

**HOLISTIC SUPPLEMENT OMEGA FATTY ACIDS: A CHALLENGE FOR SMART HEART BY SAYING NO TO ATHEROSCLEROSIS AND YES TO HOMEOSTASIS****Dhrubo Jyoti Sen\*<sup>1</sup>, Satyanand Tyagi<sup>2</sup>, Anil Kumar Gupta<sup>3</sup>, Surinder Kumar<sup>4</sup>, Sonal Dinkar Patil<sup>5</sup>, Megha Sahu<sup>6</sup>, Prabodh V. Sapkale<sup>7</sup>, Mayur Ashok Chaudhari<sup>8</sup> and Kamlesh R. Prajapati<sup>9</sup>**<sup>1</sup>Department of Pharmaceutical Chemistry, Shri Sarvajani Pharmacy College, Gujarat Technological University, Mehsana-384001, Gujarat, India.<sup>2</sup>President & Founder, Tyagi Pharmacy Association (TPA) & Scientific Writer (Pharmacy), New Delhi, India.<sup>3</sup>Jyoti Vidyapeeth Women's University, Jaipur, Discipline of Pharmaceutical Sciences, Jaipur, Rajasthan, India.<sup>4</sup>Vardhaman Mahavir Medical College (VMMC) & Safdarjung Hospital, Safdarjung Enclave, Safdarjung, New Delhi-110029, India.<sup>5</sup>Department of Pharmaceutics, Shellino Education Society's Arunamai College of Pharmacy, Mamurabad, Jalgaon, Maharashtra-425002, India.<sup>6</sup>Department of Pharmaceutical Chemistry, Smt. Kashibai Navale College of Pharmacy, Kondhwa (Bk.), Kondhwa Saswad Road, Pune, Maharashtra-411048, India.<sup>7</sup>Department of Pharmaceutical Chemistry, Shellino Education Society's Arunamai College of Pharmacy, Mamurabad, Jalgaon, Maharashtra-425002, India.<sup>8</sup>Department of Pharmacology, Shellino Education Society's Arunamai College of Pharmacy, Mamurabad, Jalgaon, Maharashtra-425002, India.<sup>9</sup>Department of Quality Assurance, Shri Sarvajani Pharmacy College, Gujarat Technological University, Mehsana-384001, Gujarat, India.**Received 28 June 2013; Revised 07 July 2013; Accepted 10 July 2013****ABSTRACT**

*Omega-3/5/6/7/9 fatty acids are considered as essential fatty acids. They are necessary for human health but the body can't make them -- you have to get them through food. Omega fatty acids can be found in fish, such as salmon, tuna and halibut, other seafood including algae and krill, some plants and nut oils. Also known as polyunsaturated fatty acids (PUFAs), omega fatty acids play a crucial role in brain function, as well as normal growth and development. They have also become popular because they may reduce the risk of heart disease. The American Heart Association recommends eating fish (particularly fatty fish such as mackerel, lake trout, herring, sardines, albacore tuna, and salmon) at least 2 times a week. Research shows that omega fatty acids reduce inflammation and may help lower risk of chronic diseases such as heart disease, cancer and arthritis. Omega fatty acids are highly concentrated in the brain and appear to be important for cognitive (brain memory and performance) and behavioral function. In fact, infants who do not get enough omega fatty acids from their mothers during pregnancy are at risk for developing vision and nerve problems. Symptoms of omega fatty acid deficiency include fatigue, poor memory, dry skin, heart problems, mood swings or depression, and poor circulation. It is important to have the proper ratio of omega-3 and omega-6 (another essential fatty acid) in the diet.*



*Omega-3 fatty acids help reduce inflammation and most omega-6 fatty acids tend to promote inflammation. The typical American diet tends to contain 14-25 times more omega-6 fatty acids than omega-3 fatty acids, which many nutritionally oriented physicians consider to be way too high on the omega-6 side. The regular diet, on the other hand, has a healthier balance between omega-3 and omega-6 fatty acids. Many studies have shown that people who follow this diet are less likely to develop heart disease. The Mediterranean diet emphasizes foods rich in omega-3 fatty acids, including whole grains, fresh fruits and vegetables, fish, olive oil, garlic, as well as moderate wine consumption.*

**KEYWORDS:** PUFA, ALA, GLA, EPA, DHA, LDL, ADHD, NSAID, Eicosanoids

## INTRODUCTION:

### OMEGA-3 FATTY ACID:

Omega-3 fatty acids (also called  $\omega$ -3 fatty acids or *n*-3 fatty acids) refers to a group of three fats called ALA (alpha linoleic acid), EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid). Common sources of animal omega-3 EPA and DHA fatty acids include fish oils, algal oil, egg oil, squid oils, krill oil and some plant oils contain the omega-3 ALA fatty acid such as sea buckthorn seed and berry oils, flaxseed oil, Sacha Inchi oil, *Echium* oil and hemp oil.<sup>1</sup> Omega-3 fatty acids are vital for normal metabolism but some of the potential health benefits of supplementation are controversial. Omega-3s are considered essential fatty acids, meaning that they cannot be synthesized by the human body except that mammals have a limited ability, when the diet includes the shorter-chained omega-3 fatty acid ALA (alpha-linolenic acid, 18 carbons and 3 double bonds), to form the more important long-chain omega-3 fatty acids, EPA (eicosapentaenoic acid, 20 carbons and 5 double bonds) and then from EPA, the most crucial, DHA (docosahexaenoic acid, 22 carbons and 6 double bonds) with even much greater inefficiency. The ability to make the longer-chained omega-3 fatty acids from ALA may also be impaired in aging. In foods exposed to air, unsaturated fatty acids are vulnerable to oxidation and rancidity and fish are much more efficient than mammals at converting the ALA to the EPA and DHA omega-3 fatty acids.<sup>2</sup> Omega-3 fatty acids are polyunsaturated fatty acids with a double bond (C=C) at the third carbon atom from the end of the carbon chain. The fatty acids have two ends, the acid (-COOH) end, which is considered the beginning of the chain, thus "alpha" and the methyl (CH<sub>3</sub>) end, which is considered the "tail" of the chain, thus "omega." The nomenclature of the fatty acid is taken from the location of the first double bond, counted from the methyl end, that is, the omega ( $\omega$ -) or the *n*- end.<sup>3</sup>

### HEALTH EFFECTS:

Supplementation does not appear to be associated with a lower risk of all-cause mortality.

### CANCER:

The evidence linking the consumption of fish to the risk of cancer is poor. Supplementation with omega-3 fatty acids does not appear to affect this risk either. A 2006 report in the *Journal of the American Medical Association*, in their review of literature covering cohorts from many countries with a wide variety of demographics, concluded that there was no link between omega-3 fatty acids and cancer. This is similar to the findings of a review by the *British Medical Journal* of studies up to February 2002 that

failed to find clear effects of long and shorter chain omega-3 fats on total mortality, combined cardiovascular events and cancer. In those with advanced cancer and cachexia, omega-3 fatty acids supplements may be of benefit, improving appetite, weight and quality of life.<sup>4</sup>

### CARDIOVASCULAR DISEASE:

Evidence does not support a beneficial role for omega-3 fatty acid supplementation in preventing cardiovascular disease (including myocardial infarction and sudden cardiac death) or stroke. Fish oil supplementation has not been shown to benefit revascularization or arrhythmia and has no effect on heart failure admission rates. Eating a diet high in fish that contain long chain omega-3 fatty acids does appear to decrease the risk of stroke. Large amounts may increase low-density lipoproteins (LDL), up to 46%, although LDL changes from small to larger, buoyant, less atherogenic particles. Omega-3 fatty acids also have mild antihypertensive effects. When subjects consumed omega-3 fatty acids from oily fish on a regular basis, their systolic blood pressure was lowered by about 3.5-5.5 mmHg. The 18 carbon alpha linolenic acid (ALA) has not been shown to have the same cardiovascular benefits that DHA or EPA may have. Some evidence suggests that people with certain circulatory problems, such as varicose veins, may benefit from the consumption of EPA and DHA, which may stimulate blood circulation, increase the breakdown of fibrin, a compound involved in clot and scar formation and, in addition, may reduce blood pressure. Evidently, omega-3 fatty acids reduce blood triglyceride levels and regular intake may reduce the risk of secondary and primary heart attack. ALA does not confer the cardiovascular health benefits of EPA and DHA. Large amounts may increase the risk of hemorrhagic stroke; lower amounts are not related to this risk; 3 grams of total EPA/DHA daily are generally recognized as safe (GRAS) with no increased risk of bleeding involved and many studies used substantially higher doses without major side effects (for example: 4.4 grams EPA/2.2 grams DHA in 2003 study).<sup>5</sup>

Among omega-3 fatty acids, neither long-chain nor short-chain forms were consistently associated with breast cancer risk. High levels of docosahexaenoic acid (DHA), however, the most abundant omega-3 PUFA (polyunsaturated fatty acid) in erythrocyte (red blood cell) membranes, were associated with a reduced risk of breast cancer. The DHA obtained through the consumption of polyunsaturated fatty acids is positively associated with cognitive and behavioral performance. In addition DHA is vital for the grey matter structure of the human brain, as well as retinal stimulation and neurotransmission.<sup>6</sup>

**INFLAMMATION:**

Although not confirmed as an approved health claim, current research suggests that the anti-inflammatory activity of long-chain omega-3 fatty acids may translate into clinical effects. For example, there is evidence that rheumatoid arthritis sufferers taking long-chain omega-3 fatty acids from sources such as fish have reduced pain compared to those receiving standard NSAIDs. Some potential benefits have been reported in conditions such as rheumatoid arthritis.<sup>7</sup>

**DEVELOPMENTAL DISORDERS:**

Although not supported by current scientific evidence as a primary treatment for ADHD, autism spectrum disorders, and other developmental differences, omega-3 fatty acids have gained popularity for children with these conditions. Omega-3 fatty acids offer a promising complementary approach to standard treatments for ADHD (Attention deficit hyperactivity disorder) and developmental coordination disorder. Fish oils appear to reduce ADHD-related symptoms in some children. A randomized, controlled trial has suggested that "fatty acid supplementation may offer a safe efficacious treatment option for educational and behavioral problems among children with DCD". There is not enough scientific evidence to support the effectiveness of omega-3 fatty acids for autism spectrum disorders. Fish oil has only a small benefit on the risk of early birth.<sup>8</sup>

**PSYCHIATRIC DISORDERS:**

Though there is some evidence that omega-3 fatty acids are related to a variety of mental disorders, they may tentatively be useful as an add-on for the treatment of depression associated with bipolar disorder and there is preliminary evidence that EPA supplementation is helpful in cases of depression.<sup>9</sup>

**COGNITIVE AGING:**

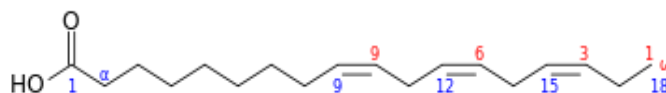
Epidemiological studies suggest that consumption of omega-3 fatty acids can reduce the risk of dementia, but evidence of a treatment effect in dementia patients is inconclusive. However, clinical evidence suggests benefits of treatment specifically in patients who show signs of cognitive decline but who are not sufficiently impaired to meet criteria for dementia.<sup>10</sup>

**ADVERSE EFFECTS:**

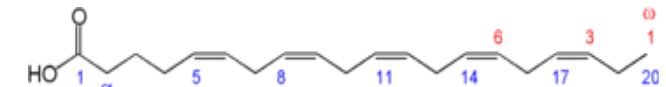
In a letter published October 31, 2000, the United States Food and Drug Administration Center for Food Safety and Applied Nutrition, Office of Nutritional Products, Labeling, and Dietary Supplements noted that known or

suspected risks of EPA and DHA consumed in excess of 3 grams per day may include the possibility of:

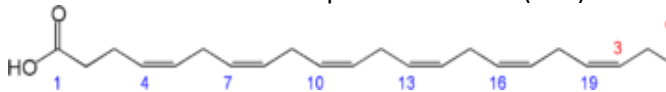
- Increased incidence of bleeding
- Hemorrhagic stroke
- Oxidation of omega-3 fatty acids, forming biologically active oxidation products
- Increased levels of low-density lipoproteins (LDL) cholesterol or apoproteins associated with LDL cholesterol among diabetics and hyperlipidemics
- Reduced glycemic control among diabetics.<sup>11</sup>

**CHEMISTRY:**

Chemical structure of alpha-linolenic acid (ALA), an essential omega-3 fatty acid, (18:3Δ<sup>9,12,15</sup>c, which means a chain of 18 carbons with 3 double bonds on carbons numbered 9, 12, and 15). Although chemists count from the carbonyl carbon (blue numbering), biologists count from the *n* ( $\omega$ ) carbon (red numbering). Note that, from the *n* end (diagram right), the first double bond appears as the third carbon-carbon bond (line segment), hence the name "*n*-3". This is explained by the fact that the *n* end is almost never changed during physiological transformations in the human body, as it is more energy-stable, and other carbohydrates compounds can be synthesized from the other carbonyl end, for example in glycerides, or from double bonds in the middle of the chain.<sup>12</sup>



Chemical structure of eicosapentaenoic acid (EPA)



Chemical structure of docosahexaenoic acid (DHA)

Omega-3 fatty acids that are important in human physiology are alpha-linolenic acid (18:3, *n*-3; ALA), eicosapentaenoic acid (20:5, *n*-3; EPA), and docosahexaenoic acid (22:6, *n*-3; DHA). These three polyunsaturates have either 3, 5, or 6 double bonds in a carbon chain of 18, 20, or 22 carbon atoms, respectively. As with most naturally-produced fatty acids, all double bonds are in the *cis*-configuration, in other words, the two hydrogen atoms are on the same side of the double bond; and the double bonds are interrupted by methylene bridges (-CH<sub>2</sub>-), so that there are two single bonds between each pair of adjacent double bonds.<sup>13</sup>

This table lists several different names for the most common omega-3 fatty acids found in nature.

#### LIST OF OMEGA-3 FATTY ACIDS:

Common name	Lipid name	Chemical name
Hexadecatrienoic acid (HTA)	16:3 ( <i>n</i> -3)	<i>all-cis</i> -7,10,13-hexadecatrienoic acid
alpha-linolenic acid (ALA)	18:3 ( <i>n</i> -3)	<i>all-cis</i> -9,12,15-octadecatrienoic acid
Stearidonic acid (SDA)	18:4 ( <i>n</i> -3)	<i>all-cis</i> -6,9,12,15-octadecatetraenoic acid
Eicosatrienoic acid (ETE)	20:3 ( <i>n</i> -3)	<i>all-cis</i> -11,14,17-eicosatrienoic acid
Eicosatetraenoic acid (ETA)	20:4 ( <i>n</i> -3)	<i>all-cis</i> -8,11,14,17-eicosatetraenoic acid
Eicosapentaenoic acid (EPA)	20:5 ( <i>n</i> -3)	<i>all-cis</i> -5,8,11,14,17-eicosapentaenoic acid
Heneicosapentaenoic acid (HPA)	21:5 ( <i>n</i> -3)	<i>all-cis</i> -6,9,12,15,18-heneicosapentaenoic acid
Docosapentaenoic acid (DPA)	22:5 ( <i>n</i> -3)	<i>all-cis</i> -7,10,13,16,19-docosapentaenoic acid
Docosahexaenoic acid (DHA)	22:6 ( <i>n</i> -3)	<i>all-cis</i> -4,7,10,13,16,19-docosahexaenoic acid
Tetracosapentaenoic acid (TCPA)	24:5 ( <i>n</i> -3)	<i>all-cis</i> -9,12,15,18,21-tetracosapentaenoic acid
Tetracosahexaenoic acid (TCHA)	24:6 ( <i>n</i> -3)	<i>all-cis</i> -6,9,12,15,18,21-tetracosahexaenoic acid

Table-1: Omega-3 Fatty Acids

#### MECHANISM OF ACTION:

The 'essential' fatty acids were given their name when researchers found that they are essential to normal growth in young children and animals, though the modern definition of 'essential' is stricter. A small amount of omega-3 in the diet (~1% of total calories) enabled normal growth, and increasing the amount had little to no additional effect on growth. Likewise, researchers found that omega-6 fatty acids (such as gamma-linolenic acid and arachidonic acid) play a similar role in normal growth. However, they also found that omega-6 was "better" at supporting dermal integrity, renal function, and parturition. These preliminary findings led researchers to concentrate their studies on omega-6, and it is only in recent decades that omega-3 has become of interest. In 1964, it was discovered that enzymes found in sheep tissues convert omega-6 arachidonic acid into the inflammatory agent called prostaglandin E<sub>2</sub>, which both causes the sensation of pain and expedites healing and immune response in traumatized and infected tissues. By 1979, more of what are now known as eicosanoids were discovered: thromboxanes, prostacyclins, and the leukotrienes. The eicosanoids, which have important biological functions, typically have a short active lifetime in the body, starting with synthesis from fatty acids and ending with metabolism by enzymes. However, if the rate of synthesis exceeds the rate of metabolism, the excess eicosanoids may have deleterious effects. Researchers found that certain omega-3 fatty acids are also converted into eicosanoids, but at a much slower rate. Eicosanoids

made from omega-3 fatty acids are often referred to as anti-inflammatory, but in fact they are just less inflammatory than those made from omega-6 fats. If both omega-3 and omega-6 fatty acids are present, they will "compete" to be transformed, so the ratio of long-chain omega-3:omega-6 fatty acids directly affects the type of eicosanoids that are produced. This competition was recognized as important when it was found that thromboxane is a factor in the clumping of platelets, which can both cause death by thrombosis and prevent death by bleeding. Likewise, the leukotrienes were found to be important in immune/inflammatory-system response, and therefore relevant to arthritis, lupus, asthma, and recovery from infections. These discoveries led to greater interest in finding ways to control the synthesis of omega-6 eicosanoids. The simplest way would be by consuming more omega-3 and fewer omega-6 fatty acids. They are required during the prenatal period for the formation of synapses and cell membranes. These processes are also essential in postnatal human development for injury response of the central nervous system and retinal stimulation.<sup>14</sup>

#### CONVERSION EFFICIENCY OF ALA TO EPA AND DHA:

The body converts short-chain omega-3 fatty acids to long-chain forms (EPA, DHA) with an efficiency below 5% in men. The omega-3 conversion efficiency is greater in women, possibly because of the importance for meeting the demands of the fetus and neonate for DHA.<sup>15</sup> These conversions occur competitively with omega-6 fatty acids,

which are essential closely related chemical analogues that are derived from linoleic acid. Both the omega-3 alpha-linolenic acid and omega-6 linoleic acid must be obtained from food. Synthesis of the longer omega-3 fatty acids from linolenic acid within the body is competitively slowed by the omega-6 analogues. Thus, accumulation of long-chain omega-3 fatty acids in tissues is more effective when they are obtained directly from food or when competing amounts of omega-6 analogs do not greatly exceed the amounts of omega-3. The conversion of ALA to EPA and further to DHA in humans has been reported to be limited, but varies with individuals. Women have higher ALA conversion efficiency than men, which is presumed to be due to the lower rate of use of dietary ALA for beta-oxidation. This suggests that biological engineering of ALA conversion efficiency is possible. It is the absolute amount of ALA, rather than the ratio of omega-3 and omega-6 fatty acids, that controls the conversion efficiency.<sup>16</sup>

**THE OMEGA-6 TO OMEGA-3 RATIO:**

Some older clinical studies indicate that the ingested ratio of omega-6 to omega-3 (especially linoleic vs alpha-linolenic) fatty acids is important to maintaining cardiovascular health. However, three studies published in 2005, 2007 and 2008, including a randomized controlled trial, found that while omega-3 polyunsaturated fatty acids are extremely beneficial in preventing heart disease in humans, the levels of omega-6 polyunsaturated fatty acids (and therefore the ratios) were insignificant. Both omega-6 and omega-3 fatty acids are essential; i.e., humans must

consume them in the diets. Omega-6 and omega-3 eighteen-carbon polyunsaturated fatty acids compete for the same metabolic enzymes, thus the omega-6:omega-3 ratio of ingested fatty acids has significant influence on the ratio and rate of production of eicosanoids, a group of hormones intimately involved in the body's inflammatory and homeostatic processes which includes the prostaglandins, leukotrienes, and thromboxanes, among others. Altering this ratio can change the body's metabolic and inflammatory state. In general, grass-fed animals accumulate more omega-3 than do grain-fed animals, which accumulate relatively more omega-6. Metabolites of omega-6 are more inflammatory (esp. arachidonic acid) than those of omega-3. This necessitates that omega-6 and omega-3 be consumed in a balanced proportion; healthy ratios of omega-6:omega-3, according to some authors, range from 1:1 to 1:4 (an individual needs more omega-3 than omega-6). Other authors believe that ratio 4:1 (when the amount of omega-6 is only 4 times greater than that of omega-3) is already healthy. Studies suggest the evolutionary human diet, rich in game animals, seafood, and other sources of omega-3, may have provided such a ratio.<sup>17</sup> Typical Western diets provide ratios of between 10:1 and 30:1 (i.e., dramatically higher levels of omega-6 than omega-3). The ratios of omega-6 to omega-3 fatty acids in some common vegetable oils are: canola 2:1, hemp 2-3:1, soybean 7:1, olive 3-13:1, sunflower (no omega-3), flax 1:3, cottonseed (almost no omega-3), peanut (no omega-3), grapeseed oil (almost no omega-3) and corn oil 46:1 ratio of omega-6 to omega-3.<sup>18</sup>

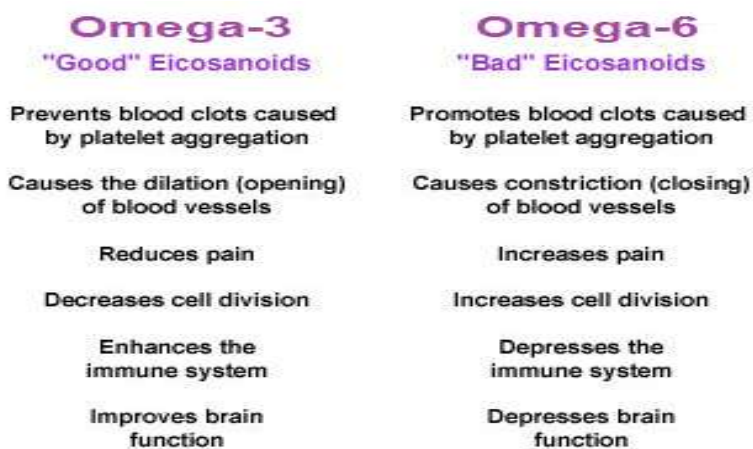


Figure 1: Omega-3 vs Omega-6

**HISTORY:**

Although omega-3 fatty acids have been known as essential to normal growth and health since the 1930s, awareness of their health benefits has dramatically increased since the 1990s. The health benefits of the long-chain omega-3 fatty acids — primarily EPA and DHA are the

best known. These benefits were discovered in the 1970s by researchers studying the Greenland Inuit Tribe. The Greenland Inuit people consumed large amounts of fat from fish, but displayed virtually no cardiovascular disease. The high level of omega-3 fatty acids consumed by the

Inuit reduced triglycerides, heart rate, blood pressure, and atherosclerosis.<sup>19</sup>

**DAILY VALUES:**

As macronutrients, fats are not assigned Dietary Reference Intakes. Macronutrients have acceptable intake (AI) levels and acceptable macronutrient distribution ranges (AMDRs) instead of RDAs. The AI for omega-3 is 1.6 grams/day for men and 1.1 grams/day for women, while the AMDR is 0.6% to 1.2% of total energy. A growing body of literature suggests that higher intakes of alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may afford some degree of protection against coronary disease. Because the physiological potency of EPA and DHA is much greater than that of ALA, it is not possible to estimate one AMDR for all omega-3 fatty acids. Approximately 10 percent of the AMDR can be consumed as EPA and/or DHA." There was insufficient evidence as of 2005 to set an upper tolerable limit for omega-3 fatty acids.<sup>20</sup> Heavy metal poisoning by the body's accumulation of traces of heavy metals, in particular mercury, lead, nickel, arsenic, and cadmium, is a possible risk from consuming fish oil supplements. Also, other contaminants (PCBs, furans, dioxins, and PBDEs) might be found, especially in less-refined fish oil supplements. In reality, however, heavy metal toxicity from consuming fish oil supplements is highly unlikely, because heavy metals selectively bind with protein in the fish flesh rather than accumulate in the oil. Global food companies have launched omega-3 fatty acid fortified bread, mayonnaise, pizza, yogurt, orange juice, children's pasta, milk, eggs, popcorn, confections, and infant formula. The American Heart Association has set up dietary recommendations for EPA and DHA due to their

cardiovascular benefits: Individuals with no history of coronary heart disease or myocardial infarction should consume oily fish or fish oils two times per week; those having been diagnosed with coronary heart disease after infarction should consume 1 g EPA and DHA per day from oily fish or supplements; those wishing to lower blood triglycerides should consume 2-4 g of EPA and DHA per day in the form of supplements.<sup>21</sup>

**FISH:**

The most widely available dietary source of EPA and DHA is cold water oily fish, such as salmon, herring, mackerel, anchovies, and sardines. Oils from these fish have a profile of around seven times as much omega-3 as omega-6. Other oily fish, such as tuna, also contain n-3 in somewhat lesser amounts. Consumers of oily fish should be aware of the potential presence of heavy metals and fat-soluble pollutants like PCBs and dioxins, which are known to accumulate up the food chain. Although fish is a dietary source of omega-3 fatty acids, fish do not synthesize them; they obtain them from the algae (microalgae in particular) or plankton in their diets.<sup>22</sup>

**FISH OIL:**

Marine and freshwater fish oil vary in content of arachidonic acid, EPA and DHA. They also differ in their effects on organ lipids. Not all forms of fish oil may be equally digestible. Of four studies that compare bioavailability of the glyceryl ester form of fish oil vs. the ethyl ester form, two have concluded the natural glyceryl ester form is better, and the other two studies did not find a significant difference. No studies have shown the ethyl ester form to be superior, although it is cheaper to manufacture.<sup>23</sup>

Common name	Grams omega-3	Common name	Grams omega-3
Herring, sardines	1.3–2	King mackerel	0.36
Mackerel	1.1–1.7	Hoki (blue grenadier)	0.41
Salmon	1.1–1.9	Gemfish	0.40
Halibut	0.60–1.12	Blue eye cod	0.31
Tuna	0.21–1.1	Sydney rock oysters	0.30
Swordfish	0.97	Tuna, canned	0.23
Greenshell	0.95	Snapper	0.22
Tilefish	0.9	Eggs, large regular	0.109
Tuna (canned, light)	0.17–0.24	Barramundi, saltwater	0.100
Pollock	0.45	Giant tiger prawn	0.100
Cod	0.15–0.24	Lean red meat	0.031
Catfish	0.22–0.3	Turkey	0.030
Flounder	0.48	Cereals, rice, pasta	0.00

Grouper	0.23	Fruit	0.00
Mahi mahi	0.13	Milk, regular	0.00
Orange roughy	0.028	Bread, regular	0.00
Red snapper	0.29	Vegetables	0.00
Shark	0.83		

Table-2: Quantity of Omega-3 Fatty Acids

**KRILL:**

Krill oil is a newly discovered source of omega-3 fatty acids. Various claims are made in support of krill oil as a superior source of omega-3 fatty acids. The effect of krill oil, at a lower dose of EPA + DHA (62.8%), was demonstrated to be similar to that of fish oil.<sup>24</sup>

Flaxseed (or linseed) (*Linum usitatissimum*) and its oil are perhaps the most widely available botanical source of the omega-3 fatty acid ALA. Flaxseed oil consists of approximately 55% ALA, which makes it six times richer than most fish oils in omega-3 fatty acids. A portion of this is converted by the body to EPA and DHA, though this may differ between men and women. 100 g of the leaves of Purslane contains 300–400 mg ALA.<sup>25</sup> ALA content as the percentage of the seed oil.

**EGGS:**

Eggs produced by hens fed a diet of greens and insects contain higher levels of omega-3 fatty acids than those produced by chickens fed corn or soybeans. In addition to feeding chickens insects and greens, fish oils may be added to their diets to increase the omega-3 fatty acid concentrations in eggs. The addition of flax and canola seeds to the diets of chickens, both good sources of alpha-linolenic acid, increases the omega-3 content of the eggs, predominantly DHA. The addition of green algae or seaweed to the diets boosts the content of DHA and EPA content, which are the forms of omega-3 approved by the FDA for medical claims. A common consumer complaint is "Omega-3 eggs can sometimes have a fishy taste if the hens are fed marine oils."<sup>26</sup>

Common name	Alternative name	Linnaean name	% ALA
Kiwifruit		<i>Actinidia deliciosa</i>	63
Perilla	Shiso	<i>Perilla frutescens</i>	61
Chia seed	chia sage	<i>Salvia hispanica</i>	58
Flax	Linseed	<i>Linum usitatissimum</i>	53-59
Lingonberry	Cowberry	<i>Vaccinium vitis-idaea</i>	49
Camelina	Gold-of-pleasure	<i>Camelina sativa</i>	36
Purslane	Portulaca	<i>Portulaca oleracea</i>	35
Black raspberry		<i>Rubus occidentalis</i>	33
Hemp		<i>Cannabis sativa</i>	19
Canola			9 – 11

Table-3: ALA Contents in Seed Oils

ALA content as the percentage of the whole food.

Common name	Linnaean name	% ALA
Flaxseed	<i>Linum usitatissimum</i>	18.1
Butternuts	<i>Juglans cinerea</i>	8.7
Hempseed	<i>Cannabis sativa</i>	8.7
Persian walnuts	<i>Juglans regia</i>	6.3
Pecan nuts	<i>Carya illinoensis</i>	0.6
Hazel nuts	<i>Corylus avellana</i>	0.1

Table-4: ALA Contents in Whole Grain

#### MEAT:

Omega 3 fatty acids are formed in the chloroplasts of green leaves and algae. While seaweeds and algae are the source of omega 3 fatty acids present in fish, grass is the source of omega 3 fatty acids present in grass fed animals. When cattle are taken off omega 3 fatty acid rich grass and shipped to a feedlot to be fattened on omega 3 fatty acid deficient grain, they begin losing their store of this beneficial fat. Each day that an animal spends in the feedlot, the amount of omega 3 fatty acids in its meat is diminished. The omega-6 to omega-3 ratio of grass-fed beef is about 2:1, making it a more useful source of omega-3 than grain-fed beef, which usually has a ratio of 4:1. The researchers found that grass-fed beef is higher in moisture content, 42.5% lower total lipid content, 54% lower in total fatty acids, 54% higher in beta-carotene, 288% higher in vitamin E (alpha-tocopherol), higher in the B-vitamins thiamin and riboflavin, higher in the minerals calcium, magnesium, and potassium, 193% higher in total omega-3s, 117% higher in CLA (cis-9 trans-11, which is a potential cancer fighter), 90% higher in vaccenic acid (which can be transformed into CLA), lower in the saturated fats linked with heart disease, and has a healthier ratio of omega-6 to omega-3 fatty acids (1.65 vs 4.84). Protein and cholesterol content were equal. In most countries, commercially available lamb is typically grass-fed, and thus higher in omega-3 than other grain-fed or grain-finished meat sources. In the United States, lamb is often finished (i.e., fattened before slaughter) with grain, resulting in lower omega-3. The omega-3 content of chicken meat may be enhanced by increasing the animals' dietary intake of grains high in omega-3, such as flax, chia, and canola. Kangaroo meat is also a source of omega-3, with fillet and steak containing 74 mg per 100 g of raw meat.<sup>27</sup>

#### MAMMALIAN BRAINS AND EYES:

The brains and eyes of mammals are extremely rich in DHA as well as other omega-3 fatty acids. DHA is a major structural component of the mammalian brain, and is in fact the most abundant omega-3 fatty acid in the brain.

#### SEAL OIL:

Seal oil is a source of EPA, DPA, and DHA. According to Health Canada, it helps to support the development of the brain, eyes and nerves in children up to 12 years of age. However, like all seal products, it is not allowed for import into the European Union.

#### OTHER SOURCES:

The microalgae *Cryptocodinium cohnii* and *Schizochytrium* are rich sources of DHA, but not EPA, and

brown algae (kelp) is a source of EPA. In 2006 the Journal of Dairy Science published a study entitled, "The Linear Relationship between the Proportion of Fresh Grass in the Cow Diet, Milk Fatty Acid Composition, and Butter Properties". The study found that butter made from the milk of grass fed cows contains substantially more CLA, vitamin E, beta-carotene, and omega-3 fatty acids than butter made from the milk of cows raised in factory farms or that have limited access to pasture. It was also found that the more fresh pasture in the cow's diet, the softer the butter.<sup>28</sup>

#### OMEGA-5 FATTY ACID:

A unique essential fatty acid obtained from the seed of the pomegranate, Omega-5 is the only known botanical form of Conjugated Linolenic Acid (CLnA), also known as Punicic Acid, and one of the most potent antioxidants known to modern science. It is an 18-carbon fatty acid possessing three double bonds, with the first double bond located between the fifth and sixth carbons. While chemically similar to Conjugated Linoleic Acid (CLA), the Omega-5 molecule is extremely unique in that it has three double bonds instead of two. Officially, its name is 9cis, 11trans, 13cis-conjugated linolenic acid.<sup>29</sup>

#### DEFINING THE OMEGA-5 MOLECULE:

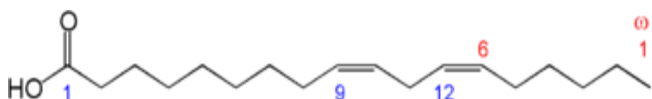
Over the last decade, universities and scientific institutions have released a wealth of research on Omega oils, so when Pomeg5 founder Tzeira Sofer first observed pomegranate seed oil's healing power several years ago, she was certain that it was due to the presence of these fatty acids. She presented the oil to medical professionals and essential fatty acid experts from around the world, including the late Dr. Zakir Ramazanov, a biochemist who had devoted much of his life to researching the benefits of unique ingredients like pomegranate seed oil. To their surprise, the extensive analysis revealed that pomegranate seed oil was not Omega 3, 6, or 9, but an Omega-5 fatty acid with a highly unusual conjugated molecular structure.<sup>30</sup>

#### THE HEALTH BENEFITS:

Omega-5 is a very powerful antioxidant, at least six times more potent than grape seed extract. It is a high-energy molecule that interferes with the production of inflammatory prostaglandins and leukotrienes that cause disease. It also blocks the conversion of diacylglycerol to arachidonic acid, mimicking the behavior of non-steroidal anti-inflammatory drugs like aspirin, but without the side effects. As a Conjugated Linolenic Acid (CLnA), Omega-5 helps repair damaged cells, and also controls and regulates glucose transport at the cell membrane level, making it particularly useful for individuals with insulin sensitivity.

It has a significant effect on the human electromagnetic field, increasing it by as much as tenfold (40-50 feet).

#### OMEGA-6 FATTY ACID:



The chemical structure of linoleic acid, a common omega-6 fatty acid found in many nuts and vegetable oils.<sup>31</sup>

**Omega-6 fatty acids** (also referred to as  $\omega$ -6 fatty acids or *n*-6 fatty acids) are a family of unsaturated fatty acids that have in common a final carbon-carbon double bond in the *n*-6 position, that is, the sixth bond, counting from the methyl end. The biological effects of the omega-6 fatty acids are largely mediated by their conversion to omega-6 eicosanoids that bind to diverse receptors found in every tissue of the body. The conversion of tissue arachidonic acid (20:4n-6) to omega-6 prostaglandin and omega-6 leukotriene hormones provides many targets for pharmaceutical drug development and treatment to diminish excessive omega-6 actions in atherosclerosis, asthma, arthritis, vascular disease, thrombosis, immune-inflammatory processes, and tumor proliferation. Competitive interactions with the omega-3 fatty acids affect the relative storage, mobilization, conversion and action of the omega-3 and omega-6 eicosanoid precursors.<sup>32</sup>

#### OMEGA-6 FATTY ACIDS:

Linoleic acid (18:2, *n*-6), the shortest-chained omega-6 fatty acid, is an essential fatty acid. Arachidonic acid (20:4) is a physiologically significant omega-6 fatty acid and is the precursor for prostaglandins and other physiologically active molecules.<sup>33</sup>

#### SUGGESTED NEGATIVE HEALTH EFFECTS:

Some medical research suggests that excessive levels of certain omega-6 fatty acids relative to certain omega-3 fatty acids may increase the probability of a number of diseases. However, scientific research indicates that air pollution, smoking, second-hand smoke, and other exogenous toxins in conjunction with the excessive intake of *n*-6 fatty acids leads to inflammation and the overexpression of the COX-2 enzyme, and not solely the excessive intake of *n*-6 fatty acids.<sup>34</sup> Modern Western diets typically have ratios of omega-6 to omega-3 in excess of 10 to 1, some as high as 30 to 1; the average ratio of omega-6 to omega-3 in the Western diet is 15/1-16.7/1. Humans are thought to have evolved with a diet of a 1-to-1 ratio of omega-6 to omega-3 and the optimal ratio is thought to be 4 to 1 or lower and it is even better if there is more omega-

3 than omega-6 (especially healthy ratio of omega-6 to omega-3 is from 1:1 to 1:4). A ratio of 2-3/1 omega-6 to omega-3 helped reduce inflammation in patients with rheumatoid arthritis. A ratio of 5/1 had a beneficial effect on patients with asthma but a 10/1 ratio had a negative effect. A ratio of 2.5/1 reduced rectal cell proliferation in patients with colorectal cancer, whereas a ratio of 4/1 had no effect. Excess omega-6 fats interfere with the health benefits of omega-3 fats, in part because they compete for the same rate-limiting enzymes. A high proportion of omega-6 to omega-3 fat in the diet shifts the physiological state in the tissues toward the pathogenesis of many diseases: prothrombotic, proinflammatory and proconstrictive. Chronic excessive production of omega-6 eicosanoids is associated with arthritis, inflammation, and cancer. Many of the medications used to treat and manage these conditions work by blocking the effects of the potent omega-6 fat, arachidonic acid. Many steps in formation and action of omega-6 hormones from omega-6 arachidonic acid proceed more vigorously than the corresponding competitive steps in formation and action of omega-3 hormones from omega-3 eicosapentaenoic acid. The COX-1 and COX-2 inhibitor medications, used to treat inflammation and pain, work by preventing the COX enzymes from turning arachidonic acid into inflammatory compounds. The LOX inhibitor medications often used to treat asthma, work by preventing the LOX enzyme from converting arachidonic acid into the leukotrienes. Many of the anti-mania medications used to treat bipolar disorder work by targeting the arachidonic acid cascade in the brain. A high consumption of omega-6 polyunsaturated fatty acids (PUFAs), which are found in most types of vegetable oil, may increase the likelihood that postmenopausal women will develop breast cancer.<sup>35</sup>

#### DIETARY LINOLEIC ACID REQUIREMENT:

Adding more controversy to the omega-6 fat issue is that the dietary requirement for linoleic acid (the key omega-6 fatty acid), has been seriously questioned, because of a significant methodology error discovered by University of Toronto scientist Stephen Cunnane. Cunnane discovered that the seminal research used to determine the dietary requirement for linoleic acid was based on feeding animals linoleic acid-deficient diets, which were simultaneously deficient in omega-3 fats. The omega-3 deficiency was not taken into account. The omega-6 oils added back systematically to correct the deficiency also contained trace amounts of omega-3 fats. Therefore the researchers were inadvertently correcting the omega-3 deficiency as well. Ultimately, it took more oil to correct both deficiencies. According to Cunnane, this error overestimates linoleic acid requirements by 5 to 15 times.<sup>36</sup>

**DIETARY SOURCES:**

The evening primrose flower (*O. biennis*) produces an oil containing a high content of gamma-linolenic acid, a type of omega-6 fatty acid. Four major food oils (palm, soybeans, rapeseed, and sunflower) provide more than 100 million metric tons annually, providing more than 32 million metric tons of omega-6 linoleic acid and 4 million metric tons of omega-3 alpha-linolenic acid.<sup>37</sup>

Dietary sources of omega-6 fatty acids include: poultry, eggs, avocado, nuts, cereals, durum wheat, whole-grain breads, most vegetable oils, evening primrose oil, borage oil, blackcurrant seed oil, flax/linseed oil, rapeseed or canola oil, hemp oil, soybean oil, cottonseed oil, sunflower seed oil, corn oil, safflower oil, pumpkin seeds, acai berry, cashews, pecans, pine nuts, walnuts, spirulina, coconut.<sup>38</sup>

**LIST OF OMEGA-6 FATTY ACIDS:**

Common name	Lipid name	Chemical name
Linoleic acid (LA)	18:2 (n-6)	<i>all-cis</i> -9,12-octadecadienoic acid
Gamma-linolenic acid (GLA)	18:3 (n-6)	<i>all-cis</i> -6,9,12-octadecatrienoic acid
Calendic acid	18:3 (n-6)	8E,10E,12Z-octadecatrienoic acid
Eicosadienoic acid	20:2 (n-6)	<i>all-cis</i> -11,14-eicosadienoic acid
Dihomo-gamma-linolenic acid (DGLA)	20:3 (n-6)	<i>all-cis</i> -8,11,14-eicosatrienoic acid
Arachidonic acid (AA)	20:4 (n-6)	<i>all-cis</i> -5,8,11,14-eicosatetraenoic acid
Docosadienoic acid	22:2 (n-6)	<i>all-cis</i> -13,16-docosadienoic acid
Adrenic acid	22:4 (n-6)	<i>all-cis</i> -7,10,13,16-docosatetraenoic acid
Docosapentaenoic acid	22:5 (n-6)	<i>all-cis</i> -4,7,10,13,16-docosapentaenoic acid
Tetracosatetraenoic acid	24:4 (n-6)	<i>all-cis</i> -9,12,15,18-tetracosatetraenoic acid
Tetracosapentaenoic acid	24:5 (n-6)	<i>all-cis</i> -6,9,12,15,18-tetracosapentaenoic acid

Table-5: Omega-6 Fatty Acids

**OMEGA-7 FATTY ACIDS:**

These are a class of unsaturated fatty acids in which the site of unsaturation is seven carbon atoms from the end of the carbon chain. The two most common omega-7 fatty acids in nature are palmitoleic acid and

vaccenic acid. Rich sources include macadamia nut oil and sea buckthorn oil. The monounsaturated omega-7 fatty acids have the general chemical structure  $CH_3-(CH_2)_5-CH=CH-(CH_2)_n-CO_2H$ .<sup>39</sup>

Common name	Lipid name	Chemical name
None	12:1 (n-7)	5-Dodecenoic acid
None	14:1 (n-7)	7-Tetradecenoic acid
Palmitoleic acid	16:1 (n-7)	9-Hexadecenoic acid
Vaccenic acid	18:1 (n-7)	11-Octadecenoic acid
Paullinic acid	20:1 (n-7)	13-Eicosenoic acid
None	22:1 (n-7)	15-Docosenoic acid
None	24:1 (n-7)	17-Tetracosenoic acid

Table-6: Omega-7 Fatty Acids

**OMEGA-9 FATTY ACID:**

Omega-9 fatty acids ( $\omega$ -9 fatty acids or *n*-9 fatty acids) are a family of unsaturated fatty acids which have in common a final carbon-carbon double bond in the omega-

9 position; that is, the ninth bond from the methyl end of the fatty acid.<sup>40</sup>

Background: Some omega-9 fatty acids are common components of animal fat and vegetable oil. Two omega-9 fatty acids important in industry are:

- Oleic acid (18:1, *n*-9), which is a main component of olive oil, macadamia oil and other monounsaturated fats
- Erucic acid (22:1, *n*-9), which is found in rapeseed, wallflower seed, and mustard seed. Rapeseed with high erucic acid content is grown for commercial use in paintings and coatings as a drying oil. Canola oil comes from a cultivar of the rapeseed plant that has been bred, or in some cases genetically modified, to contain very little erucic acid.<sup>41</sup>

Unlike omega-3 fatty acids and omega-6 fatty acid, omega-9 fatty acids are not classed as essential fatty acids (EFA). This is both because they can be created by the human body from unsaturated fat, and are therefore not essential in the diet, and because the lack of an omega-6 double bond keeps them from participating in the reactions that form the eicosanoids. Under severe conditions of EFA deprivation, mammals will elongate and desaturate oleic acid to make mead acid, (20:3, *n*-9). This has been documented to a lesser extent in one study following vegans, vegetarians and semi-vegetarians who followed unbalanced diets.<sup>42</sup>

**OMEGA-9 FATTY ACIDS:**

oleic acid	18:1 ( <i>n</i> -9)	9-octadecenoic acid
elaidic acid	18:1 ( <i>n</i> -9)	( <i>E</i> )-octadec-9-enoic acid
gondoic acid	20:1 ( <i>n</i> -9)	11-eicosenoic acid
mead acid	20:3 ( <i>n</i> -9)	5,8,11-eicosatrienoic acid
erucic acid	22:1 ( <i>n</i> -9)	13-docosenoic acid
nervonic acid	24:1 ( <i>n</i> -9)	15-tetracosenoic acid

Table-7: Omega-9 Fatty Acids

**CONCLUSION:**

Several sources of information suggest that human beings evolved on a diet with a ratio of omega-6 to omega-3 essential fatty acids (EFA) of ~ 1 whereas in Western diets the ratio is 15/1–16.7/1. Western diets are deficient in omega-3 fatty acids, and have excessive amounts of omega-6 fatty acids compared with the diet on which human beings evolved and their genetic patterns were established. Excessive amounts of omega-6 polyunsaturated fatty acids (PUFA) and a very high omega-6/omega-3 ratio, as is found in today’s Western diets, promote the pathogenesis of many diseases, including cardiovascular disease, cancer, and inflammatory and autoimmune diseases, whereas increased levels of omega-3 PUFA (a low omega-6/omega-3 ratio) exert suppressive effects. In the secondary prevention of cardiovascular disease, a ratio of 4/1 was associated with a 70% decrease in total mortality. A ratio of 2.5/1 reduced rectal cell proliferation in patients with colorectal cancer, whereas a ratio of 4/1 with the same amount of omega-3 PUFA had no effect. The lower omega-6/omega-3 ratio in women with breast cancer was associated with decreased risk. A ratio of 2–3/1 suppressed inflammation in patients with rheumatoid arthritis, and a ratio of 5/1 had a beneficial effect on patients with asthma, whereas a ratio of 10/1 had adverse consequences. These studies indicate that the optimal ratio may vary with the disease under

consideration. This is consistent with the fact that chronic diseases are multigenic and multifactorial. Therefore, it is quite possible that the therapeutic dose of omega-3 fatty acids will depend on the degree of severity of disease resulting from the genetic predisposition. A lower ratio of omega-6/omega-3 fatty acids is more desirable in reducing the risk of many of the chronic diseases of high prevalence in Western societies, as well as in the developing countries, that are being exported to the rest of the world.

**REFERENCES:**

1. Freemantle, E.; Vandal, M. N.; Tremblay-Mercier, J.; Tremblay, S. B.; Blachère, J. C.; Bégin, M. E.; Thomas Brenna, J.; Windust, A. *et al.* (2006). "Omega-3 fatty acids, energy substrates, and brain function during aging". *Prostaglandins, Leukotrienes and Essential Fatty Acids* **75** (3): 213.
2. Chaiyasit, W.; Elias, R. J.; McClements, D. J.; Decker, E. A. (2007). "Role of Physical Structures in Bulk Oils on Lipid Oxidation". *Critical Reviews in Food Science and Nutrition* **47** (3): 299–317.
3. Evangelos C. Rizos, MD, PhD; Evangelia E. Ntzani, MD, PhD; Eftychia Bika, MD; Michael S. Kostapanos, MD; Moses S. Elisaf, (2012). "Association Between Omega-3 Fatty Acid Supplementation and Risk of Major

- Cardiovascular Disease Events A Systematic Review and Meta-analysis". *JAMA* **308** (10): 1024–1033.
4. Sala-Vila, A; Calder, PC (2011). "Update on the relationship of fish intake with prostate, breast, and colorectal cancers." *Critical reviews in food science and nutrition* **51** (9): 855–71.
  5. MacLean, CH; Newberry, SJ; Mojica, WA; Khanna, P; Issa, AM; Suttrop, MJ; Lim, YW; Traina, SB; Hilton, L; Garland, R; Morton, SC (2006). "Effects of omega-3 fatty acids on cancer risk: a systematic review." *JAMA: the Journal of the American Medical Association* **295** (4): 403–15.
  6. MacLean, Catherine H. et al. (2006). "Effects of n-3 Fatty Acids on Cancer Risk". *JAMA* **295** (4): 403–415.
  7. Lee Hooper et al. (2006). "Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review". *BMJ* **332** (7544): 752–760.
  8. Colomer R, Moreno-Nogueira JM, García-Luna PP et al. (2007). "N-3 fatty acids, cancer and cachexia: a systematic review of the literature". *Br. J. Nutr.* **97** (5): 823–31.
  9. Kwak, SM; Myung, SK; Lee, YJ; Seo, HG; for the Korean Meta-analysis Study, Group (2012). "Efficacy of Omega-3 Fatty Acid Supplements (Eicosapentaenoic Acid and Docosahexaenoic Acid) in the Secondary Prevention of Cardiovascular Disease: A Meta-analysis of Randomized, Double-blind, Placebo-Controlled Trials". *Archives of Internal Medicine* **172** (9): 686–94.
  10. Kotwal, Sradha; David Sullivan, Vlado Perkovic, Bruce Neal (2008). "Omega 3 Fatty Acids and Cardiovascular Outcomes: Systematic Review and Meta-Analysis". *Circ Cardiovasc Qual Outcomes* **5** (6): 808–18.
  11. Delgado-Lista, J; Perez-Martinez, P; Lopez-Miranda, J; Perez-Jimenez, F (2012). "Long chain omega-3 fatty acids and cardiovascular disease: a systematic review". *The British journal of nutrition*. 107 Suppl 2: S201–13.
  12. Appel LF, Miller ER, Sidler AJ, Whelton PK (1993). "Does supplementation of diet with 'fish oil' reduce blood pressure? A meta-analysis of controlled clinical trials". *Archives of Internal Medicine* **153** (12): 1429–1438.
  13. von Schacky C. (2003). "The role of omega-3 fatty acids in cardiovascular disease". *Curr. Atheroscler. Rep.* **5** (2): 139–45.
  14. Morris, Martha C.; Sacks, Frank; Rosner, Bernard (1993). "Does fish oil lower blood pressure? A meta-analysis of controlled trials". *Circulation* **88** (2): 523–533.
  15. Mori, Trevor A.; Bao, Danny Q.; Burke, Valerie; Puddey, Ian B.; Beilin, Lawrence J. (1993). "Docosahexaenoic acid but not eicosapentaenoic acid lowers ambulatory blood pressure and heart rate in humans". *Hypertension* **34** (2): 253–260.
  16. Garton, G. A. (1960). "Fatty Acid Composition of the Lipids of Pasture Grasses". *Nature* **187** (4736): 511.
  17. Duckett, S. K., D. G. Wagner, et al. (1993). "Effects of time on feed on beef nutrient composition". *J Anim Sci* **71** (8): 2079–2088.
  18. Azcona, J.O., Schang, M.J., Garcia, P.T., Gallinger, C., R. Ayerza (h), and Coates, W. (2008). "Omega-3 enriched broiler meat: The influence of dietary alpha-linolenic omega-3 fatty acid sources on growth, performance and meat fatty acid composition". *Canadian Journal of Animal Science* **88** (2): 257–269.
  19. Vincent JT van Ginneken, Johannes PFG Helsper, Willem de Visser, Herman van Keulen and Willem A Brandenburg (2011). "Polyunsaturated fatty acids in various macroalgal species from north Atlantic and tropical seas". *Lipids in Health and Disease* **10** (104): 104.
  20. Couvreur, S.; Hurtaud, C.; Lopez, C.; Delaby, L.; Peyraud, J.-L. (2006). "The Linear Relationship Between the Proportion of Fresh Grass in the Cow Diet, Milk Fatty Acid Composition, and Butter Properties". *Journal of Dairy Science* **89** (6): 1956–69.
  21. Simopoulos, A. P. (2002). "Polyunsaturated fatty acids in biology and diseases. The importance of the ratio of omega-6/omega-3 essential fatty acids". *Biomedecine & Pharmacotherapy* **56** (8): 365–379.
  22. Lands, William E.M. (2005). "Dietary fat and health: the evidence and the politics of prevention: careful use of dietary fats can improve life and prevent disease". *Annals of the New York Academy of Sciences* (Blackwell) **1055**: 179–192.
  23. Hibbeln, Joseph R.; Nieminen, Levi R.G.; Blasbalg, Tanya L.; Riggs, Jessica A.; Lands, William E. M. (2006). "Healthy intakes of n-3 and n-6 fatty acids: estimations considering worldwide diversity". *American Journal of Clinical Nutrition* (American Society for Nutrition) **83** (6, supplement): 1483S–1493S.
  24. Okuyama, Hirohmi; Ichikawa, Yuko; Sun, Yueji; Hamazaki, Tomohito; Lands, William E. M. (2007). "ω3 fatty acids effectively prevent coronary heart disease and other late-onset diseases: the excessive linoleic acid syndrome". *World Review of Nutritional Dietetics. World Review of Nutrition and Dietetics* (Karger) **96** (Prevention of Coronary Heart Disease): 83–103.
  25. Viswanathan Natarajan, Yutong Zhao (2009). "Regulation of COX-2 Expression and IL-6 Release by Particulate Matter in Airway Epithelial Cells". *Am. J. Respir. Cell Mol. Biol.* **40**: 19–30.

26. Swenberg JA, Calderón-Garcidueñas L (2004). "Brain inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution." *Toxicol Pathol* **32**: 650–658.
27. Andrew J. Dannenberg, Dimitrios Moraitis (2005). "Levels of Cyclooxygenase-2 Are Increased in the Oral Mucosa of Smokers: Evidence for the Role of Epidermal Growth Factor Receptor and Its Ligands". *Cancer Res* **65**: 664–670.
28. Hsiao LD, Yang CM (2009). "Cigarette smoke extract induces COX-2 expression via a PKC $\alpha$ /c-Src/EGFR, PDGFR/PI3K/Akt/NF- $\kappa$ B pathway and p300 in tracheal smooth muscle cells." *Am J Physiol Lung Cell Mol Physiol* **297**: 892–902.
29. Patricia J. Sime, Christine A. Martey (2004). "Cigarette smoke induces cyclooxygenase-2 and microsomal prostaglandin E2 synthase in human lung fibroblasts: implications for lung inflammation and cancer". *AJP - Lung Physiol* **287**: 981–991.
30. Simopoulos, Artemis P. (2003). "Importance of the ratio of omega-6/omega-3 essential fatty acids: evolutionary aspects". *World Review of Nutrition and Dietetics*. World Review of Nutrition and Dietetics (Karger) **92** (Omega-6/Omega-3 Essential Fatty Acid Ratio: The Scientific Evidence): 1–174.
31. Smith, William L. (2008). "Nutritionally essential fatty acids and biologically indispensable cyclooxygenases". *Trends in Biochemical Sciences* (Elsevier) **33** (1): 27–37.
32. Wada, M.; Delong, CJ; Hong, YH; Rieke, CJ; Song, I; Sidhu, RS; Yuan, C; Warnock, M et al. (2007). "Enzymes and receptors of prostaglandin pathways with arachidonic acid-derived versus eicosapentaenoic acid-derived substrates and products. Nutritionally essential fatty acids and biologically indispensable cyclooxygenases". *J. Biol. Chem. (ASBMB)* **282** (31): 22254–22266.
33. Cleland, Leslie G.; James, Michael J.; Proudman, Susanna M. (2006). "Fish oil: what the prescriber needs to know". *Arthritis Research & Therapy* (BioMed Central) **8** (1): 202.
34. Mickleborough, Timothy D. (2005). "Dietary omega-3 polyunsaturated fatty acid supplementation and airway hyperresponsiveness in asthma". *The Journal of Asthma* (Informa Healthcare) **42** (5): 305–314.
35. Broughton, K. Shane; Johnson, Cody S.; Pace, Bobin K.; Liebman, Michael; Kleppinger, Kent M. (2005). "Reduced asthma symptoms with n-3 fatty acid ingestion are related to 5-series leukotriene production". *American Journal of Clinical Nutrition* (American Society for Nutrition) **65** (4): 1011–1017.
36. Lee, H.J.; Rao, J.S.; Rapoport, S.I.; Bazinet, R.P. (2007). "Antimanic therapies target brain arachidonic acid signaling: lessons learned about the regulation of brain fatty acid metabolism". *Prostaglandins, Leukotrienes and Essential Fatty Acids* (Elsevier) **77** (5): 239–246.
37. Sonestedt, Emily; Ericson, Ulrika; Gullberg, Bo; Skog, Kerstin; Olsson, Håkan; Wirfält, Elisabet (2008). "Do both heterocyclic amines and omega-6 polyunsaturated fatty acids contribute to the incidence of breast cancer in postmenopausal women of the Malmö diet and cancer cohort?". *The International Journal of Cancer* (UICC International Union Against Cancer) **123** (7): 1637–1643.
38. Yong Q. Chen, et al. (2007). "Modulation of prostate cancer genetic risk by omega-3 and omega-6 fatty acids". *The Journal of Clinical Investigation* **117** (7): 1866–1875.
39. Pala, Valeria; Krogh, Vittorio; Muti, Paola; Chajès, Véronique; Riboli, Elio; Micheli, Andrea; Saadatian, Mitra; Sieri, Sabina et al. (2001). "Erythrocyte Membrane Fatty Acids and Subsequent Breast Cancer: a Prospective Italian Study". *JNCL* **93** (14): 1088–95.
40. Cunnane, Stephen C. (2003). "Problems with essential fatty acids: time for a new paradigm?". *Progress in Lipid Research* **42** (6): 544–568.
41. Mukherjee, Kumar D.; Kiewitt, Irmgard (1980). "Formation of (n-9) and (n-7) cis-monounsaturated fatty acids in seeds of higher plants". *Planta* **149** (5): 461–463.
42. Phinney SD, Odin RS, Johnson SB, Holman RT (1990). "Reduced arachidonate in serum phospholipids and cholesteryl esters associated with vegetarian diets in humans". *Am. J. Clin. Nutr.* **51** (3): 385–92.