Modulation of the Arachidonic Cascade with ω3 Fatty Acids or Analogues: Potential Therapeutic Benefits

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Abstract: Increasing interest in the role of ω3 fatty acids has arisen in these latest years since evidence of their implication in the cardioprotective fish based diet of the Inuit has been demonstrated. Furthermore, several *in vitro*, *in vivo* and epidemiological studies support the benefit of this fatty acids intake in various pathological states such as in the cardiovascular, cancer, inflammation, psychiatric, paediatric, pulmonary, dermatological and ophthalmologic fields. This review will focus on metabolism and pharmacological implication of ω3 fatty acids intake as well as its interest in the prevention or treatment of the above-mentioned pathologies.

Keywords: ω3 fatty acid, ω6/ω3 ratio, cardiovascular disease, cancer, inflammation, psychiatric disorders

1. INTRODUCTION

a. General

During the past few years, there has been an increasing interest in the role of ω3 fatty acids (FA) found in pelagic fish and fish oils, predominantly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [1, 2, 3]. The basis of this heightened interest in dietary intakes of EPA and DHA essentially comes from epidemiological studies indicating that increased consumption of fish as a source of ω3 FA is often associated with decreased mortality as well as morbidity from cardiovascular events [4]. For example, the typical North American diet provides mainly saturated and ω6 FA and only 0.10 – 0.15 g of ω3 FA (EPA and DHA) per day [5, 6]. While, on the opposite, the high-fat traditional Greenland Inuit diet provides up to several grams of EPA and DHA daily in the form of marine mammals (seal, whale), wildfowl and various fish [7, 8] (Table I). It has long been recognised that disease pattern from the Inuit, when compared with those from the population of Denmark, exhibits a significantly lower rate of death from acute myocardial infarction despite only moderate differences in blood cholesterol levels [9]. This difference is not correlated with the total amount of ω3 FA intake but rather with the ω6/ω3 FA ratio ingested. Indeed, lipid intake consists of saturated, monounsaturated and polyunsaturated FA among which ω6 and ω3 FA are distinguishable depending on the position of the first unsaturation.

b. Sources

Omega-3 FA are long chain polyunsaturated FA with the first of many double bonds beginning with the third carbon atom (when counting from the methyl end of the FA molecule) while in ω6 FA, the first unsaturation begins with the sixth carbon atom (Fig. **1**). Polyunsaturated FA sources are numerous but only three 20 carbons FA (C_{20}-FA) are stored in membranes: ω3 eicosapentaenoic acid (EPA) (20 carbons, 5 double bonds), ω6 arachidonic acid (AA) (20 carbons, 4 double bonds) and ω6 di-homo-γ-linolenic acid (DHGLA) (20 carbons, 3 double bonds). Depending on the nature of the alimentation, they are ingested directly or as precursors which are then desaturated and elongated in those C_{20}-FA. The fish-based ω3 polyunsaturated FA consist mainly of EPA and DHA (22 carbons, 6 double bonds). Whereas plant foods and vegetable oils lack EPA and DHA, some contain varying amounts of the ω3 FA α-linolenic acid (ALA), an 18 carbon FA with 3 double bonds which is a precursor of EPA. Many vegetable oils are greatly enriched in ω6 FA (mainly as linoleic acid – LA – in corn, safflower, sunflower and soybean oils), although canola oil, flaxseeds and walnuts are also rich sources of ALA [9]. Linoleic acid (LA) (18 carbons, 2 double bonds) is the precursor of AA which is naturally abundant in animal products meat and eggs.

Table 1. Omega-3 Fatty Acid Content (EPA and DHA) of Several Fishes (adapted from [9])

Product	Concentration of EPA + DHA
Mackerel	2500 mg/100 g
Herring	1700 mg/100 g
Salmon	1200 mg/100 g
Trout (rainbow)	500 mg/100 g
Halibut	400 mg/100 g
Tuna (skipjack)	400 mg/100 g
Shrimp	300 mg/100 g
Cod	300 mg/100 g

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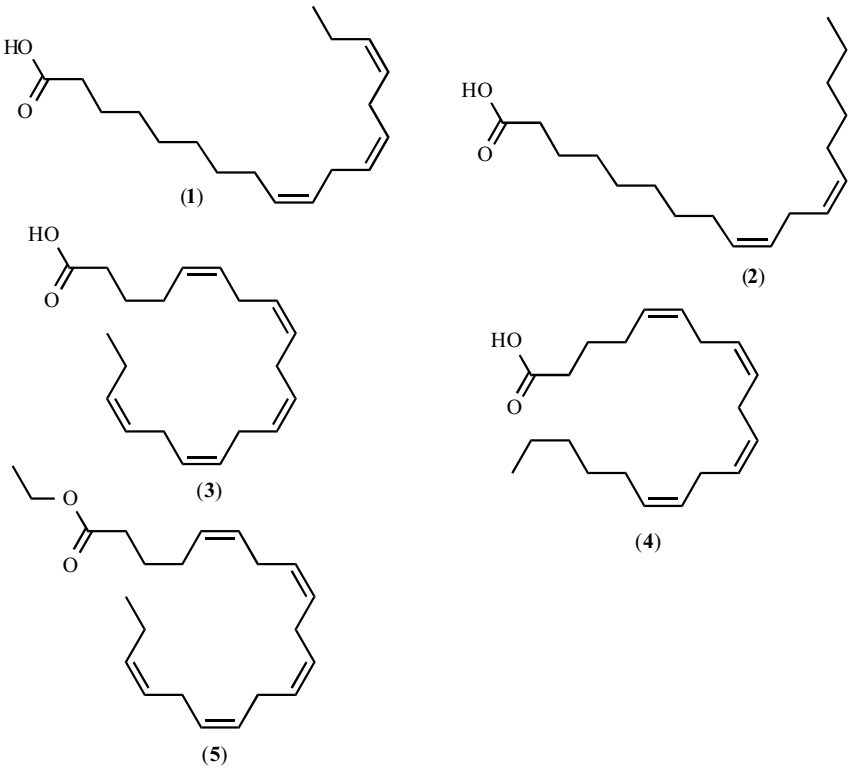

Fig. (1). Chemical structures of ω3 and ω6 C_{20}-FA and their C_{18}-FA precursors. Ethyl eicosapentaenoate is an ω3 C_{20}-FA analogue.

(1) α-Linolenic acid (ALA) C18:3 ω3; (2) Linoleic acid (LA) C18:2 ω6; (3) Eicosapentaenoic acid (EPA) C20:5 ω3; (4) Arachidonic acid (AA) C20:4 ω6; (5) Ethyleicosapentaenoate.

c. Fatty Acids Metabolism

Eicosanoids are lipid mediators produced by oxidation of C_{20}-FA (AA, EPA, DHGLA) (Fig. **2**). Whatever the FA considered, three pathways generate, depending on the enzyme implicated, three families of metabolites. Cyclooxygenases (COX) generate prostanoids (prostaglandins, thromboxanes, prostacyclin), lipoxygenases (LOX) generate leukotrienes and epoxygenases, epoxy derivatives. Arachidonic acid in the membranes serves as substrate for the enzymes cyclooxygenases and

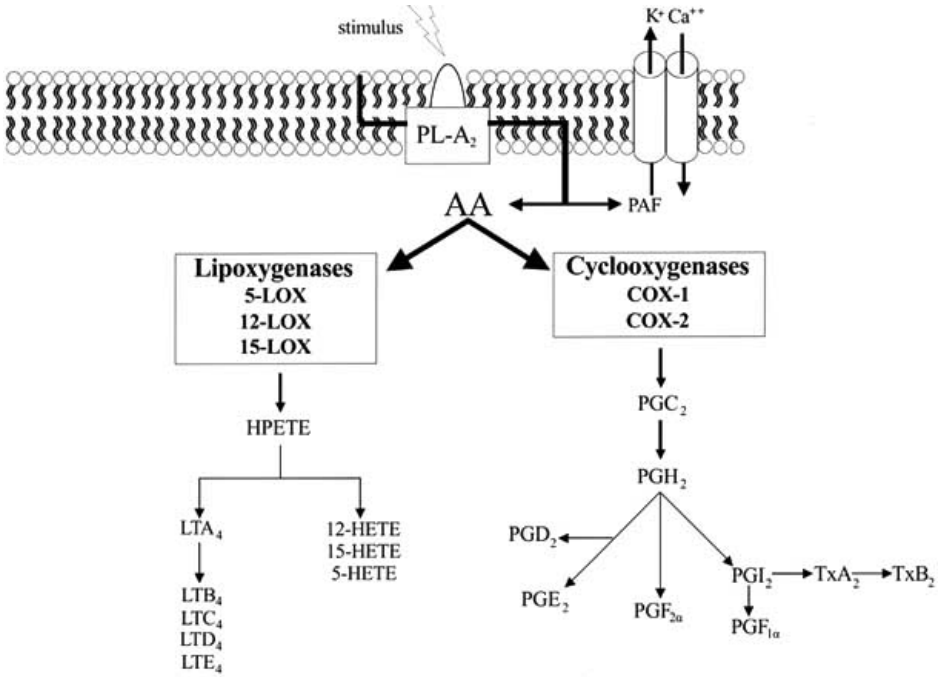

Fig. (2). Arachidonic cascade: cyclooxygenases and lipoxygenases pathways (PLA_2: phospholipase A_2, PAF: platelet activating factor, HPETE: hydroperoxyeicosatetraenoic acid, HETE: hydroxyeicosatetraenoic acid).

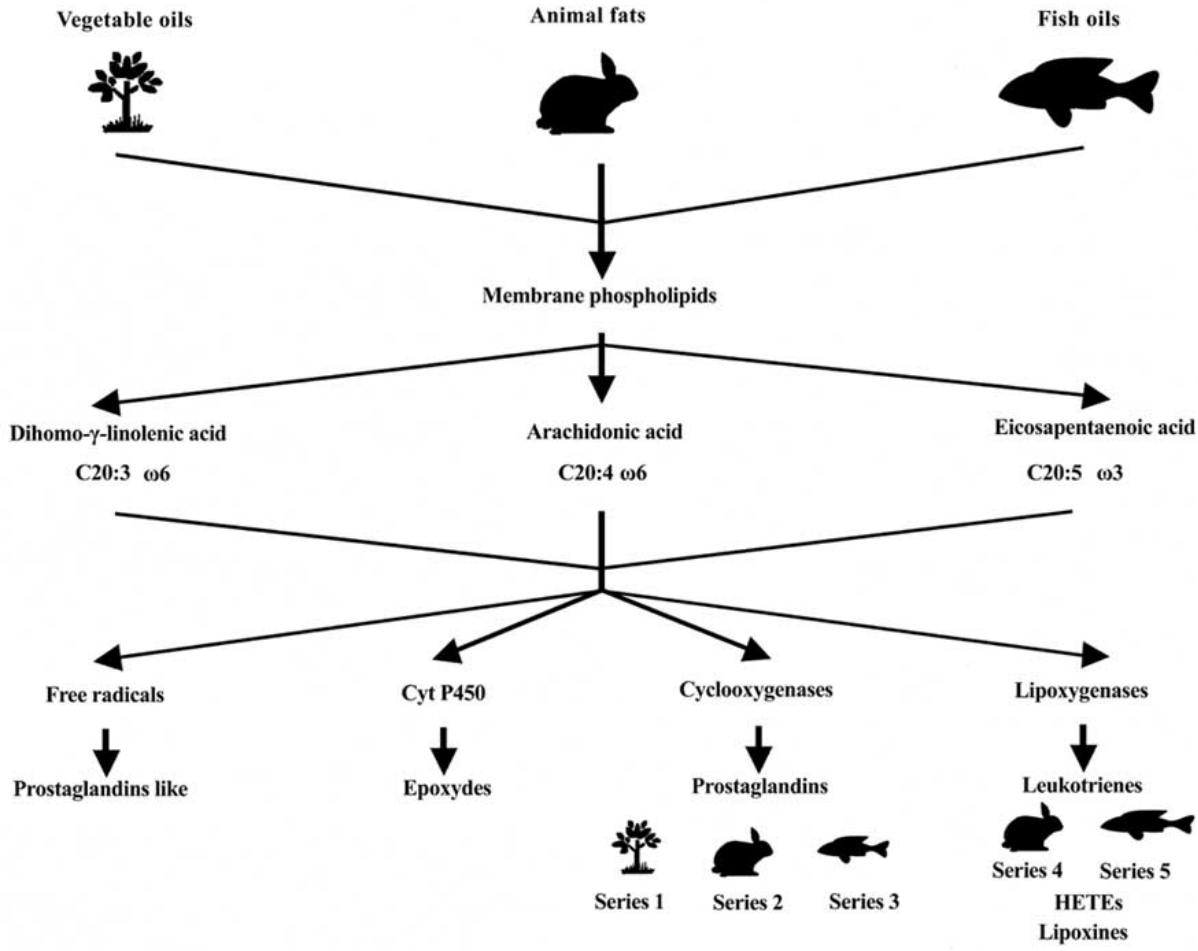

Fig. (3). Biosynthesis of distinct eicosanoids subtypes following fatty acids dietary intakes.

lipoxygenases and is converted into prostaglandins (PGs), prostacyclin, thromboxane (TXA) and leukotrienes. Those eicosanoids influence numerous physiological activities such as platelet aggregation, gastrointestinal and renal homeostasis, vascular constriction. They are also implicated in pathological conditions such as cancer and inflammation. Arachidonic acid, the major FA, is stored in membranes in phospholipids. Nevertheless the cellular FA acid pattern may be modulated by the diet: when ω3 FA are ingested, they are incorporated in the membranes and subsequently the ω3/ω6 ratio increases. A competition for the enzymes between ω3 and ω6 substrates therefore occurs. Depending on the nature of the C_{20} precursor, varying on the number and position of the unsaturations, different series of metabolites are obtained (Fig. **3**). When di-homo-γ-linolenic acid (C20:3 ω6) is the substrate of cyclooxygenase, prostaglandins of series 1 are obtained while arachidonic acid (C20:4 ω6) engenders PGs and TXA of series 2 and eicosapentaenoic acid (C20:5 ω3) PGs and TXA of series 3 (Fig. **4**). Those different series exert distinct physiological effects: for example PGE_1 tends to have anti-inflammatory properties and is immune-enhancing while PGE_2 is a highly inflammatory substance and PGE_3 tends to be mildly anti-inflammatory and immune-enhancing. Thromboxane A_2 causes platelet aggregation and vasoconstriction, TXA_3 is a weak platelet aggregator and vasoconstrictor while prostaglandin I_3 (PGI_3) displays quite similar antiaggregatory and vasodilatative effects of prostacyclin (PGI_2). With lipoxygenase as enzyme and EPA as substrate, the 5-series leukotrienes are generated. They have partially antagonist biological effects compared with the AA metabolites: LTB_4 is a more potent vasoconstrictor and chemotaxis agent than LTB_5.

The ω6 polyunsaturated FA, arachidonic acid, gives rise to the eicosanoid family of inflammatory mediators (prostaglandins, leukotrienes and related metabolites) and through these regulates the activities of inflammatory cells, the production of cytokines and the various balances within the immune system [10]. It has been shown that a dietary increase of polyunsaturated ω3 FA reduced strongly the production of interleukins (IL) IL-1 β, IL-2, IL-6 and TNF-α (tumour necrosis factor-α). In contrast, diets with a higher supply of linoleic acid (ω6) increased significantly the production of pro-inflammatory cytokines, like TNF-α [11, 12].

2. REVIEW OF THE LITERATURE

1. Inflammation

Since inflammation is the main event related to eicosanoids production, it is obvious that many studies have been conducted in order to analyse the modifications induced *in vivo* and *in vitro* by presence of ω3 FA as a competitive

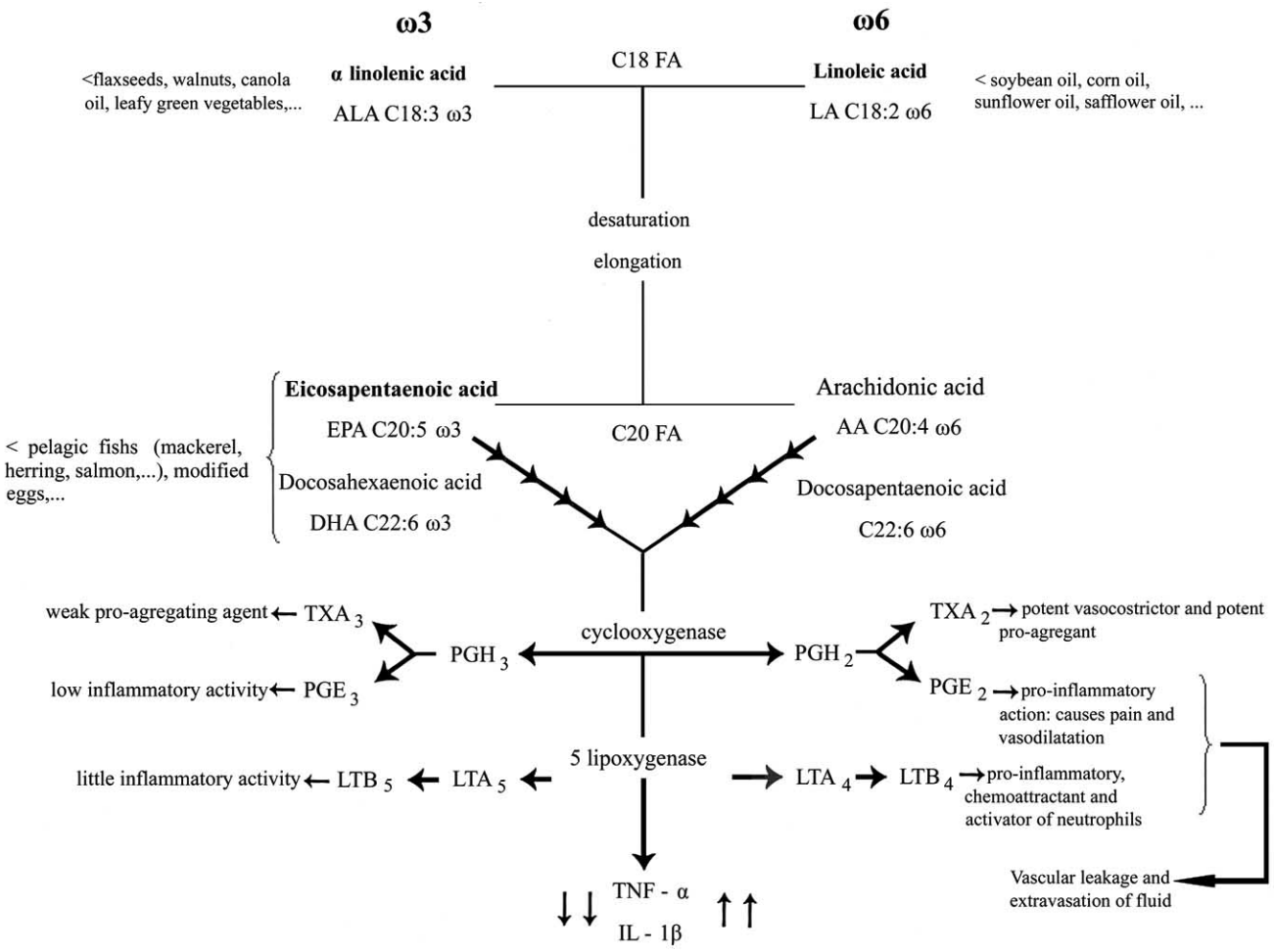

Fig. (4). Metabolisation of ω3 or ω6 FA by cyclooxygenase and 5 lipoxygenase.

substrate with ω6 FA arachidonic acid in the COX pathway. Formation of PGE_3 (mildly anti-inflammatory and immune enhancing properties) and LTB_5 (weak inducer of inflammation and weak chemotaxic agent) instead of PGE_2 (highly inflammatory substance) and LTB_4 (potent pro-inflammatory agent and powerful inducer of neutrophil chemotaxis and adherence) may have clinical impact on miscellaneous pathologies. This was confirmed in the following studies.

In vitro, a parenteral ω3 FA emulsion (Omegaven®) significantly reduced TNF-α production in LPS-stimulated macrophages, with a 46% reduction in TNF-α from baseline observed with conventional lipidic emulsion (ω6, Lipovenos®) [13].

Altering eicosanoid mediator precursor availability by infusion of ω3 FA from fish oil increased anti-inflammatory cytokines production in a model of acute pancreatic in rats. Together with improved renal and respiratory function, it suggests that the systemic response to pancreatic injury is attenuated, confirming that the AA derived mediators are generated from ω6 FA and have strong proinflammatory effects while the EPA-derived mediators generated from ω3 FA are less active or even exhibit anti-inflammatory effects [14].

In the treatment of inflammatory bowel diseases such as ulcerative colitis and Crohn's disease the use of polyunsaturated long-chain FA may act by reducing low-grade active inflammation rather than by preventing reinitiation of the inflammatory process from a truly quiescent state. Whether this treatment is applicable to all patients is not fully elucidated. Nevertheless, taken together, all the studies suggest the effectiveness of those new therapeutic approaches, not only when conventional treatment fails or when it is not possible to treat chronically, but also, in some instances, as first choice [15].

When assessing the benefits of dietary supplementation with fish oils in several inflammatory and autoimmune diseases in humans, including rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis, lupus erythematosus, multiple sclerosis and migraine headaches in placebo-controlled trials, a significant benefit (including decreased disease activity and a lowered use of anti-inflammatory drugs) is observed [16]. Preoperative intake for 5 days of a formula enriched with ω3 FA and arginine before colorectal neoplasm surgery improves the immuno-metabolic response and decreases the infection rate but postoperative prolongation with such supplemented formula has no additional benefit [17].

2. Cardiovascular

Considering the assessed background of ω3 in cardiovascular risks prevention and knowing the biological roles of ω3 derived eicosanoids in platelet aggregation and blood vessel constriction, ω3 FA supplementation has been investigated in numerous cardiovascular disease patterns. The balance of the engendered metabolites is important for regulation of physiological processes. The profile of eicosanoids varies from cell to cell; platelets convert AA to TXA_2, whereas vascular endothelium produces mainly prostacyclin. TXA_2 is a potent vasoconstrictor which induces platelet aggregation and PGI_2 is a potent vasodilatator which prevents platelets aggregation. Balance between these two eicosanoids maintains normal haemostasis and any alteration in the TXA_2/PGI_2 ratio will affect thrombosis, haemostatic plug formation and atherogenesis. Alteration in dietary fat may modify TXA_2/PGI_2 balance since it appears that EPA is converted into TXA_3, a weak pro-aggregating agent and PGI_3, a potent anti-aggregating and vasodilatator agent. Therefore, the overall effect of fish consumption is a decrease in platelet aggregation and increased bleeding time, which is the main biochemical basis of their cardioprotective effects.

EPA and DHA increase systemic arterial compliance which reflects arterial elasticity and appears to predict future cardiovascular events. Their consumption tends also to reduce pulse pressure and total vascular resistance, effects that may reduce the risk of adverse cardiovascular events [18]. Among the effects of diets enriched in DHA hypotensive properties have been demonstrated. One mechanism that can lower blood pressure is the direct dilation of arterioles by docosahexaenoic metabolites. Vascular endothelium contains cytochrome P-450 epoxygenases that transform the AA into epoxyeicosatrienoic acids, potent dilators of coronary arterioles and activators of large-conductance calcium-activated potassium channels. Analogous activations occur for docosahexaenoate and its five cytochrome P-450 epoxygenase metabolites, epoxydocosapentaenoates potently dilate coronary microvessels and are the most potent fatty epoxides known to activate calcium-activated potassium channels in coronary smooth muscle cells. Those both actions may contribute to the hypotensive effects of dietary fish oils [19]. Other benefits of ω3 FA include improved endothelial function, increased HDL2-cholesterol concentrations, reduced triacylglycerol-rich lipoprotein concentrations, reduced postprandial lipaemia, and reduced remnant concentrations. In contrast, LDL-cholesterol concentrations have often been noted to rise and the potential of increased oxidizability of LDLs is potentially adverse with lipid modification, but this potential can be overcome with vitamin E supplementation [20].

A US prospective cohort study with 12 years of follow-up with 43671 men aged 40 to 75 years suggests that eating fish once per month or more can reduce the risk of ischemic stroke [21], possibly through potential mechanisms of decreased blood pressure, reduced platelet aggregation, and enhanced deformability of erythrocyte cells [22]. If consumption of fish is increased to several times per week, it does not increase the risk of haemorrhagic stroke [23]. A 43% reduction in the 10-years risk of myocardial infarction mixture was estimated in healthy women consuming 4 g EPA + DHA and 2 g of γ-linolenic acid (GLA) (18 carbon atoms, 3 double bonds, ω6, precursor of DHGLA) daily. This consumption favourably altered blood lipid and fatty acid profiles [24].

Numerous mechanisms of action for the favourable effect of dietary ω3 FA on factors implicated in the pathogenesis of atherosclerosis have been described. Occlusion of aortocoronary venous bypass grafts is reduced after 1 year by daily ingestion of 4 g fish-oil concentrate. Moreover, currently, food sources rich in ω3 FA are thought to be beneficial in secondary prophylaxis after a myocardial infarction [25]. Omega-3 FA may be also particularly beneficial and should be considered in patients with documented risks for sudden cardiac death: the risk of it was found to be reduced by 45 – 81% as suggested by epidemiological and clinical trial data reviewed from biomedical literature since 1966 by Caroll and al. [26]. Results from experimental studies in animals suggest that recent dietary intake of those components, compared with saturated and monounsaturated fats, reduces vulnerability to ventricular fibrillation, a life-threatening cardiac arrhythmia that is a major cause of ischemic heart disease mortality. A similar effect occurs in humans: the dietary intake of long-chain ω3 FA from seafood is associated with a reduced risk of cardiac arrest [27]. The mechanism of the antiarrhythmic action of ω3 FA has been studied in spontaneously contracting cultured cardiac myocytes of neonatal rats. An antiarrhythmic action is obtained with dietary ω3 and ω6 FA; saturated FA and the monounsaturated oleic acid induced no such action. The action of those FA is to electrically stabilize myocytes in the heart by increasing the electrical stimulus required to elicit an action potential by 50% and prolonging the relative refractory time by 150%. These electrophysiological effects result from an action of the free FA to modulate sodium and calcium currents in the myocytes. The FA also modulate sodium and calcium channels and have anticonvulsant activity in brain cells [28].

In patients suffering from sickle cell disease, treatment with dietary ω3 FA for 1 year reduced the frequency of pain episodes requiring presentation to the hospital (from 7.8 events to 3.8 events/year). This treatment concurrently decreased plasma levels of products of thrombin generation (prothrombin fragment 1.2) and plasma levels of thrombolytic products (D-dimer and plasmin:antiplasmin (PAP) complex) and thrombin:antithrombin (TAT) complex, implying that the reduction in pain events was related to ω3

FA-dependent inhibition of prothrombotic activity in sickle cell disease [29].

3. Cancer

Increased synthesis of prostaglandins is frequently observed in several tumour progression models in animals and numerous tumoural cell lines secrete more prostaglandins compared to corresponding healthy tissues. Those prostaglandins are able to interfere with cells growth, immunocompetence and cellular adhesion [30, 31]. Therefore the role of ω3 FA in cancer has been investigated.

The role of a qualitatively and quantitatively altered nutrition for the development of cancer in human is largely recognised. While the human life expectancy is continuously expanding and the World Health Organization is predicting a dramatic rise in the number of patients that will get cancer and die from it in the next decades, it is useful to attempt to understand the real impact of nutrition at the level of the oncogenesis mechanisms. Oxidative stress, methylation deficit and imbalance in the ratio of ω3 and ω6 FA represent situations directly linked to nutrition and which contribute to an increased risk for cancer development. The understanding of the mechanisms by which nutrition affects these processes should better stimulate health professionals to consider with more attention what their patients are eating [32]. The results of animal studies have demonstrated that the consumption of ω3 FA can slow the growth of cancer xenografts, increase the efficacy of chemotherapy and reduce the side effects of the chemotherapy or of the cancer. Molecular mechanisms postulated to contribute to the multiple benefits of ω3 FA include:

- suppressing the expression of cyclooxygenase in tumours, thus decreasing proliferation of cancer cells and reducing angiogenesis in the tumour;

- decreasing the expression of AP-1 and ras, two oncogenes implicated in tumour promotion;

- inducing differentiation of cancer cells;

- suppressing nuclear factor-kappa B activation and bd-expression, thus allowing apoptosis of cancer cells; and

- reducing cancer-induced cachexia [33].

Eicosapentaenoic acid supplementation has demonstrated inhibition of tumour growth, potentially through alterations in the expression of the pro-angiogenic VEGF. The mechanism(s) of EPA as an inhibitor of tumour-related angiogenic growth factors may be associated with COX-2 enzyme fatty acid metabolism and deserves further study [34]. Tavani *et al.* reported that data from case-control studies, conducted in Italy and Switzerland between 1991 and 2001, have been analysed to evaluate the role of ω3 polyunsaturated FA intake in the aetiology of cancer of oral cavity and pharynx, esophagus, large bowel, breast and ovary. These results suggest that ω3 FA decrease the risk of cancers [35]. The consumption of fatty fish, which contains large amounts of ω3 FA, may lower the risk of hormone-responsive cancers. In Sweden, a country with a wide range of high fatty fish consumption, its consumption was inversely associated with endometrial cancer risk [36]. High-fat diets rich in polyunsaturated ω6 FA stimulate mammary carcinogenesis and tumour progression; the long-chain ω3 FA exert inhibitory effects. Prominent among the biochemical mechanisms involved is the regulation of eicosanoid biosynthesis from dietary linoleic acid; both prostaglandins resulting from cyclooxygenase activity, and the leukotrienes and hydroxy-FA produced under the influence of the lipoxygenases are involved in mammary carcinogenesis, tumour cell growth and apoptosis, angiogenesis, invasion and metastasis. A shift towards the typical high-fat Western diet, rich in ω6 and poor in ω3 FA, may be a major factor in the increasing breast cancer incidence and mortality rates in Japanese women. A nutritional intervention comprising dietary ω3 FA supplementation and, in populations consuming a high fat diet a reduction in total fat and ω6 FA intake, may have a place not only in breast cancer prevention, but as an adjunct to the surgical treatment of the breast cancer patient [37]. Diets rich in phytoestrogens and ω3 FA contained in flaxseed inhibited the established human breast cancer growth and metastasis in a nude mice model, and this effect is partly due to its downregulation of insulin-like growth factor I and epidermal growth factor receptor expression [38]. Marine FA may have an antitumor effect also on prostate tumour cells. A 12 years study following up 47882 men concluded that eating fish more than three times per week was associated with a reduced risk of prostate cancer, and the strongest association was for metastatic cancer compared with infrequent consumption, i.e., less than twice per month. Each additional daily intake of 0.5 g of marine FA from food was associated with a 24% decreased risk of metastatic cancer [39].

Dietary ω3 FA are also interesting in non-hormonal cancers since supplementation with those FA possesses significant tumour suppressing properties on the growth of human colon carcinoma xenograft in athymic nude mice. Histopathologic examination and expression array analyses (human cytokine and apoptosis arrays) support the tumour growth inhibition data and the primary tumour suppressing FA is docosahexaenoic acid [40]. In patients with sporadic adenomatous colorectal polyps, supplementation with ω3 FA (EPA (4.1 g/day) and DHA (3.6 g/day)) for 12 weeks exerts a rapid beneficial effect on rectal mucosal proliferation and therefore may protect high-risk subjects from colon cancer [41]. Fatty acid composition of dietary fat would be one of the detrimental factors in colon cancer development. Fats containing ω6 FA (e.g. corn oil) enhance and ω3 FA (e.g. fish oil) reduce chemically-induced colon cancer in animal studies. A diet containing mustard oil (containing ω3 FA) compared with corn and fish oils treated groups on azoxymethane-induced colon cancer in rats gave the following results: colon tumour incidence and multiplicity were found to be 90, 75, and 50% and 1.7, 0.8, and 0.4 tumours/rat in corn, fish and mustard oil treated groups respectively [42]. The effect of fats depends not only on the quantity, but also on their composition in specific FA. Moreover, fats are peroxidizable, and peroxidation products as well as antioxidants play a role in the pathogenic process of colorectal cancer [43]. An epidemiological study suggests that independently of total energy intake, substituting AA by butyrate, ALA, or ω3 FA (EPA) may reduce colorectal cancer risk [44].

A population-based prospective study following 5,885 residents for 14 years found linearly decreasing relative risk for lung cancer with increased frequency of consumption of fresh fish and shellfish [45].

4. Pregnancy – Paediatry

ω3 FA intake is very important during pregnancy for the child as well as for the mother.

In rats , the maternal dietary FA composition influences maternal and fetal plasma and tissue composition, and an increase in dietary ω3 FA decreases the amount of AA in maternal and fetal tissues [46]. Nevertheless, the 1994-1996 U.S. Department of Agriculture/ARS Continuing Survey of Food Intakes by Individuals, a nationally representative analysis of consumption, provided data on intakes of FA of pregnant or lactating women. Mean individual daily intakes of ω6 fats were more than 200% of recommended upper limits proposed by National Institutes of Health, and intakes of ω3 fats were only 20-60% of recommended adequate intakes [47]. This may be damageable because the fetus, especially during the last trimester of pregnancy, has high DHA requirements. It must be provided by the mother, since fetal DHA synthesis is negligible in this stage of development [48]. About 67 mg DHA/day is estimated to be accumulated by the fetus during the third trimester of gestation [49] and fetal demand for DHA may not be entirely satisfied in multiple pregnancies. Therefore a greater maternal intake of DHA should be encouraged in some pregnancies for optimal tissue perfusion [50]. Omega-3 FA intake is also implicated in the duration of gestation: it increased significantly when DHA intake from eggs until parturition was increased during the last trimester of pregnancy [51]. In preterm births, the maternal percent of total arachidonic acid in red blood cells and plasma was increased versus controls at delivery. Maternal red blood cell EPA and ω3/ω6 ratios were also lower in preterm cases than in controls at delivery [52].

Because mothers selectively transferred DHA to their fetuses to support optimal neurological development during pregnancy, mothers may increase their risk of suffering major depressive symptoms in the postpartum period if sufficient dietary intake is not provided. Both lower DHA content in mothers' milk and lower seafood consumption are associated with higher rates of postpartum depression [53].

Disturbance in thromboxane and prostacyclin biosynthesis has been observed in preeclampsia [54]. High-dose supplements of fish oil reduce thromboxane TXA_2 synthesis in nonpregnant human subjects and were therefore proposed as a means of preventing various small-vessel disorders, including preeclampsia. High-dose ω3 FA intake (1.6 g/day) in pregnancy significantly reduced maternal thromboxane TXA_2 synthesis. These results may provide a basis for a possible role of fish oil in managing patients at risk for preeclampsia [55]. The possible protective effect of breast milk against atopic manifestations in infancy, i.e. atopic eczema, has been controversial for the last decades. Besides the methodological problems, differences in the composition of human milk could explain these controversies. Low levels of ω3 FA in human milk, and particularly a high AA:EPA ratio in maternal milk and serum phospholipids in the infants, were related to the development of symptoms of allergic disease at 18 months of age [56]. The relative levels of DHA and total ω3 long-chain FA were lower and the ratio of total ω6 to ω3 long chain FA was higher in the allergic children than in the controls [57].

The sleep patterns of infants born to mothers with higher plasma phospholipid DHA suggest greater CNS maturity (by study of sleep and wake states of newborns) [58] and research has shown that long chain FA are associated with improved visual and cognitive development: breast-fed children had higher IQ scores compared with children who received an infant formula that did not contain long chain FA [59]. Maternal intake of very-long-chain ω3 FA during pregnancy and lactation may be favourable for later mental development of children. The children's mental processing scores at 4 years of age correlated significantly with maternal intake of DHA and EPA during pregnancy [60] confirming this way the predominant role of those FA in the neuronal development of fetuses.

5. Psychiatric and Neurological Disorders

The ratio of membrane ω3 to ω6 FA can be modulated by dietary intake. This ratio influences neurotransmission and prostaglandin formation, processes that are vital in the maintenance of normal brain function [61]. A depletion in DHA induces cognitive deficits in rats. This deficit appears to represent a deficit in higher order learning [62]. The FA also modulate sodium and calcium channels and have anticonvulsant activity in brain cells [63]. Ethyl-eicosapentaenoate was administered to patients suffering of miscellaneous psychiatric disorders: borderline personality disorders, depression and schizophrenia.

One gram of ethyl-eicosapentaenoate given for 8 weeks to female subjects with borderline personality disorders in a placebo-controlled, double blind study was shown to be superior to placebo in diminishing aggression as well as the severity of depressive symptoms. This may be a safe and effective form of monotherapy for women with moderately severe borderline personality disorder [64]. In major depression, all studies revealed a significant decrease of the ω3 FA and/or an increase in the ω6/ω3 ratio in plasma and/or in the membranes of the red cells. Parallel to these modifications, other biochemical perturbations have been reported in major depression, particularly an activation of the inflammatory response system, resulting in an increase of the pro-inflammatory cytokines (interleukins: IL-1β, IL-6 and interferon γ) and eicosanoids (among others, prostaglandin E_2) in the blood and the cerebrospinal fluid of depressed patients. Therefore, ω3 FA could be associated with different levels in the pathophysiology of major depression, on the first hand through their role in the membrane fluidity which influences diverse steps of neurotransmission and, on the other hand, through their function as precursor of pro-inflammatory cytokines and eicosanoids disturbing neurotransmission. Hence, antidepressants could exhibit an immunoregulating effect by reducing the release of pro-inflammatory cytokines, by increasing the release of endogenous antagonists of pro-inflammatory cytokines like IL-10 and, finally, by acting like inhibitors of cyclooxygenase [65]. Ethyl-

eicosapentaenoate was tested in depressed patients who had low basal blood levels of EPA. Patients with persistent depression despite ongoing treatment with an adequate dose of a standard antidepressant receiving 1g/day of ethyl-eicosapentanoate for 12 weeks in addition to unchanged background medication felt strong beneficial effects on depression, anxiety, sleep, lassitude, libido, and suicidality [66]. Ethyl-eicosapentaenoate may be also an effective and well-tolerated add-on treatment in schizophrenia [67].

6. MISCELLANEOUS

a. Pulmonary

Dietary changes in ω3 FA affect the composition of lipid membranes, the production of eicosanoids, and neutrophil chemotaxis. Hence, there is clear evidence of an effect of those FA on potential modulators of lung disease. Animal studies showed that EPA or GLA supplementation of animals exposed to endotoxins results in decreased effects on TXB_2 and pulmonary vascular resistance. Small human trials confirmed that supplementation with EPA results in decreased generation of leukotrienes by neutrophils. Hence, a protective effect of such FA in lung disease is biologically plausible. Epidemiologic studies showed possible protective effects against asthma in children. Fish consumption is protective against physician-diagnosed emphysema and chronic bronchitis and low spirometry values in smoking patients. Persons with cystic fibrosis have lower concentrations of essential FA in their plasma lipids than do healthy control subjects. Persons with atopy have also been reported to have lower ratios of ω3 to ω6 FA in plasma lipids than healthy control subjects [68]. For childhood asthma the major modifiable dietary environmental risk factors are lack of breastfeeding and low intake of ω3 FA. Observational studies have shown a 30%-50% reduction in childhood asthma with exclusive breastfeeding for three months, and similar reductions in children who eat fish regularly [69]. In patients who are at risk for acute respiratory distress syndrome, decreased levels of GLA (ω6 series), ALA and EPA (ω3 series) are observed. These results suggest that lipid peroxides and alteration in essential FA metabolism may have a role in the pathogenesis of acute respiratory distress syndrome [70].

b. Skin

Systemic administration of ω3 FA has been investigated in prevention and treatment of miscellaneous dermatological disorders and diseases.

Psoriasis is a chronic skin disease characterised by scaling and inflammation; it affects between 1 and 2 % of the United States population. In its most typical form, psoriasis results in patches of thick, red skin covered with silvery scales. The disease may also affect the fingernails, the toenails, and the soft tissues inside the mouth and genitalia. About 15 % of people with psoriasis have joint inflammation that produces arthritis symptoms. Treatments of this incapacitating disease consist of local or even systemic drug administration and also phototherapy. In patients with guttate psoriasis, intravenous infusion of an ω3 FA rich lipid emulsion compared with emulsion containing ω6 FA appeared to be of some benefit [71]. In a double-blind, randomised, parallel group, multicentric study, patients affected by severe chronic plaque-type psoriasis received daily infusions with either ω3 FA-based lipid emulsion or a conventional ω6-lipid preparation for 14 days. Intravenous ω3 FA administration was determined effective and was related to changes in inflammatory eicosanoid generation since neutrophil 4- versus 5-series leukotriene generation and platelet 2- versus 3- thromboxane generation were determined [72]. Orally-administered ω3 FA are reported to be particularly effective in reducing the effects of UV exposure on skin and therefore could potentially have a major effect on the incidence of skin cancers and photo-ageing. The mechanisms of action of those FA appear to depend on their anti-inflammatory properties, acting to reduce the UV-induced release of cytokines and other mediators from a variety of skin cell types [73]. In response to UVB-irradiation keratinocytes release a variety of cytokines and prostaglandins, including TNF-α, IL-1α, IL-6, and PGE_2. As previously exposed, ω3 FA can modulate cytokine synthesis, resulting in higher TNF-α and IL-1α expressions, both in non-irradiated and UVB-irradiated keratinocytes. EPA treatment results also in decreased PGE_2 and IL-6 secretion after UVB-irradiation. In contrast to EPA, oleic acid (monounsaturated FA) and LA (ω6) treatments did not result in higher TNF-α or IL-1α levels in non-irradiated or UVB-irradiated keratinocytes, indicating that the observed effects are specific for EPA [74]. The varied effects of different classes of dietary FA on carcinogenesis suggest that FA composition is also an important determining factor in tumour development. The association between dietary ω3 and ω6 FA intake and risk of squamous cell carcinoma of the skin was investigated and a consistent tendency for a lower risk of squamous cell carcinoma of the skin with higher intakes of ω3 FA was determined [75].

c. Eyes

Docosahexaenoic acid increases membrane fluidity, improving neurogenesis, synaptogenesis and the activity of retinal photoreceptors [76] and it accumulates in rod outer segment disks and synaptic terminals. It plays an important role in disordering disk membranes and in providing an adequate environment for conformational rhodopsin changes and in modifying the activity of retinal enzymes since a decrease of DHA content in the retina has been shown to affect visual function in monkey [77]. Docosahexaenoic acid significantly enhances visual acuity maturation and in newborns with ω3 FA deficiency light sensitivity of retinal rod photoreceptors is significantly reduced [78]. The relationship between intake of total and specific types of fat and risk for advanced age-related macular degeneration, the leading cause of irreversible blindness in adults was evaluated. Diets high in ω3 FA and fish were inversely associated with risk for age-related macular degeneration when intake of LA was maintained low [79].

3. CONCLUSION

Omega-3 FA craze began when low myocardial infarction rate and massive fatty fish consumption by Inuit were found to be correlated [7, 9]. Because they are atoxic and their side

effects are very common (bad taste, dyspepsia), one could say they only exhibit favourable properties. Therefore their roles were investigated in epidemiological studies concerning numerous pathologies. Indeed, benefits of increasing ω3/ω6 ratio were broadly demonstrated and key metabolites TXA_3, PGE_3, LTB_5 and PGI_3 were identified. Knowledge of their pharmacological properties supports their implication especially in the cardiovascular, inflammation and cancer fields. In regards to all those favourable implications of ω3 FA in numerous diseases patterns, fish consumption, fish oil or ω3 FA supplementation appear as evident. Many alimentary supplements, containing fish oil or ω3 FA, are available. Yet the easiest and most suitable ω3 FA source might be alimentation: fatty fishes (mackerel, herring, salmon, halibut, tuna,…) or ω3 enriched food. Omega-3 enriched foods consist among others of meat, margarine, milk and particularly eggs. The egg yolk of enhanced ω3 eggs has been modified by altering the hens' diet, feeding them with vegetable ω3 FA precursors. Consumption of all those various ω3 FA sources should be encouraged since large body of literature suggests that western diets are deficient in ω3 FA and have excessive amounts of ω6 FA compared with the diet on which human beings evolved and their genetic patterns were established. Excessive amounts of ω6 FA and a very high ω6/ω3 ratio may promote the pathogenesis of many diseases, including cardiovascular disease, cancer, and inflammatory and autoimmune diseases, whereas increased levels of ω3 FA (and therefore a low ω6/ω3 ratio) exert suppressive effects. The optimal ω6/ω3 ratio to provide 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 ω3 FA will depend on the degree of severity of disease resulting from the genetic predisposition [80]. This therapeutic dose depends also on socio-economical factors since intakes of EPA and DHA are found highest in women older than 40 years of age, those of Asian/Pacific descent, households with income greater than 350% of the poverty level, and women with at least 1 year of college education [81]. Therefore the adequate dose to recommend must still be determined before ω3 FA are widely dispensed as a preventive agent for numerous pathologies.

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ABBREVIATION

AA	=	Arachidonic acid
ALA	=	α-Linolenic acid
COX	=	Cyclooxygenase(s)
DHA	=	Docosahexaenoic acid
DHGLA	=	Di-homo-γ-linolenic acid
EPA	=	Eicosapentaenoic acid
FA	=	Fatty acid(s)
GLA	=	γ-Linolenic acid
IL	=	Interleukin
LA	=	Linoleic acid
LOX	=	Lipoxygenase(s)
LTB	=	Leukotriene
PGs	=	Prostaglandins
TNF-α	=	Tumour necrosis factor-α
TXA	=	Thromboxane
VEGF	=	Vascular endothelial growth factor

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