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Review Article

ROLE OF *ω-3* POLYUNSATURATED FATTY ACIDS IN INFLAMMATION AND RHEUMATOID ARTHRITIS DISORDERS

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Abstract

Reviewing the relationships between polyunsaturated FAs (PUFAs) with inflammation and rheumatoid arthritis disorders, the PUFAs containing ω-3, ω-6 and ω-9, these ω-3FAs levels were correlated with ω-6: ω-3 ratios including arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Based on previously-reports, the levels of ω-3 FAs considered being as a 'lower risk' category for inflammation and rheumatoid arthritis. Certain PUFAs ratios may aid in inflammation and rheumatoid arthritis-related risk assessment. PUFA are the most effective for the production of oil with high concentration of DHA and EPA content significantly.

Key words: Inflammatory diseases, rheumatoid arthritis, polyunsaturated fatty acids.

Introduction

Polyunsaturated fatty acids (PUFAs), α-linolenic acid (ALA) is an essential ω-3 FAs (ω-3FAs) which are important in human nutrition. Other acids such as α-linolenic acid (18:3, *ω-3*; ALA), eicosapentaenoic acid (20:5, *ω-3*; EPA), and docosahexaenoic acid (22:6, *ω-3*; DHA) are also important for human nutrition. Mostly naturally-produced FAs are in *cis*-configuration where they are more easily transformable. The *trans*-configuration results in much more stable chains those are very difficult to further break or transform, forming longer chains that aggregate in tissues and lacking the necessary hydrophilic properties. However, *ω-3* compounds are still more fragile than *ω-6* because the last double bond is geometrically and electrically more exposed, notably in the natural *cis* configuration. A number of dietary factors have irritant or immunological effects in the gut, which allow an anti-inflammatory effect. There are also factors that can be enriched in the diet to achieve anti-inflammatory effects, such as ω-3-PUFAs. The ethylesterized ω-3-FAs, such as E-EPA and combinations of E-EPA and E-DHA, have drawn attention as more effective products than the traditional ones. The health benefits of ω-3PFAs (DHA and EPA) are the best known. The high level of ω-3FAs in diet may reduce triglycerides, heart rate, blood pressure, and atherosclerosis. The health claim status to EPA and DHA, stating that consumption of EPA and DHA ω-3FAs may reduce the risk of coronary heart disease (US FDA. 2004). It also has recognized the importance of DHA ω-3FAs, helps the normal development of the brain, eyes and nerves. PUFAs have also been reported as other health benefits. ω-3FAs have been known as essential to normal growth and health, awareness of their health benefits (Holman, 1998)

Table 1: *ω-3* content as the percentage of ALA in the seed oil.

S.No.	Common name	Alternative name	Linnaean name	% *ω-3*
1	Chia	chia sage	*Salvia hispanica*	64
2	Kiwifruit	Chinese gooseberry	*Actinidia chinensis*	62
3	Perilla	Shiso	*Perilla frutescens*	58
4	Flax	linseed	*Linum usitatissimum*	55
5	Lingonberry	Cowberry	*Vaccinium vitis-idaea*	49
6	Camelina	Gold-of-pleasure	*Camelina sativa*	36
7	Purslane	Portulaca	*Portulaca oleracea*	35
8	Black Raspberry		*Rubus occidentalis*	33

Table 2: *ω-3* content as the percentage of ALA in the whole food.

S. No.	Common name	Linnaean name	% *ω-3*
1	Flaxseed	*Linum usitatissimum*	18.1
2	Butternuts	*Juglans cinerea*	8.7
3	Hempseed	*Cannabis sativa*	8.7
4	Walnuts	*Juglans regia*	6.3
5	Pecan nuts	*Carya illinoinensis*	0.6
6	Hazel nuts	*Corylus avellana*	0.1

An intense interest in the health benefits of ω3-PUFAs, their active component, cis-EPA and cis-DHA. Both EPA and DHA have several benefits on cardiovascular disorders, autoimmune, inflammatory diseases and cancer. The beneficial effects of ω3 PUFA are attributed to eicosanoid synthesis such as prostaglandins (PGs), thromboxanes (TXs) and leukotrienes (LTs). The importance of these FAs to infant nutrition is particularly relevant because DHA is important for fetal and term-infant neural development. Although PUFA can be synthesized in the body by elongation and desaturation of ALA, ingestion of the preformed molecules usually is more effective. Lipases are known to have little reactivity on PUFA (e.g., γ-linolenic acid, AA, EPA and DHA), and these acids can be enriched by selective hydrolysis, direct esterification of glycerol with EPA and DHA, and interesterification (Bastos & de Oliveira, 2002).

Biological sources of PUFAs

Flax seeds produce linseed oil, which has very high *ω-3* content. Six times richer than most fish oils in *ω-3*, flax (or linseed) (*Linum usitatissimum*) and its oil are perhaps the most widely available botanical source of *ω-3*. Flaxseed oil consists of approximately 55% ALA (α-linolenic acid). Flax, like chia, contains approximately three times as much *ω-3* as *ω-6*. 15 grams of flaxseed oil provides ca. 8 grams of ALA, which is converted in the body to EPA and then DHA at an efficiency of 5–10% and 2–5%, respectively. The most widely available 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 *ω-3* as *ω-6*. Other oily fish such as tuna also contain *ω-3* in somewhat lesser amounts. Consumers of oily fish should be aware of the potential presence of heavy metals and fat-soluble pollutants which may accumulate up the food chain. Although fish is a dietary source of *ω-3* FAs, fish do not synthesize them; they obtain them from the algae or plankton in their diet (DeFilippis, and Laurence, 2007). Cold water fish are the highest source of ω-3 FAs. Other foods contain these FAs as well, however, in smaller amounts. The recommendations are to have 7 to 11 grams of ω-3 FAs each week. Milk and cheese may also be good sources of *ω-3*. One study showed that half a pint of milk provides 10% of the recommended daily intake (RDI) of ALA, while a piece of organic cheese the size of a matchbox may provide up to 88%. The microalgae *Crypthecodinium cohnii* and *Schizochytrium* are rich sources of DHA (22:6 *ω-3*) and can be produced commercially in bioreactors. This is the only source of DHA acceptable to vegans. Oil from brown algae is a source of EPA. Walnuts are one of few nuts that contain appreciable *ω-3* fat, with approximately a 1:4 ratio of *ω-3* to *ω-6*. Acai palm fruit also contains *ω-3* FAs. It is also found in combination with ω-6, ω-9 and shark liver oil. Some vegetables contains noteworthy amount of *ω-3*, including strawberries and broccoli (Okuyama, 2001; Griffin, 2008).

The fatty acid (FA) composition of serum (or plasma) phospholipid has become established as a valid biochemical marker for assessing the physiological status of various FAs including predictive correlations with the dietary intakes of fish-derived ω-3 FAs including EPA (20:5 ω-3) and DHA (22:6 ω-3) (Hjartaker *et al.*,1997; Kobayashi *et al.*, 2001). Population studies have shown an inverse relation between total ω-3 FAs in blood serum phospholipid and the risk for coronary heart disease with percentages of total ω-3 ≥ 7.2 being associated with a 31% lower risk (Grimble *et al.*, 2002; Curtis *et al.*, 2000). Furthermore, DHA levels (as percent of total FAs in serum phospholipid) of ≥ 4.5 have been associated with a 34% lower risk for coronary heart disease (Simon *et al.*, 1995; Holub and Holub. 2004). With respect to the risk of fatal ischemic heart disease, EPA+DHA (summed) levels amounting to at least 4.6% of total FAs in the serum phospholipid were associated with a 70% lower risk as compared to those with much lower levels of these FAs (Holub and Holub. 2004; Lemaitre *et al.*, 2003). Since the ω-6 FA, AA (20:4 n-6), found in abundance in various cells and tissues including serum phospholipid can be readily converted into pro-inflammatory eicosanoids and other products associated with inflammatory processes and chronic disorders in contrast to EPA (Cleland *et al., 2005*), the AA: EPA ratio in serum phospholipid has been studied in relation to the risk of chronic disorders. These studies have, as an example, indicated that the AA/EPA ratio in serum (or plasma) phospholipid correlates positively with clinical symptoms of depression; furthermore, higher ratios of AA: DHA were associated with greater neuroticism. Others have implicated the abundance of the summed ω-6 relative to the ω-3 FAs in human plasma phospholipid with respect to chronic disorders (Trebunová, *et al.*, 2007; Holub, *et al.*, 2009).

Complete FA profiles of their serum phospholipid, the following were of interest:

- to determine the relationship between the percentage of total FAs in serum phospholipid as total ω-3, DHA, and (EPA+ DHA)-risk factors for coronary heart disease and fatal ischemic heart disease (plus other chronic disorders) to the various ratios (ω-6:ω-3, AA:EPA, AA:DHA, and AA:(EPA+DHA);
- to compare the relative strengths of these correlations (fatty acid percentages with ratios);
- to determine the corresponding cut-points (95 percentile) for the (ω-6:ω-3), AA:EPA, AA:DHA, and AA:(EPA+DHA) ratios which are associated with a 95% likelihood of the percentage of total FAs in serum phospholipid as ω-3, DHA, and EPA+DHA being in the aforementioned 'lower-risk' category (Simon *et al.,* 1995; Holub and Holub. 2004; Lemaitre *et al.,* 2003).

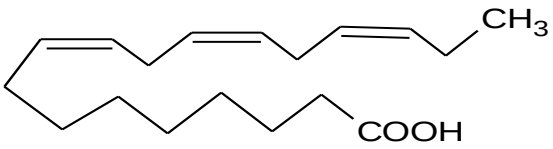
With regard to anti-inflammatory effects of diet away from the gut, altering the balance of dietary PUFA in favour of *ω-3* PUFA provides the best documented examples of effective dietary intervention. PUFA are essential macronutrients of which there are two non-interchangeable classes, *n*-6 and *ω-3*. These FAs are metabolized to mediators that regulate cardiovascular homeostasis and inflammation. *n*-6 rich diets tend to be pro-inflammatory and, by comparison diets rich in *ω-3* PUFA are antiinflammatory. The difference is explained by the action of *ω-3* PUFA as competitive inhibitors of enzymes that metabolize *n*-6 fats and by the lesser biological activities of most *ω-3* mediators, compared with their *n*-6 counterparts. Fish oils are a particularly rich source of desirable long chain *ω-3* PUFA. Fish oil has been used with benefit in the treatment of inflammatory diseases of joints and other organs and tissues. A potential collateral benefit is reduced risk for adverse cardiovascular events, which are increased in rheumatoid arthritis (RA). Lack of knowledge amongst physicians of relevant biochemistry, evidence of efficacy, dose response relationships, latency in effect, availability of affordable preparations and tactics for discussing issues efficiently with patients appears to be a barrier to broader clinical use (Cleland *et al., 2005*).

Fish oil is rich in the long chain *ω-3* FAs EPA (20:5 *ω-3*) and DHA (22:5 *ω-3*), which can displace AA (20:4 *ω-6*) from cell membranes. These *ω-3* FAs are also released with AA by phospholipases and act as substrate inhibitors of conversion of AA by COX and the terminal synthases to the pro-inflammatory oxygenated inflammatory mediators known as eicosanoids. EPA is structurally identical to AA with the exception of its additional *ω-3* double bond and can be converted to eicosanoids that resemble *ω-6* eicosanoids but have the additional *ω-3* double bond. This structural difference is sufficient to confer substantial differences in activity between *ω-6* LTB4, a very potent chemo-toxin and leucocyte agonist and *ω-3* LTB5, which is a weak chemotoxin and weak agonist. *ω-3* TXA3 appears to lack the potency of *ω-6* TXA2, which is an aggregator of platelets and vasoconstrictor. *ω-3* prostaglandin E3 (PGE3) seems to have similar oedomogenic activity to *ω-6* PGE2, but very little PGE3 is produced by monocytes either from endogenous or exogenous EPA in vitro. *ω-6* prostacyclin (PGI2) and *ω-3* PGI3 are thought to have similar activities as agents for vascular patency. In addition to these effects on inflammatory eicosanoid synthesis, dietary fish oils have been shown to reduce the production of the inflammatory cytokines IL-1β and TNF-α by monocytes stimulated in vitro. These cytokines are important effector molecules in inflammatory responses and TNF α blocking agents are now used widely to treat rheumatoid disease that has proven refractory to less expensive therapies. In vitro studies have also shown inhibition of release of the metalloproteinases that are implicated in the tissue damage that is the hallmark of RA and other inflammatory diseases (Caughey *et al.,* 1996; Grimble *et al.,* 2002; Curtis *et al.,* 2000).

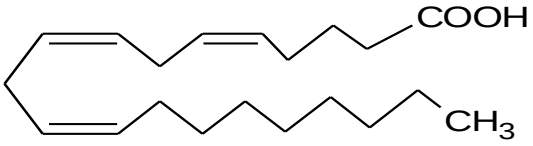
Epidemiological studies, the possibility of an anti-inflammatory effect of dietary long chain *ω-3* FAs (Kromann and Green. 1980). In this regard, they contrast with continental Inuits, for whom meat from grazing animals, such as caribou, contribute to the diet. Thus, extreme case in which the diet is comprised of foods very rich in long chain *ω-3* fats (7-10g/day) and poor in *ω-6* fats. With the introduction of market foods, the *ω-3* dominance of their aboriginal diet has been diluted by Western products with a higher *ω-6* FA content. The very high *ω-3* content of the Greenland Inuit diet needs to be recognized when extrapolating the putative bleeding tendency of the Inuits to the possible risks of fish oil supplements taken against the background of an *ω-6* abundant Western diet. Immunogenetic studies of circumpolar Inuits have shown a high frequency of alleles of human leucocyte antigens (HLA) HLA DRB1 0401 and HLA-B27 that in other populations have been associated with increased risk for a variety of arthritides and other inflammatory conditions (Welinder *et al.,* 2000; Harvald. 1989).

For example, HLA DR B1 0404 is associated with increased risk for and severity of RA. HLA B27 is associated with spondyloarthritis, seronegative arthritis, uveitis and the peripheral arthritis, conjunctivitis and urethritis of Reiter's syndrome. Since these genotypes have been found in a high proportion of Inuits, one can speculate that they may, through strong antigen presentation of certain peptides, provide a selective advantage in relation to defence against particular infections, which may be critical in the context of an anti-inflammatory *ω-3* dominant diet. These same antigen presentation phenotypes may lead to unwanted inflammation and auto-immunity when the diet is rich in pro-inflammatory *ω-6* fats. Epidemiological studies of the Japanese, whose traditional diet contains about 3G long chain *ω-3* fats, equivalent to an anti-inflammatory dose of

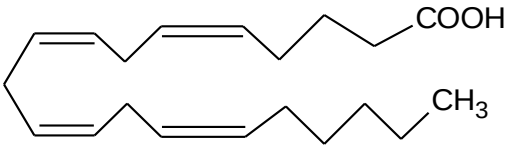
fish oil in Western studies, is also revealing (Kohsokabe *et al.*,1986; Shichikawa *et al.*, 1981; Shapiro *et al.*, 1996). Collectively, the above studies suggest that a diet rich in long chain *ω-3* FAs may be protective against RA



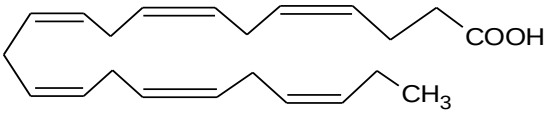
Alpha-linolenic acid (ALA)



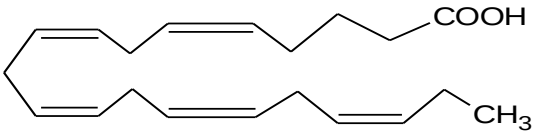
Eicosatrienoic Acid



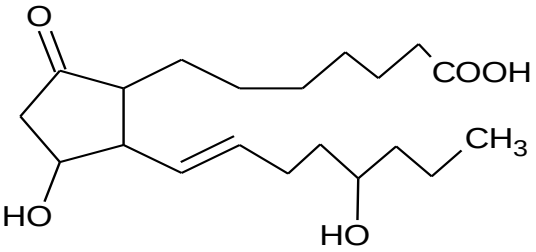
Arachidonic Acid (AA)



Docosahexaenoic acid (DHA)



Eicosapentaenoic Acid (EPA)



Prostaglandin (PGE)

Fig. 1: Structure of α linolenic acid (ALA) arachidonic acid (AA), Docosahexaenoic acid (DHA) prostaglandin (PGE) and eicosapentaenoic acid (EPA)

The effects of fish oil feeding has yielded mixed results in animal models of inflammation. Fish oil diets have been shown to have a striking protective effect when used prophylactically in mice genetically predisposed to systemic lupus (Prickett *et al.*, 1981). A fish oil diet is also effective when introduced after the emergence of signs of murine lupus, but less effective than when used prophylactically (Robinson *et al.*, 1986). A fish oil diet increased the frequency but not the severity of collagen-induced arthritis in mice (Prickett *et al.*, 1984) and results in rats with adjuvant-induced arthritis were strain specific (Robinson. 1991). This latter model causes universally severe disease in susceptible strains and is resistant to a number of other treatments that are effective in all but the most severe forms of RA in humans. Collectively, the animal studies support an anti-inflammatory effect of dietary long chain ω-3 fats, but caution that this effect cannot be generalized to all inflammatory diseases.

Rheumatoid Arthritis

Multiple studies have shown symptomatic benefit in RA with fish oil treatment. The anti-inflammatory dose appears to be at least 2.6g long chain ω-3 FAs per day (Cleland *et al.*, 2003). This dose requires 9 standard fish oil capsules per day. Most studies have used 15–20 standard fish oil capsules per day to deliver 4.5–6g long chain *ω-3* FAs per day. The salient benefits have been reduced joint pain and tenderness. There is usually a latency of six to twelve weeks from the introduction of fish oil to symptomatic response, which appears shorter with higher doses. The need for the analgesic effect of non-steroidal anti-inflammatory drugs (NSAIDs) is reduced by fish oil treatment. Fish oil has been mainly tested as an adjunct to long acting therapies for RA, known as the disease modifying anti-inflammatory drugs (DMARDs) (James *et al.*, 1997).

Safety of fish oil with long term use in anti-inflammatory doses

As there is no previously documented experience with long term use of fish oils in anti-inflammatory doses, this question requires special attention. Through our Pilot Early Arthritis Study (open label fish oil), we have an experience with anti-inflammatory doses of fish oil extending over a period of more than 6 years for some patients. In the quest of cost efficiency, we have developed a method for giving bottled fish oil on juice in a way that masks the fishy taste of the oil. Initially, we used a commercially available cod liver oil preparation that contained EPA 100mg, DHA 100mg, vitamin D 80u, vitamin A 610u per mL. The recommended dose was 20mL daily, which delivers 4g long chain *ω-3* FA per day, 1600u cholecalciferol and 12,500u vitamin A. Compliance with the regimen was reflected in plasma phospholipids EPA (Cleland *et al.*, 2003). A mean increase in both vitamin D and vitamin A levels was seen at 12 months (Fig 3). Some vitamin D levels approached or slightly exceeded the upper limit of the normal reference range, but all were far below levels at which vitamin D toxicity has been reported (Mason *et al.*, 1980). A single patient who displayed hypercalcaemia was found to have primary hyperparathyroidism. In some cases slight elevations of vitamin A above the reference range were also seen. Patients were monitored for bone mineral density and no difference in bone loss was seen relative to RA patients no taking fish oil. Notwithstanding, because recent reports show higher levels of vitamin A supplementation correlate inversely with bone mineral density (Promislow *et al.*,

2002), we decided to switch from use of cod liver oil to a fish body oil, since fish body oils contain trace amounts only of fat soluble vitamins. As there was no available retail supply of fish oil other than in capsules, we purchased fish oil in bulk and arranged bottling in our hospital pharmacy. We advised a 15mL dose of this preparation, which delivers 4.5g long chain ω-3 FAs daily. Long term use of fish oil raises concerns regarding the possible ingestion of industrial toxins found in fish. The presence of mercury in the meat of carnivorous fish has attracted considerable attention. Mercuric chloride is not lipophilic and mercury is not present in fish oils. A greater concern is polychlorinated biphenyls (PCBs), which are lipophilic and are present in trace amounts in fish oil. Components of this family are produced as byproducts of chemical synthetic reactions and are not biodegradable. Processes that generate these compounds have been outlawed but PCBs persist to varying degrees in the environment. Since they are relatively volatile they can be removed using standard fractionation processes such as molecular distillation. Notwithstanding, taking anti-inflammatory doses of fish oils harvested from industrial regions without adequate processing could involve ingestion of PCBs at or above currently recommended intakes, albeit below intakes prior to institution of avoidance measures.

Effectiveness of fish oil in other inflammatory disease

Fish oil supplements have been shown to reduce relapse in Crohn's disease by more than 60% and to reduce substantially loss of renal function and progression to end stage renal failure in IgA nephropathy (Belluzzi *et al.,* 1996; Donadio *et al.,* 1994). Some, but not all, variants of psoriasis have been shown to respond to fish oil treatment (Mayser *et al.,* 2002). Control of systemic lupus has been shown to improve with fish oil supplements (Walton *et al.,* 1991; Ioannou and Isenberg. 2002). Dietary fish oil has been shown to improve outcomes in ischaemic heart disease, to which patients with RA are especially prone (Burr *et al.,* 1989; GISSI. 1999). Cardiovascular benefits of fish oil include a myocardial membrane stabilizing effect, reduced incidence of malignant arrhythmias and sudden death, improved blood pressure control, reduction in raised plasma triglycerides and, in experimental animals, and anti-atherogenic effect (Leaf *et al.,* 1999).

Bleeding tendency and fish oil supplements

Fish oil supplementation may lead to an increased bleeding tendency, this has not been our experience. The concerns centre on an extrapolation from a putatively increased bleeding times in Greenland Inuits (Dyerberg and Bang. 1979) and somewhat increased incidence of apoplexy (Kromann and Green. 1980). The latter is likely multifactorial with high dietary salt intake potentially a factor. The bleeding time data from Greenland Inuit studies show a moderate increase in bleeding time (Dyerberg and Bang. 1979). Whether this putative effect seen in Inuits with very high dietary long chain *ω-3* intake and low *n* -6 diet will translate to Westerners in whom an *ω-3* rich fish oil supplement is being taken against the background of a Western diet abundant in *n* -6 FAs is doubtful. In any case, we have compared competitor AA and EPA in platelets of patients with RA on long term therapy with fish oil (>3years) with those reported for Greenland Inuits. The AA is far more suppressed and the EPA higher in the Inuits than the fish oil treated patients. Thus, on biochemical grounds a lesser effect on platelet function in patients on fish oil can be expected than seen in Inuits. Also, it has been reported that consumption of 3.4g/day of ω-3 fats in conjunction with 300 mg/day of aspirin had no effect on bleeding time, or episodes of bleeding in patients undergoing coronary artery bypass surgery (Eritsland *et al.,* 1995).

Favourable interactions between fish oil and anti-inflammatory drugs

As discussed above, fish oil reduces recourse to NSAIDs for analgesia in RA and thereby reduces risk for upper GI haemorrhage. Fish oil contrasts with the highly selective COX-2 inhibitor rofecoxib, which has been associated with increased serious cardiovascular events, by reducing risk for these events (Bombardier *et al.,* 2000; Calder. 2004). Anti-inflammatory doses of fish oil have been shown to reduce the hypertensive and nephrotoxic effects of cyclosporine (Darlametsos and Varonos. 2001).

Oils containing n -6 gamma linolenic acid (GLA)

Oils rich in GLA may have anti-inflammatory effects. The putative biochemical basis for this effect is relative accumulation of the elongation product of GLA, dihomogamma linolenic acid (DGLA) which, like EPA, can compete in metabolic pathway that are usually dominated by AA. The result is fewer AA derived eicosanoids with production of homologous metabolites products of DGLA such as PGE1 (one less double bond than AA derived PGE2). GLA rich oils appear to reduce symptoms in RA but available evidence is far less than that for fish oil in RA (Zurier *et al.,* 1996).

Anti-inflammatory and rheumatoid arthritis benefits

Perilla oil is rich in the ω-3 FAs, on metabolism gives EPA and DHA, which can displace AA from cell membranes. These ω-3 FAs are also released with AA by phospholipases and act as substrate inhibitors of conversion of AA by COX and the terminal synthases to the pro-inflammatory oxygenated inflammatory mediators known as eicosanoids. EPA is structurally identical to AA with the exception of its additional ω-3 double bond and can be converted to eicosanoids that resemble eicosanoids. In addition to these effects on inflammatory eicosanoid synthesis, perilla oils have been shown to reduce the production of the inflammatory cytokines IL-1β and TNFα by monocytes stimulated in vitro. These cytokines are important effector molecules in inflammatory responses and TNFα blocking agents are now used widely to treat rheumatoid disease that has proven refractory to less expensive therapies. In vitro

studies have also shown inhibition of release of the metalloproteinases that are implicated in the tissue damage that is the hallmark of RA and other inflammatory diseases (Osakabe et al. 2005; Osakabe, et al. 2004; Banno, et al. 2004; James, et al. 2000).It has been reported that conversion of ALA to EPA and further to DHA in humans is limited, but varies with individuals. Women have higher ALA conversion efficiency than men, probably due to the lower rate of utilization of dietary ALA for β-oxidation. PUFAs reduce recourse to NSAIDs for analgesia in RA and thereby reduces risk for upper GI haemorrhage. Perilla oil contrasts with the highly selective COX-2 inhibitor rofecoxib, which has been associated with increased serious cardiovascular events, by reducing risk for these events. The result is fewer AA derived eicosanoids with production of homologous metabolites products such as PGE1 (one less double bond than AA derived PGE2). ALA rich oils appear to reduce symptoms in RA but available evidence is far less than that for perilla oil in RA (Osakabe, et al. 2005; Banno, et al. 2004; Calder, 2004; James, et al. 2000; Borchers, et al. 1997)Faeces of rats before dry Faeces of rats

Rheumatoid arthritis

The in-vitro anti-inflammatory activity of *ω-3* acids translates into clinical benefits. Cohorts of neck pain patients and of RA sufferers have demonstrated benefits comparable to those receiving standard NSAIDs. Those who follow a Mediterranean-style diet tend to have less heart disease, higher HDL ("good") cholesterol levels (Kris-Etherton, *et al.*, 2001), and higher proportions of *ω-3* in tissue highly unsaturated FAs (Lands, William E.M. 2003).

ω Fatty Acids: ω−3; ω−6; ω−9 fatty acid

The ω-3 FAs (popularly known as ω−3 FAs or ω-3 FAs) are a family of unsaturated FAs that have in common a final carbon–carbon double bond in the *ω-3* position; that is, the third bond from the methyl end of the FA. Important nutritionally essential *ω-3* FAs include α-ALA, EPA, and DHA, all of which are polyunsaturated. The human body cannot synthesize *ω-3* FAs *de novo*, but it can form 20-carbon unsaturated *ω-3* FAs (like EPA) and 22-carbon unsaturated *ω-3* FAs (like DHA) from the eighteen-carbon *ω-3* FA α-linolenic acid. These conversions occur competitively with *ω-6* FAs, which are essential closely related chemical analogues that are derived from linoleic acid. Both the *ω-3* α-linolenic acid and *ω-6* linoleic acid are essential nutrients which must be obtained from food. Synthesis of the longer *ω-3* FAs from linolenic acid within the body is competitively slowed by the *ω-6* analogues. Thus accumulation of long-chain *ω-3* FAs in tissues is more effective when they are obtained directly from food or when competing amounts of *ω-6* analogs do not greatly exceed the amounts of *ω-3*.

Biological significance

Health benefits

The α-linolenic acid has not been shown to have the same cardiovascular benefits as DHA or EPA. Currently there are many products on the market which claim to contain health promoting 'ω 3', but contain only α-linolenic acid (ALA), not EPA or DHA. These products contain mainly higher plant oils and must be converted by the body to create DHA and therefore considered less efficient. DHA and EPA are made by microalgae that live in seawater. These are then consumed by fish and accumulate to high levels in their internal organs. In fish, DHA can be produced directly from microalgae as a vegetarian source. People with certain circulatory problems, such as varicose veins, benefit from such supplements containing EPA and DHA which stimulate blood circulation, increase the breakdown of fibrin, a compound involved in clot and scar formation, and additionally have been shown to reduce blood pressure (Morris, *et al.*, 1993;Mori, *et al.*, 1993). There is strong scientific evidence that *ω-3* FAs reduce bloodtriglyceride levels (Sanders, *et al.*, 1997; Davidson *et al.*, 2007) and regular intake reduces the risk of secondary and primary heart attack (Bucher *et al.*, 2002; Willett, *et al.*, 1993; Stone. 1996). Some benefits have been reported in conditions such as RA (Fortin *et al.*, 1995), and cardiac arrhythmias (Pignier, *et al.*, 2007). There is preliminary evidence that *ω-3* FAs supplementation might be helpful in cases of depression (Su, *et al.*, 2003; Naliwaiko, *et al.*, 2004) and anxiety (Green, *et al.*, 2006; Yehuda *et al.*, 2005). Studies report highly significant improvement from *ω-3* FAs supplementation alone and in conjunction with medication (Nemets, *et al.*, 2002). The study, has found no connection between depression in heart patients and supplements containing *ω-3* FAs (Caryn Rabin, 2009). Some research showed that PUFAs intake may reduce the risk of ischemic and thrombotic stroke (Iso, *et al.*, 2001). However, very large amounts may actually increase the risk of hemorrhagic stroke. Lower amounts are not related to this risk (Iso, *et al.*, 2001), 3 grams of total EPA/DHA daily are considered safe 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) (Su, *et al.*, 2003; Catherine *et al.* 2006; Hooper *et al.* 2006).

Cancer prevention

Several studies report possible anti-cancer effects of *ω-3* FAs (particularly breast, colon and prostate cancer) (Augustsson, Katarina; *et al.* 2003;De Deckere, E.A. 1999). Ω-3 FAs reduced prostate tumor growth, slowed histopathological progression, and increased survival (Yong Q. Berquin, *et al.* 2007). Among ω-3 FAs (ω-3), neither long-chain nor short-chain forms were consistently associated with breast cancer risk. High levels of DHA, however, the most abundant ω-3 PUFA (ω-3) in erythrocyte membranes, were associated with a reduced risk of breast

cancer (Pala V, *et al.* 2001). A trial found that a supplement of EPA helped cancer patients retain muscle mass (Ryan *et al.*, 2009).

Cardiovascular disease prevention

The results of major clinical study, patients with myocardial infarction treatment, 1 gram per day of *ω-3* FAs reduced the occurrence of cardiovascular death (Marchioli R. 2002). In April 2006, reported review studies into *ω-3* FAs, found in abundance in oily fish. It concluded that they do not have a significant protective effect against cardiovascular disease (Trivedi, Bijal. 2006). This meta-analysis was controversial (Wang, *et al.*, 2006; Mozaffarian, D. and Rimm, EB. 2006), that indicated decreases in total mortality and cardiovascular incidents (i.e. myocardial infarctions) associated with the regular consumption of fish and fish oil supplements. Several studies published, Japanese men with unhealthy blood sugar levels were randomly assigned to receive 1800 mg daily of EPA (an *ω-3* essential FA from fish oil) with the other half being a control group. The thickness of the carotid arteries and certain measures of blood flow were measured before and after supplementation. This went on for approximately two years. A total of 60 patients (30 in the E-EPA group and 30 in the control group) completed the study. Those given the EPA had a statistically significant decrease in the thickness of the carotid arteries along with improvement in blood flow. The authors indicated that this was the first demonstration that administration of purified EPA improves the thickness of carotid arteries along with improving blood flow in patients with unhealthy blood sugar levels (Mita, *et al.*, 2007). In another study published in 2007, patients with high triglycerides and poor coronary artery health were given 4 grams a day of a combination of EPA and DHA along with some monounsaturated FAs. Those patients with very unhealthy triglyceride levels (above 500 mg/dl) reduced their triglycerides on average 45% and their VLDL cholesterol by more than 50%. VLDL is a bad type of cholesterol and elevated triglycerides can also be deleterious for cardiovascular health (McKenney, JM, Sica, D 2007). Another study on the benefits of EPA was published in 2007. This study involved over 18,000 patients with unhealthy cholesterol levels. The patients were randomly assigned to receive either 1,800 mg a day of E-EPA with a statin drug or a statin drug alone. The trial went on for a total of five years. It was found at the end of the study those patients in the E-EPA group had superior cardiovascular function. Non-fatal coronary events were also significantly reduced in the E-EPA group. The authors concluded that EPA is a promising treatment for prevention of major coronary events, especially non-fatal coronary events (Yokoyama, *et al.*, 2007). Similar to those who consume high amounts of *ω-3* FAs from fatty fish - also tend to have higher proportions of *ω-3*, increased HDL cholesterol and decreased triglycerides (fatty material in the blood) and less heart disease. Eating walnuts (the ratio of *ω-3* to *ω-6* is circa 1:4 respectively was reported to lower total cholesterol by 4% relative to controls when people also ate 27% less cholesterol (Zambón, *et al.*, 2000). A study showed serum levels of EPA is inversely related to the levels of anti-oxidized-LDL antibodies. Oxidative modification of LDL is thought to play an important role in the development of atherosclerosis (Garrido-Sánchez, *et al.*, 2008).

Immune function

Another study regarding fish oil, Sixty four healthy Danish infants from nine to twelve months of age received either cow's milk or infant formula alone or with fish oil. It was found that those infants supplemented with fish oil had improvement in immune function maturation with no apparent reduction in immune activation (Damsgaard, *et al.*, 2007).

Brain health

The study on ω-3 FAs, a group of mice were genetically modified to develop accumulation of amyloid and tau proteins in the brain similar to that seen in people with poor memory. The mice were divided into four groups with one group receiving a typical American diet (with high ratio of ω-6 to ω-3 FAs being 10 to 1). The other three groups were given food with a balanced 1 to 1 ω-6 to ω-3 ratio and two additional groups supplemented with DHA plus long chain ω-6 FAs. After three months of feeding, all the DHA supplemented groups were noted to have a lower accumulation of β-amyloid and tau protein. Some research suggests that these abnormal proteins may contribute to the development of memory loss in later years (Green, *et al.*, 2007). There is also a study published regarding ω-3 supplementation in children with learning and behavioral problems. For the first fifteen weeks of this study, the children were given polyunsaturated FAs (ω-3 and ω-6, 3000 mg a day), PUFAs plus multi-vitamins and minerals or placebo. After fifteen weeks, all groups crossed over to the PUFAs plus vitamins and mineral supplement. Parents were asked to rate their children's condition after fifteen and thirty weeks. After thirty weeks, parental ratings of behavior improved significantly in nine out of fourteen scales. The study is the largest PUFA trial to date with children falling in the poor learning and focus range. The results support those of other studies that have found improvement in poor developmental health with essential FAs supplementation (Sinn, and Janet 2007; Lee, *et al.*,2007). A study (Bousquet, *et al.*, 2008) examining whether ω-3 exerts neuroprotective action in Parkinson's disease found that it did, using an experimental model, exhibit a protective effect (much like it did for Alzheimer's disease as well). The scientists exposed mice to either a control or a high ω-3 diet from two to twelve months of age and then treated them with a neurotoxin commonly used as an experimental model for Parkinson's. The scientists found that high doses of ω-3 given to the experimental group completely prevented the neurotoxin-induced decrease of

dopamine that ordinarily occurs. Since Parkinson's is a disease caused by disruption of the dopamine system, this protective effect exhibited could show promise for future research in the prevention of Parkinson's disease. However, fish oil has been shown to have no effect on cognitive performance in older individuals without dementia (van de Rest, *et al.,* 2008).

Psychiatric disorders

ω-3 FAs are thought by some to have membrane-enhancing capabilities in brain cells. One medical explanation is that *ω-3* FAs play a role in the fortification of the myelin sheaths. Not coincidentally, *ω-3* FAs comprise approximately eight percent of the average human brain according to Dr. David Horrobin, a pioneer in FA research. Another major researcher in studying essential FAs, who gave ω-3 its name, surmised how *ω-3* components are analogous to the human brain by stating that "DHA is structure, EPA is function." A benefit of *ω-3* FAs is helping the brain to repair damage by promoting neuronal growth (Trivedi, Bijal 2006). In a six-month study involving people with schizophrenia and Huntington's disease who were treated with E-EPA or a placebo, the placebo group had clearly lost cerebral tissue, while the patients given the supplements had a significant increase of grey and white matter (Nemets, *et al.,* 2006). In the prefrontal cortex (PFC) of the brain, low brain *ω-3* FAs are thought to lower the dopaminergic neurotransmission in this brain area, possibly contributing to the negative and neurocognitive symptoms in schizophrenia. This reduction in dopamine system function in the PFC may lead to an overactivity in dopaminergic function in the limbic system of the brain which is suppressively controlled by the PFC dopamine system, causing the positive symptoms of schizophrenia. This is called the *ω-3* PUFA/dopamine hypothesis of schizophrenia (Ohara, 2007). This mechanism may explain why *ω-3* supplementation shows effects against both positive, negative and neurocognitive symptoms in schizophrenia. Consequently, the past decade of *ω-3* FA research has procured some Western interest in *ω-3* FAs as being a legitimate 'brain food.' Still, recent claims that one's intelligence quotient, psychological tests measuring certain cognitive skills, including numerical and verbal reasoning skills, are increased on account of *ω-3* FAs consumed by pregnant mothers remain unreliable and controversial. An even more significant focus of research, however, lies in the role of *ω-3* FAs as a non-prescription treatment for certain psychiatric and mental diagnoses and has become a topic of much research and speculation.

In 1998, a small double-blindplacebo-controlled study in thirty patients diagnosed with bipolar disorder. The study showed that subjects in the *ω-3* group were less likely to experience a relapse of symptoms in the study. Moreover, the *ω-3* group experienced significantly more recovery than the placebo group. However, the study notes that the improvement in the *ω-3* group was too small to be clinically significant. Several epidemiological studies suggest covariation between seafood consumption and rates of mood disorders. Biological marker studies indicate deficits in ω−3 FAs in people with depressive disorders, while several treatment studies indicate therapeutic benefits from ω-3 supplementation. A similar contribution of ω-3 FAs to coronary artery disease may explain the well-described links between coronary artery disease and depression. Deficits in ω-3 FAs have been identified as a contributing factor to mood disorders and offer a potential rational treatment approach." In 2004, a study found that 100 suicide attempt patients on average had significantly lower levels of EPA in their blood as compared to controls (Freeman, *et al.,* 2006; Lin, and Kuan-Pin 2007;Mischoulon, *et al.,* 2009). The preponderance of epidemiologic and tissue compositional studies supports a protective effect of ω-3 EFA intake, particularly EPA and DHA, in mood disorders. Meta-analyses of randomized controlled trials demonstrate a statistically significant benefit in unipolar and bipolar depression. The results were highly heterogeneous, indicating that it is important to examine the characteristics of each individual study to note the differences in design and execution. There is less evidence of benefit in schizophrenia. EPA and DHA appear to have negligible risks and some potential benefit in major depressive disorder and bipolar disorder, but results remain inconclusive in most areas of interest in psychiatry. Health benefits of ω-3 EFA may be especially important in patients with psychiatric disorders, due to high prevalence rates of smoking and obesity and the metabolic side effects of some psychotropic medications." Another published report in 2007, based on clinical trials, found that ω-3 PUFAs significantly improved depression in patients with both unipolar and bipolar disorder. A small trial, suggests that E-EPA, has an advantage over placebo in major depressive disorder (Food and Nutrition Board, 2005).

ω-3 and ω-6 FAs

There are two types of PUFAs that must be obtained through the diet because they can not be made by the human body. ω-3 FAs may be important in preventing many health problems, including heart disease, RA, cancer and improving mood and memory enhancer.

The ω-6 to ω-3 ratio

The biological effects of the ω-3 are largely mediated by their interactions with the ω-6 FAs.The ratio is the ratio of grams ω-6 FAs to grams ω-3 FAs in a food. The ratio is helpful to use when choosing foods because it is important not to eat too many more ω-6 FAs than ω-3 FAs. The current recommendation is 4 grams or less of ω-6 FA for every 1 gram of ω-3 FA. Choose foods whose ω-6/ω-3 ration is less than 4. The Clinical studies indicate that the ratio of *ω-6* to *ω-3* (especially Linoleic vs α-Linolenic) FAs is important to maintaining cardiovascular health. Both *ω-3* and *ω-6* FAs are essential, i.e. humans must consume them in the diet. *ω-3* and *ω-6* compete for the same metabolic enzymes,

thus the *ω-6*:*ω-3* ratio will significantly influence the ratio of the ensuing eicosanoids (hormones), (e.g. PGs, LKs, TXs etc.), and will alter the body's metabolic function. Generally, grass-fed animals accumulate more *ω-3* than do grain-fed animals which accumulate relatively more *ω-6*. Metabolitesof *ω-6* are significantly more inflammatory (esp. AA) than those of *ω-3*. This necessitates that *ω-3* and *ω-6* be consumed in a *balanced proportion*; healthy ratios of *ω-6*: *ω-3* range from 1:1 to 4:1 (Tribole, 2006; Simopoulos, 2003; Simopoulos *et al.*, 2000). Studies suggest that the evolutionary human diet, rich in game animals, seafood and other sources of *ω-3*, may have provided such a ratio. Here are the ratios of *ω-6* to *ω-3* FAs in some common oils: canola 2:1, soybean 7:1, olive 3–13:1, sunflower (no *ω-3*), flax 1:3, cottonseed (almost no *ω-3*), peanut (no *ω-3*), grapeseed oil (almost no *ω-3*) and corn oil 46 to 1 ratio of *ω-6* to *ω-3* (Goyens, *et al.* l 2006).

Conversion efficiency of ALA to EPA and DHA

It has been reported that conversion of ALA to EPA and further to DHA in humans is limited, but varies with individuals. Women have higher ALA conversion efficiency than men, probably due to the lower rate of utilization of dietary ALA for β-oxidation. The absolute amount of ALA, rather than the ratio of ω-3 and ω-6 FAs, which affects the conversion.

Daily values of PUFAs in diet

As macronutrients, fats are not assigned recommended daily allowances. The acceptable intake (AI) for *ω-3* is 1.6 grams/day for men and 1.1 grams/day for women A growing body require higher intakes of ALA, EPA, and DHA that may afford some degree of protection against coronary heart disease. The physiological potency of EPA and DHA is much greater than that for ALA. There was insufficient evidence as of 2005 to set a UL (upper tolerable limit) for *ω-3* FAs. The FDA recommends that total dietary intake of *ω-3* FAs from fish not exceed 3 grams per day, of which no more than 2 grams per day are from nutritional supplements.

Discussion

The ω-3 PUFA as DHA and EPA. These FAs compete with AA and inhibit its synthesis from LA by competing as substrates for COX enzyme as well as for the 2-position on membrane phospholipids. AA is the precursor of 2-series PG and TXA2 and 4-series leukotreienes (LTB4), while the products of EPA are 3- series of these eicoisanoids, PGI3 and PGE3 (physiologically inactive) and LTB5, which is less potent than LTB4. Thus the net result is homeostatic balance towards a more vasodilatory state, less platelet aggregation and inflammation. Because of these effects, EPA has been implicated in the low incidence of atherosclerosis among Eskimos, who basically eat fish. The other sources of PUFA are marine mammals and vegetables like soyabean, butternuts and common beans It has also been suggested that EPA plays a protective role in the progression of chronic renal failure (CRF). However, these findings are controversial since multifactorial mechanisms appear to be involved in its pathogenesis. Besides inflammatory responses, altered PG synthesis, coagulation abnormalities, and alterations in lipid metabolism observed in some models of CRF, the hemodynamic changes, such as increased glomerular pressure and flow are also important for progression of CRF. It has been proven that PUFA can prevent or slow down the decline in renal function in a variety of animal models of renal disease. In various studies, a positive effect of the use of linoleic acid on renal function had been described. However, this was not the case in all animal models studied. A more consistent pattern with positive effects could be found with the use of ω-3 PUFA mixtures, although one study had only reported unfavorable findings. Up to now, studies on the effect of fish oil on renal function in patients with chronic renal insufficiency are relatively rare. In all the studies glomerular filtration rate increased, there was rise in effective renal plasma flow and a fall in filtration fraction. There was a tendency for proteinuria to fall. These changes suggest an efferent arteriolar vasodilatation. Nevertheless, it should be emphasized that the individual reaction was variable, with sometimes a considerable fall in renal function. The reaction could neither be predicted from either the underlying cause of the chronic renal insufficiency, nor from the initial severity of renal function loss. Long- terrn studies directed towards the possible preservation of renal function with fish oil have been reported in patients with IgA nephropathy. The results are contradictory. Therefore the verdict regarding the usefulness of fish oil on renal function in patients with chronic renal insufficiency remains open (Reddy *et al.*, 2002). In view of the above considerations the present study was undertaken to evaluate the role of PUFA in the prevention of progression of chronic renal disease, effect on proteinuria and lipid metabolism in patients with chronic renal disease (Bastos & de Oliveira. 2002). In summary, patients on PUFA, the rate of rise of creatinine was slower and there was improvement in protienuria and serum albumin levels though it did not reach statistical significance. In both the groups there was reduction in serum triglyceride and cholesterol levels on follow up but the reduction in triglyceride level was statistically significant only in non PUFA group . We conclude that the role of PUFA in prevention of progression of chronic renal disease is not conclusive and may need larger controlled studies (Cappelli et al. 1997; Raffaele *et al.*, 1993; Leaf and Weber. 1988; Tsukamoto *et al.*, 1982).

Conclusion

The 'essential' FAs were given their name when researchers found that they were essential to normal growth in young children and animals. A small amount of ω-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 ω-6 FAs (such as

γ-linolenic acid and AA) play a similar role in normal growth. However, they also found that ω-6 was "better" at supporting dermal integrity, renal function, and parturition. These preliminary findings led researchers to concentrate their studies on ω-6, and it was only in recent decades that ω-3 has become of interest. The ω-6 AA was converted by the body into pro-inflammatory agents called PGs. Eicosanoids: TX, prostacyclins and the LTs. The eicosanoids, which have important biological functions, typically have a short active lifetime in the body, starting with synthesis from FAs and ending with metabolism by enzymes. However, if the rate of synthesis exceeds the rate of metabolism, the excess eicosanoids may have deleterious effects. The ω-3 is also converted into eicosanoids, but at a much slower rate. Eicosanoids made from ω-3 fats are often referred to as anti-inflammatory, but in fact they are just less pro-inflammatory than those made from ω-6 fats. If both ω-3 and ω-6 are present, they will "compete" to be transformed, so the ratio of ω-3: ω-6 directly affects the type of eicosanoids that are produced. This competition was recognized as important when it was found that TX is a factor in the clumping of platelets, which leads to thrombosis. The LTs were similarly found to be important in immune/inflammatory-system response, and therefore relevant to arthritis, lupus, and asthma. These discoveries led to greater interest in finding ways to control the synthesis of ω-6 eicosanoids. The simplest way would be by consuming more ω-3 and fewer ω-6 FAs. The ω-3 FA EPA forms in the body potent antiinflamatory nanomolecules, called resolvins. The ω-3s also turn into other antiinflammatory molecules called maresins and ω-3-oxylipins, which partly explain the versatile health effects of PUFAs.

References

Andrew PDF, Sperling LS Understanding ω-3's. http://www.biovita.fi/suomi/pdf/ understanding_ω3.pdf. Retrieved 21 October 2007.

Azcona JO, Schang MJ, Garcia PT, Gallinger C, Ayerza R and Coates W (2008) Ω-3 enriched broiler meat: The influence of dietary alpha-linolenic ω-3 fatty acid sources on growth, performance and meat fatty acid composition. *Canadian Journal of Animal Science* **88**: 257-269. DOI: 10.4141/CJAS07081

Basant KP (2006) High-resolution magnetic resonance imaging sinc-interpolation-based subvoxel registration and semi-automated quantitative lateral ventricular morphology employing threshold computation and binary image creation in the study of fatty acid interventions in schizophrenia, depression, chronic fatigue syndrome and Huntington's disease. *Int. Rev. Psychiatry* **18(2)**: 149–154. DOI: 10.1080/09540260600583015

Bastos DHM and de Oliveira JG (2002). Enzymic Enhancement of ω3 Polyunsaturated FAs Content in Brazilian Sardine Oil. *Acta Farm. Bonaerense* **21(2)**: 85-88.

Beckermann B, Beneke M and Seitz I (1990) Comparative bioavailability of eicosapentaenoic acid and docasahexaenoic acid from triglycerides, free FAs and ethyl esters in volunteers. *Arzneimittel-Forschung* **40(6)**: 700–704.

Bell JG, MacKinlay EE, Dick JR, MacDonald DJ, Boyle RM and Glen ACA (2004) Essential fatty acids and phospholipase A2 in autistic spectrum disorders. *Prostaglandins Leukot. Essent. FAs.* **71(4)**: 201–204. DOI: 10.1016/j.plefa.2004.03.008

Belluzzi A, Brignola C, Campieri M, Pera A, Boschi S and Miglioli M (1996) Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. *N. Engl. J. Med.* **334**: 1557-1560. DOI: 10.1056/NEJM199606133342401

Berquin IM, Min Y, Wu R, Wu J, Perry D, Cline JM, Thomas MJ, Thornburg T, Kulik G, Smith A, Edwards IJ, D'Agostino R, Zhang H, Wu H, Kang JX and Chen YQ (2007). Modulation of prostate cancer genetic risk by ω-3 and ω-6 FAs. *J. Clin. Invest.* **117(7)**: 1866–1875. DOI: 10.1172/JCI31494

Bijal T (2006) The good, the fad, and the unhealthy. *New Scientist* **191(2570)**: 42–49. DOI: 10.1016/S0262-4079(06)60559-9

Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK, Schnitzer TJ and Weaver A (2000) Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with RA. *N. Engl. J. Med*. **343**: 1520-1528. DOI: 10.1056/NEJM200011233432103

Boris N, Ziva S and Belmaker RH (2002) Addition of ω-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am. J. Psychiatry* **159(3)**: 477–479. DOI: 10.1176/appi.ajp.159.3.477

Bousquet M, Saint-Pierre M, Julien C, Salem N, Cicchetti F and Calon F (2008) Beneficial effects of dietary ω-3 polyunsaturated fatty acid on toxin-induced neuronal degeneration in an animal model of Parkinson's disease. *Fed. Am. Soc. Exper. Bio. J.* **22(4)**: 1213–1225. DOI: 10.1096/fj.07-9677com

Bucher HC, Hengstler P, Schindler C and Meier G (2002) *ω-3* polyunsaturated FAs in coronary heart disease: a meta-analysis of randomized controlled trials. *Am. J. Med.* **112 (4)**: 298–304. DOI: 10.1016/S0002-9343(01)01114-7

Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, Elwood PC and Deadman NM (1989) Effect of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* **334**: 757-61. DOI: 10.1016/S0140-6736(89)90828-3

Calabrese JR, Rapport DJ and Shelton MD (1999) Fish oils and bipolar disorder: A promising but untested treatment. *Arch. Gen. Psychiatry* **56 (5)**: 413–414. DOI: 10.1001/archpsyc.56.5.413

Calder PC (2004) ω-3 FAs and cardiovascular disease: evidence explained and mechanisms explored. *Clin. Sci*. **107**: 1-11. DOI: 10.1042/CS20040119

Cappelli P. di Liberato L, Stuard S and Ballone E (1997) ω-3 poly unsaturated fatty acid supplementation in chronic progressive renal disease. *J. Nephrol.* **10(3)**: 157-62.

Catherine HM, Newberry SJ, Mojica WA, Khanna P, Issa AM, Suttorp MJ, Lim YW, Traina SB, Hilton L, Garland R and Morton SC (2006) Effects of *ω-3* FAs on Cancer Risk: a systematic review. *JAMA* **295 (4)**: 403–415. DOI: 10.1001/jama.295.4.403

Caughey GE, Mantzioris E, Gibson RA, Cleland LG and James MJ (1996) The effect on human tumor necrosis factor a and interleukin-1b production of diets enriched in ω-3 FAs from vegetable oil or fish oil. *Am. J. Clin. Nutr*. **63**: 116-122.

Charles C (2004) *The End of the Line: How overfishing is changing the world and what we eat*. Ebury Press, London 2004.

Cleland LG, James MJ and Proudman SM (2003) The role of fish oils in the treatment of RA. *Drugs* **63**: 845-853. DOI: 10.2165/00003495-200363090-00001

Cleland LG, Proudman SM, Hall C, Stamp LK, McWilliams L, Wylie N, Neumann M, Gibson RA and James MJ (2003) A biomarker of ω-3 compliance in patients taking fish oil for RA. *Lipids* **38**: 419-424. DOI: 10.1007/s11745-003-1078-9

Cunnane SC (2006). Survival of the fattest: the key to human brain evolution. M S-Medecine Sciences, **22 (6–7)**: 659–663. DOI: 10.1051/medsci/20062267659

Curtis CL, Hughes CE, Flannery CR, Little CB, Harwood JL and Caterson B (2000) ω-3 FAs specifically modulate catabolic factors involved in articular cartilage degradation. *J. Biol. Chem.* **275**: 721-724. DOI: 10.1074/jbc.275.2.721

Damsgaard, Camilla T, Lauritzen, Lotte; Kjær, Tanja M.R, Holm, Puk M.I, Fruekilde, Maj-Britt; Michaelsen, Kim F and Hanne F (2007). Fish oil supplementation modulates immune function in healthy infants. *J. Nutr*. **137 (4)**: 1031–1036.

Dariush M and Eric BR (2006) Fish intake, contaminants, and human health: evaluating the risks and the benefits. *JAMA* **296(15)**: 1885–1899. DOI: 10.1001/jama.296.15.1885

Darlametsos IE and Varonos DD (2001) Role of prostanoids and endothelins in the prevention of cyclosporine-induced nephrotoxicity. *Prostaglandins Leukot Essent FAs*, **64**: 231-239. DOI: 10.1054/plef.2001.0265

Davidson MH, Stein EA, Bays HE, Maki KC, Doyle RT, Shalwitz RA, Ballantyne CM and Ginsberg HN (2007) Efficacy and tolerability of adding prescription ω-3 FAs 4 g/d to Simvastatin 40 mg/d in hypertriglyceridemic patients: An 8-week, randomized, double-blind, placebo-controlled study. *Clin. Ther*. **29(7)**: 1354–1367. DOI: 10.1016/j.clinthera.2007.07.018

De Catenna R, Caprioli R, Giannessi D, Sicari R, Galli C, Carr L and Rindi P (1993) ω-3 FAs reduce proteinuria in patients with chronic glomerular disease. *Kidney International* **44**: 843-850. DOI: 10.1038/ki.1993.320

De Deckere EA (1999) Possible beneficial effect of fish and fish *ω-3* polyunsaturated FAs in breast and colorectal cancer. *Eur. J. Cancer Prev.* **8(3)**: 213–221. DOI: 10.1097/00008469-199906000-00009

Dean O. (2006-05-02). The Dark Side of Good Fats. *Newsweek*: p. 2. http://www.newsweek.com/ id/137192. Retrieved 2008-06-14.

Donadio JV, Jr Bergstralh EJ, Offord KP, Spencer DC and Holley KE (1994) A controlled trial of fish oil in IgA nephropathy. Mayo Nephrology Collaborative Group. *N Engl J Med*, **331**: 1194-1199. DOI: 10.1056/NEJM199411033311804

Duk-Hee L, In-Kyu L, Soo-Hee J, Michael S, David RJ (2007) Association between serum concentrations of persistent organic pollutants and insulin resistance among nondiabetic adults: results from the National Health and Nutrition Examination Survey 1999–2002. *Diabetes Care*, **30 (3)**: 622–628. DOI: 10.2337/dc06-2190

Dyerberg J, Bang HO (1979) Haemostatic function and platelet polyunsaturated FAs in Eskimos. *Lancet* **2**: 433-435. DOI: 10.1016/S0140-6736(79)91490-9

Erasmus, Udo (1986) Fats and Oils. Alive books, Vancouver, ISBN 0-920470-16-5 p. 263 (round-number ratio within ranges given.)

Eritsland J, Arnesen H, Seljeflot I and Kierulf P (1995) Long-term effects of ω-3 polyunsaturated FAs on haemostatic variables and bleeding episodes in patients with coronary artery disease. *Blood Coagul Fibrinolysis*, **6**: 17-22. DOI: 10.1097/00001721-199502000-00003

Evelyn T. The Ultimate Ω-3 Diet. New York. McGraw-Hill. 2007 ISBN 13:978-0-07-146986-9

Falk-Petersen S, *et al.* (1998). Lipids and FAs in ice algae and phytoplankton from the Marginal Ice Zone in the Barents Sea. *Polar Biology* **20(1)**: 41–47. DOI: 10.1007/s003000050274

Food and Nutrition Board, Institute of Medicine of the National Academies (2005), pp.423and 770

Fortin PR, Lew RA, Liang MH, Wright EA, Beckett LA, Chalmers TC, Sperling RI. (1995). Validation of a meta-analysis: The effects of fish oil in RA. *J Clin Epidemiol*, **48(11):** 1379–1390. DIO: 10.1016/0895-4356(95)00028-3

Freeman MP, Hibbeln JR, Wisner KL, et al. (2006) Ω-3 FAs: evidence basis for treatment and future research in psychiatry. *J Clin Psychiatry*, **67(12)**: 1954-1967. DOI: 10.4088/JCP.v67n1217

Garrido-Sánchez L, García-Fuentes E, Rojo-Martínez G, Cardona F, Soriguer F, Tinahones FJ. (2008). Inverse relation between levels of anti-oxidized-LDL antibodies and eicosapentanoic acid (EPA). *Br J Nut*, **22**: 1–5.

GISSI Prevenzione Investigators. (1999) Dietary supplementation with ω-3 polyunsaturated FAs and vitamin E after

myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet*, **354**: 447-455. DOI: 10.1016/S0140-6736(99)07072-5

Goyens Petra LL, *et al.* (2006). Conversion of alpha-linolenic acid in humans is influenced by the absolute amounts of alpha-linolenic acid and linoleic acid in the diet and not by their ratio. *American Journal of Clinical Nutrition,* **84(1**): 44. Retrieved 21 October 2007.

Green KN, Martinez-Coria H, Khashwji H, Hall EB, Yurko-Mauro KA, Ellis L, LaFerla FM. (2007). Dietary docosahexaenoic acid and docosapentaenoic acid ameliorate amyloid-β and tau pathology via a mechanism involving presenilin 1 levels. *J Neuroscience*, **27(16)**: 4385–4395. DOI: 10.1523/JNEUROSCI.0055-07.2007

Griffin BA (2008). "How relevant is the ratio of dietary *ω-6* to *ω-3* polyunsaturated FAs to cardiovascular disease risk? Evidence from the OPTILIP study". *Curr. Opin. Lipidol.* **19 (1)**: 57-62. DOI: 10.1097/MOL.0b013e3282f2e2a8

Grimble RF, Howell WM, O'Reilly G, Turner SJ, Markovic O, Hirrell S, East JM, and Calder PC. (2002). The ability of fish oil to suppress tumor necrosis factor alpha production by peripheral blood mononuclear cells in healthy men is associated with polymorphisms in genes that influence tumor necrosis factor alpha production. *Am J Clin Nutr*, **76**: 454-459.

Harvald B. (1989) Genetic epidemiology of Greenland. *Clin Genet*, **36**: 364-367. DOI: 10.1111/j.1399-0004.1989.tb03214.x

Hibbeln JR, Nieminen LR, Blasbalg TL, Riggs JA, Lands WE. (2006). Healthy intakes of *ω-3* and *ω-6* FAs: estimations considering worldwide diversity. *Am J Clin Nutr*. **83**(6 Suppl): 1483S–1493S.

Hillary B, Puri KB. (2004) *The Natural Way to Beat Depression: the groundbreaking discovery of EPA to change your life.* London. Hodder and Stoughton. 2004.

Hjartaker A, Lund E, Bjerve KS. (1997) Serum phospholipid fatty acid composition and habitual intake of marine foods registered by a semi-quantitative food frequency questionnaire. *Eur J Clin Nutr*, **51(11)**: 736-742. DOI: 10.1038/sj.ejcn.1600475

Holman RT (1998). The slow discovery of the importance of ω 3 essential FAs in human health. *J. Nutr.* **128** (2 Suppl): 427S–433S.

Holub BJ, Wlodek M, Rowe W and Piekarski J (2009) Correlation of ω-3 levels in serum phospholipid from 2053 human blood samples with key fatty acid ratios. *Nutrition Journal* **8**:58. DOI: 10.1186/1475-2891-8-58

Holub DJ and Holub BJ (2004) Ω-3 FAs from fish oils and cardiovascular disease. *Mol. Cell Biochem*. **263**:217-225. DOI: 10.1023/B:MCBI.0000041863.11248.8d

Hooper L, *et al.* (2006). Risks and benefits of ω 3 fats for mortality, cardiovascular disease, and cancer: systematic review. *BMJ* **332**: 752–760. DOI: 10.1136/bmj.38755.366331.2F

Huan, M, *et al.* (2004). "Suicide attempt and *ω-3* fatty acid levels in red blood cells: a case control study in China". *Biol Psychiatry* **56(7):** 490–496. DOI: 10.1016/j.biopsych.2004.06.028

Ioannou Y, Isenberg DA. (1002) Current concepts for the management of systemic lupus erythematosus in adults: a therapeutic challenge. *Postgrad .Med .J*. **78**: 599-606. DOI: 10.1136/pmj.78.924.599

Iso, H, Rexrode, K.M, Stampfer, M.J, Manson, J.E, Colditz, G.A, Speizer, F.E, Hennekens, C.H, Willett, W.C. (2001). Intake of fish and ω-3 FAs and risk of stroke in women. *JAMA* **285 (3)**: 304–312. DOI: 10.1001/jama.285.3.304

James MJ, Cleland LG (1997) Dietary ω-3 FAs and therapy for RA. *Semin. Arthritis. Rheum.* **27**: 85-97. DOI: 10.1016/S0049-0172(97)80009-1

James MJ, Gibson RA, Cleland LG. (2000) Dietary polyunsaturated FAs and inflammatory mediator production. *Am J Clin Nutr*, **71** (suppl): 343S-8S.

Jennifer W. Nut Grower's Guide: The Complete Handbook for Producers and Hobbyists. Retrieved 21 October 2007.

Katarina A, *et al.* (2003). A prospective study of intake of fish and marine FAs and prostate cancer. *Cancer Epidemiology, Biomarkers & Prevention* **2 (1)**: 64–67.

Kobayashi M, Sasaki S, Kawabata T, Hasegawa K, Akabane M, Tsugane A. (2001) Single measurement of serum phospholipid fatty acid as a biomarker of specific fatty acid intake in middle-aged Japanese men. *Eur J Clin Nutr*, **55**: 643-650. DOI: 10.1038/sj.ejcn.1601194

Kohsokabe S, Murakami H, Yamaguchi K, Tsuboi N, Murata M, Komori T, Inoue K, Hayashi T, Ito H. (1986) Prevalence of positive rheumatoid factor and results of a follow-up study in a population of 20,000. *Ryumachi*, 26: 147-52.

Kris-Etherton P, Eckel RH, Howard BV, St Jeor S, Bazzarre TL. (2001). AHA Science Advisory: Lyon Diet Heart Study. Benefits of a Mediterranean-style, National Cholesterol Education Program/ American Heart Association Step I dietary pattern on cardiovascular disease. *Circulation*, 103(13): 1823–1825. DOI: 10.1161/01.CIR.103.13.1823

Kromann N, Green A. (1980) Epidemiological studies in the Upernavik district, Greenland. *Acta Med. Scand*, 208: 401-406. DOI: 10.1111/j.0954-6820.1980.tb01221.x

Kuang CC. (2001) *FAs in Foods and Their Health Implications*. Rout ledge Publishing. New York, New York. 2001.

Kuan-Pin S, Shih-Yi H, Chih-Chiang C, Winston WS. (2003). Ω-3 FAs in major depressive disorder: A preliminary double-blind, placebo-controlled trial. *Eur Neuropsychopharmacol*, **13(4)**: 267–271.

Lands, William E.M. Fish, Ω-3 and Human Health, Champaign. AOCS Press. 2005 ISBN 1-893997-81-2

Lawson LD, Hughes BG. (1988). Absorption of eicosapentaenoic acid and docosahexaenoic acid from fish oil triacylglycerols or fish oil ethyl esters co-ingested with a high-fat meal. *Biochem Biophys Res Commun* **156** (2): 960–963. DOI: 10.1016/S0006-291X(88)80937-9

Leaf A, Kang JX, Xiao YF, Billman GE. (1999) ω-3 FAs in the prevention of cardiac arrhythmias. *Lipids*, **34** Suppl: S187-9. DOI: 10.1007/BF02562284

Leaf A, Weber PC. (1988) cardiovascular effects of ω-3 FAs. *NEJM*, **318**: 549-554. DOI: 10.1056/NEJM198803033180905

Lemaitre RN, King IB, Mozaffarian D, Kuller LH, Tracy RP, Siscovick DS. (2003) ω-3 Polyunsaturated FAs, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: The Cardiovascular Heart Study. *Am J Clin Nutr*, **77**: 319-325.

Lois S. *The Food Industry's Greed*. How Misleading Labeling of Ω-3 Foods Undermines American Health.

Marchioli R. (2002). Early protection against sudden death by ω-3 polyunsaturated FAs after myocardial infarction: time-course analysis of the results of the GISSI-Prevenzione. *Circulation*, **105**: 1897–1903. DOI: 10.1161/01.CIR.0000014682.14181.F2

Martha CM, Frank S, Bernard R. (1993). Does fish oil lower blood pressure? A meta-analysis of controlled trials. *Circulation* **88 (2)**: 523–533. DOI: 10.1161/01.CIR.88.2.523

Mason RS, Lissner D, Grunstein HS, Posen S. (1980) A simplified assay for dihydroxylated vitamin D metabolites in human serum: application to hyper- and hypovitaminosis D. *Clin Chem*, **26**: 444-50.

Mayser P, Grimm H, Grimminger F. (2002) ω-3 FAs in psoriasis. *Br J Nutr*, **87**: S77-82. DOI: 10.1079/BJN2001459

McKenney, James M, Sica, Domenic (2007). Prescription ω-3 FAs for the treatment of hypertriglyceridemia. *Am J Health-Sys Pharm*, **64(6)**: 595–605. DOI: 10.2146/ajhp060164

Michel O, Suzanne C, De Paul R (2002). Consumption of seafood and preterm delivery. Encouraging pregnant women to eat fish did not show effect. *BMJ (Clinical Research Ed.)*, **324** (7348): 1279. DOI: 10.1136/bmj.324.7348.1279

Mischoulon D, Papakostas GI, Dording CM, et al. (2009). A double-blind, randomized controlled trial of ethyl-eicosapentaenoate for major depressive disorder. *J Clin Psychiatry*. **70(12)**: 1636-1644. DOI: 10.4088/JCP.08m04603

Mita, T; Watada H, Ogihara T, Nomiyama T, Ogawa O, Kinoshita J, Shimizu T, Hirose T, Tanaka Y, Kawamori R (2007). Eicosapentaenoic acid reduces the progression of carotid intima-media thickness in patients with type 2 diabetes. *Atherosclerosis*, **191(1)**: 162–167. DOI: 10.1016/j.atherosclerosis.2006.03.005

Mozaffarian D, Ascherio A, Hu FB, Stampfer MJ, Willett WC, Siscovick DS, Rimm EB. (2005). Interplay between different polyunsaturated FAs and risk of coronary heart disease in men. *Circulation*, 111(2): 157–64. DOI: 10.1161/01.CIR.0000152099.87287.83

Naliwaiko K, Araújo RL, da Fonseca RV, Castilho JC, Andreatini R, Bellissimo MI, Oliveira BH, Martins EF, Curi R, Fernandes LC, Ferraz AC. (2004). Effects of fish oil on the central nervous system: a new potential antidepressant?. *Nutritional Neuroscience*, **7(2)**: 91–99. DOI: 10.1080/10284150410001704525

Natalie S, Janet B. (2007). Effect of supplementation with polyunsaturated FAs and micronutrients on learning and behavior problems associated with child ADHD. *J Dev Behav Pediatrics* **28(2)**: 82–91. DOI: 10.1097/01.DBP.0000267558.88457.a5

Nemets H, Nemets B, Apter A, Bracha Z, Belmaker RH. (2006). Ω-3 treatment of childhood depression: A controlled, double-blind pilot study. *Am J Psychiatry* **163 (6)**: 1098–1100. DOI: 10.1176/appi.ajp.163.6.1098

Ohara K. (2007). The *ω-3* polyunsaturated fatty acid/dopamine hypothesis of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*, 3**1(2)**: 469–474. DOI: 10.1016/j.pnpbp.2006.11.013

Okuyama H. (2001). High *ω-6* to *ω-3* ratio of dietary FAs rather than serum cholesterol as a major risk factor for coronary heart disease. *Eur J Lipid Sci Technol*, **103**: 418–422. DOI: 10.1002/1438-9312(200106)103:6%3C418: AID-EJLT418%3E3.0.CO;2-#

Pala V, *et al.* (2001). Erythrocyte Membrane FAs and Subsequent Breast Cancer: a Prospective Italian Study. *JNCL*, **93(14)**: 1088. DOI: 10.1093/jnci/93.14.1088

Pao-Yen L, Su K-P (2007). A Meta-Analytic Review of Double-Blind, Placebo-Controlled Trials of Antidepressant Efficacy of Ω-3 FAs. *J Clin Psychiatry* **68 (7):** 1056–1061. DOI: 10.4088/JCP.v68n0712

Pignier C, Revenaz C, Rauly-Lestienne, I, Cussac, D, Delhon, A, Gardette, J, Le Grand, B. (2007). Direct protective effects of poly-unsaturated FAs, DHA and EPA, against activation of cardiac late sodium current. *Basic Research in Cardiology*, **102 (6)**: 553–564. DOI: 10.1007/s00395-007-0676-x

Pnina G, Haggai H, Assaf M, Sofi M, Gadi P and Abraham W (2006). Red cell membrane ω-3 FAs are decreased in nondepressed patients with social anxiety disorder. *Eur Neuropsychopharmacol*, **16(2)**: 107–113. DOI: 10.1016/j.euroneuro.2005.07.005

Prickett JD, Robinson DR and Steinberg AD (1981) Dietary enrichment with the polyunsaturated fatty acid eicosapentaenoic acid prevents proteinuria and prolongs survival in NZB x NZW F1 mice. *J. Clin. Invest*. **68**: 556-559. DOI: 10.1172/JCI110288

Prickett JD, Trentham DE, Robinson DR. (1984) Dietary fish oil augments the induction of arthritis in rats immunized with type II collagen. *J. Immunol*. **132**: 725-729.

Promislow JH, Goodman-Gruen D, Slymen DJ, Barrett- Connor E (2002) Retinol intake and bone mineral density in the elderly: the Rancho Bernardo Study. *J. Bone Miner Res.* **17**: 1349-1358. DOI: 10.1359/jbmr.2002.17.8.1349

Rabin RC (2009) Regimens: Ω-3 Fats Fail to Lift Depression in Heart Patients. *The New York Times*.

Reddy VS, Dakshinamurty KV, Sherke RL and Prasad TN (2002) Ω-3 Polyunsaturated FAs in the prevention of progression of chronic renal disease. *Indian J. Nephrol.* **12**: 6-9.

Richardson AJ and Ross MA (2000) Fatty acid metabolism in neurodevelopmental disorder: a new perspective on associations between attention-deficit/hyperactivity disorder, dyslexia, dyspraxia and the autistic spectrum. *Prostaglandins Leukot. Essent. FAs.* **63(1–2):** 1–9.

Robinson DR, Prickett JD, Makoul GT, Steinberg AD and Colvin RB (1986) Dietary fish oil reduces progression of established renal disease in (NZB x NZW)F1 mice and delays renal disease in BXSB and MRL/1 strains. *Arthritis Rheum*. **29**: 539-46. DOI: 10.1002/art.1780290412

Robinson DR (1991) Alleviation of autoimmune disease by dietary lipids containing ω-3 FAs. *Rheum. Dis. Clin. North Am.* **17**: 213-222.

Robson A (2006) Shellfish view of ω-3 and sustainable fisheries. *Nature* **444**: 1002. DOI: 10.1038/4441002d

Robson A (2007) Preventing the diseases of civilisation: shellfish, the ω-3:6 balance and human health. *Shellfish News* **23**: 25–27.

Ryan AM, Reynolds JV, Healy L, *et al.* (2009). Enteral nutrition enriched with eicosapentaenoic acid (EPA) preserves lean body mass following esophageal cancer surgery: results of a double-blinded randomized controlled trial. *Ann. Surg.* **249 (3)**: 355–363. DOI: 10.1097/SLA.0b013e31819a4789

Sanders TAB, Oakley FR, Miller GJ, Mitropoulos KA, Crook D and Oliver MF (1997) Influence of *ω-6* versus *ω-3* polyunsaturated FAs in diets low in saturated FAs on plasma lipoproteins and hemostatic factors. *Arteriosclerosis, Thrombosis, and Vascular Biology*. **17(12)**: 3449–3460. DOI: 10.1161/01.ATV.17.12.3449

Scher J and Pillinger M (2005) 15d-PGJ2: The anti-inflammatory prostaglandin?. *Clinical Immunology*, **114(2)**: 100–109. DOI: 10.1016/j.clim.2004.09.008

Shapiro JA, Koepsell TD, Voigt LF, Dugowson CE, Kestin M and Nelson JL (1996) Diet and RA in women: A possible protective effect of fish consumption. *Epidemiol.* **7**: 256-63. DOI: 10.1097/00001648-199605000-00007

Shichikawa K, Takenaka Y, Maeda A, Yoshino R, Tsujimoto M, Ota H, Kashiwade T and Hongo I. (1981) A longitudinal population survey of RA in a rural district in Wakayama. *The Ryumachi.* **21** (Suppl): 35-43.

Simon JA, Hodgkins ML, Browner WS, Neuhaus JM, Bernert JT and Hulley SB (1995) Serum FAs and the risk of coronary heart disease. *Am. J. Epidemiol*. **142**:469-476.

Simopoulos AP, Leaf A, Salem Jr N (2000). Statement on the essentiality of and recommended dietary intakes for *ω-6* and *ω-3* FAs. *Prostaglandins Leukot Essent FAs*, **63**: 119–121.

Simopoulos, AP (2003). Importance of the ratio of ω-6/ω-3 essential FAs: evolutionary aspects. *World Review of Nutrition and Dietetics*, **92**: 1–174. DOI: 10.1159/000073788

Sjúrður FO, Niels JS. (2002). Low consumption of seafood in early pregnancy as a risk factor for preterm delivery: prospective cohort study". *BMJ (Clinical Research Ed.)*, **324 (7335)**: 447. DOI: 10.1136/bmj.324.7335.447

Stoll AL, *et al.* (1999). Ω 3 FAs in bipolar disorder: A preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry*, 56(5): 407–412. DOI: 10.1001/archpsyc.56.5.407

Stone, Neil J. (1996). Fish consumption, fish oil, lipids, and coronary heart disease. *Circulation*, 94 (9): 2337–2340. DOI: 10.1161/01.CIR.94.9.2337

Susan A. (2006). *The Queen of Fats: Why Ω-3s Were Removed from the Western Diet and What We Can Do to Replace Them*. University of California Press, September 2006.

Trebunová A, Vasko L, Svedová M, Kasteľ R, Tucková M, Mach P. (2007). The influence of ω-3 polyunsaturated FAs feeding on composition of FAs in fatty tissues and eggs of laying hens. *Deutsche Tierärztliche Wochenschrift*, **114(7)**: 275–279.

Trevor AM, Bao, Danny QB, Valerie B, Ian B P, Lawrence JB. (1993). Docosahexaenoic acid but not eicosapentaenoic acid lowers ambulatory blood pressure and heart rate in humans. *Hypertension* **34 (2)**: 253–260.

Tribole EF. (2006). Excess Ω-6 Fats Thwart Health Benefits from Ω-3 Fats. *BMJ*332: 752–760. Retrieved 2008-03-23.

Tsukamoto Y, Okubo M, Yoneda T, Marumo F and Nakamura H (1982) Effects of PUFA on serum lipids in patients with chronic renal failure. *Nephron* **31(3)**: 236-41. DOI: 10.1159/000182652

Udo E (1993) *Fats That Heal, Fats That Kill*. 3rd ed. Burnaby (BC): Alive Books.

United States Food and Drug Administration (2004) FDA announces qualified health claims for ω-3 FAs. Press release. http://www.fda.gov/SiteIndex/ucm108351.htm. Retrieved 2006-07-10.

van de Rest O, Geleijnse JM, Kok FJ, van Staveren WA, Dullemeijer C, OldeRikkert MGM, Beekman A TF and de Groot CPGM (2008) Effect of fish oil on cognitive performance in older subjects. *Neurology* **71(6)**: 430–438. DOI: 10.1212/01.wnl.0000324268.45138.86

Walter CW, Stampfer, MJ, Colditz, GA, Speizer FE, Rosner BA and Hennekens CH (1993) Intake of trans FAs and risk of coronary heart disease among women. *The Lancet* **341 (8845)**: 581–585. DOI: 10.1016/0140-6736(93)90350-P

Walton AJ, Snaith ML, Locniskar M, Cumberland AG, Morrow WJ and Isenberg DA (1991) Dietary fish oil and the severity of symptoms in patients with systemic lupus erythematosus. *Ann. Rheum. Dis*. **50**: 463-466. DOI: 10.1136/ard.50.7.463

Wang C, Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B, Jordan HS and Lau J (2006) *ω-3* FAs from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *Am. J. Clin. Nutr*. **84 (1)**: 5–17.

Welinder L, Graugaard B and Madsen M (2000) HLA antigen and gene frequencies in Eskimos of East Greenland. *Eur. J .Immunogenet*. **27**: 93-97. DOI: 10.1046/j.1365-2370.2000.00209.x

Willett WC (2007) The role of dietary ω-6 FAs in the prevention of cardiovascular disease. *J. Cardiovasc. Med.* **8**: Suppl 1:S42-S45. DOI: 10.2459/01.JCM.0000289275.72556.13

William EML (2003) Diets could prevent many diseases. *Lipids*, **38(4)**: 317–321. DOI: 10.1007/s11745-003-1066-0

Yehuda S, Rabinovitz S and Mostofsky DI (2005) Mixture of essential FAs lowers test anxiety. *Nutritional Neuroscience*, 8**(4)**: 265–267. DOI: 10.1080/10284150500445795

Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K and Shirato K (2007) Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet* **369(9567)**: 1090–1098. DOI: 10.1016/S0140-6736(07)60527-3.

Young G and Conquer J (2005) Ω-3 FAs and neuropsychiatric disorders. *Reprod. Nutr. Dev,*. **45(1)**: 1–28. DOI: 10.1051/rnd:2005001

Zambón D, Sabaté J, Muñoz S, Campero B, Casals E, Merlos M, Laguna JC and Ros E (2000) Substituting walnuts for monounsaturated fat improves the serum lipid profile of hypercholesterolemic men and women: A randomized crossover trial. *Annals of Internal Medicine* **132(7)**: 538–546. DOI: 10.7326/0003-4819-132-7-200004040-00005

Zurier RB, Rossetti RG, Jacobson EW, DeMarco DM, Liu NY, Temming JE, White BM and Laposata M (1996) gamma-Linolenic acid treatment of RA. A randomized, placebo-controlled trial. *Arthritis Rheum*. **39**: 1808-17. DOI: 10.1002/art.1780391106