adjustments may be required, especially in those taking fish oil supplements at doses ≥ 3 g daily.[97]

Pregnancy and lactation.

Fish oil supplements appear to be safe in pregnancy and lactation at normal therapeutic doses.[97]

Interactions

Anticoagulant and antiplatelet drugs	Clinical evidence reports no increased risk of bleeding with the combined use of fish oils with anticoagulant or antiplatelet drugs at normal therapeutic doses.[97-100] Clinical research shows that taking 3-6 g daily of fish oils does not significantly increase INR when used by patients taking warfarin.[102]
Antihypertensive drugs	Fish oil supplements provide a modest, yet consistent blood pressure lowering effect and may have additive effects. Monitor for hypotension.[97,100]
Non-steroidal anti-inflammatory drugs (NSAIDs)	Fish oil supplements can help to reduce inflammation, pain and swelling and additive beneficial effects are theoretically possible.[98,99]
Orlistat	Concomitant intake may theoretically result in decreased absorption of fish oil. Separate doses by at least 2 hours.[97]

**References available on request.*

Directions for use: Adults: 2 softgels, 1-2 times daily or as directed by a health care practitioner.

WARNINGS: Dietary supplements can only be of assistance if dietary intake is inadequate. Advise your doctor of any medicine you take during pregnancy, particularly in your first trimester.

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