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Critical Review

Dietary Stearidonic Acid Is a Long Chain (n-3) Polyunsaturated Fatty Acid with Potential Health Benefits[1,2]

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Abstract

The therapeutic and health-promoting effects of (n-3) long-chain PUFA (LCPUFA) from fish are well known, although these same benefits may not be shared by their precursor, α-linolenic acid (ALA). World-wide agencies and scientific organizations (i.e. FDA, AHA, International Society for the Study of Fatty Acids and Lipids, Institute of Medicine, WHO, etc.) have made similar dietary recommendations for (n-3) LCPUFA; however, due to concerns regarding the safety of consuming fish, alternative sources of (n-3) LCPUFA are being investigated. One such lipid is stearidonic acid (SDA), a naturally occurring (n-3) PUFA that may have similar biological properties to eicosapentaenoic acid (EPA), a major (n-3) PUFA in fish oil. Existing and novel plant sources rich in SDA are being cultivated and promoted as potential alternatives to marine-based (n-3) PUFA. This critical review provides a direct comparison of SDA with other dietary (n-3) PUFA under similar experimental conditions. The comparative results suggest that SDA shares many of the biological effects of (n-3) LCPUFA and functions most similarly to dietary EPA compared with ALA when consumed in a typical Western diet. Therefore, although SDA may not replace fish as a major dietary source of (n-3) LCPUFA, it could become a prominent surrogate for EPA in the commercial development of foods fortified with (n-3) PUFA. J. Nutr. 139: 5–10, 2009.

Introduction

Stearidonic acid [SDA;[3] 18:4(n-3)] is an (n-3) long-chain PUFA (LCPUFA) that is a metabolic intermediate in the conversion of α-linolenic acid [ALA; 18:3(n-3)] to eicosapentaenoic acid [EPA; 20:5(n-3)] and docosahexaenoic acid [DHA; 22:6(n-3)] (**Fig. 1**). Highly unsaturated (n-3) PUFA (fatty acids >3 double bonds), have been linked to reductions in cardiovascular disease (1), inflammation (2), cancer (3,4), and neurological disorders (5). As a highly unsaturated (n-3) PUFA whose unsaturation index is less than that of EPA and DHA, SDA potentially will possess improved stability characteristics, enhancing its commercial value. Similarly, if its biological effects were to mimic those of its downstream cousins, EPA and DHA, SDA could become a valuable tool in meeting current recommended intakes for LCPUFA (6). The purpose of this paper is to provide a direct comparison of the effects of dietary SDA compared with other fatty acids of the (n-3) family. There are many studies demonstrating positive effects of (n-3) PUFA on health promotion and disease prevention; however, this article uniquely reviews those studies that directly compare SDA to other (n-3) fatty acids.

Dietary sources. The major dietary source of SDA is from seafood. As a component of fish and other seafood, SDA is a minor (n-3) fatty acid, contributing 0.5–2% of the total fatty acids, whereas EPA and DHA typically contribute 15–20% (7). However, some mackerel contain as much as 7% SDA, but this is unusually high (8). Seaweed (*Undaria pinnatifida*) also contains SDA (0.7–1.9 mg/g dry weight) (9). SDA is not generally found in most terrestrial plant sources and is rarely found in commonly consumed vegetables, fruits, seeds, nuts, or commercial oils. However, plants from the Boraginaceae, Grossulariaceae, Caryophyllaceae, and Primulaceae families are unique because of their SDA contents. Dietary sources from plants of the Boraginaceae family are by far the most common (i.e. seed oils from echium and borage). By weight, echium oil is the richest commercially available plant source of SDA (3.5–9.0%) (10–12), followed by species of the Grossulariaceae family (i.e. currant seed oils, *Ribes nigrum*) at 2–6% (13,14). Leaf lipids of certain types of flowering plants from the Caryophyllaceae, Primulaceae, and Boraginaceae families may have the highest concentrations on a weight basis of any plant source, with levels as high as 21% (15).

In light of the reported health benefits associated with (n-3) LCPUFA, safety, shelf life and palatability issues with fish and fish oils, and over-fishing are of concern (16,17). As such, there is

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[3] Abbreviations used: ALA, α-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IL, interleukin; LCPUFA, long-chain PUFA; PGE_2, prostaglandin E_2; SDA, stearidonic acid.
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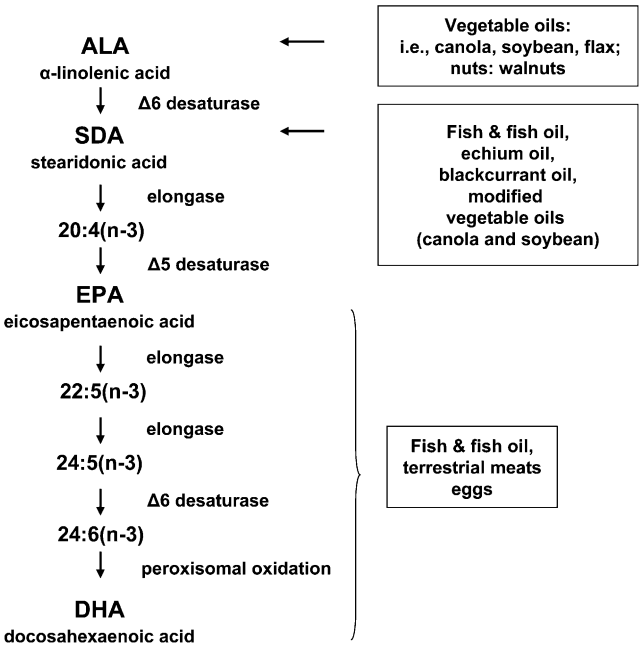

FIGURE 1 Metabolic pathway of (n-3) PUFA and their primary dietary sources. Reproduced and slightly modified from (6) with permission from the corresponding author and publisher.

a need and desire to identify and develop alternative sources of (n-3) LCPUFA. Thus, SDA has been targeted as a potential biologically active surrogate for (n-3) LCPUFA, such as EPA, because of its relatively efficient conversion following consumption. However, current plant sources that naturally contain SDA have yet to be adapted for wide-scale production and the yields are low and variable, thus compromising economic competitiveness (18).

In response to a growing need, current technology has advanced to a point where common vegetable oils now contain SDA by expressing the appropriate desaturases required for its production in the parent plants. For example, conventional canola (*Brassica napus*) oil has been modified to contain as much as 23% of its fatty acid pool as SDA (18). This was accomplished by generating transgenic canola lines using an expression vector containing $\Delta 6$ and $\Delta 12$ desaturases derived from the fungus *Mortierella alpina* and the $\Delta 15$ desaturase from canola or by generating an F1 hybrid by crossing a transgenic line containing the $\Delta 6$ and $\Delta 12$ desaturases with one containing high expression of $\Delta 15$ desaturase (18). Alternatively, Sato et al. (19) transfected the cDNA of $\Delta 6$ desaturase from borage (*Borago officinalis*) into soybean (*Glycine max*), generating a variety of transgenic soybean lines with levels of SDA between 0.6 and 4.2% of the fatty acid pool. These technological breakthroughs could be important given the fact that there now is a world-wide market for foods that are enriched and fortified with (n-3) LCPUFA (6).

The ability to generate safe and inexpensive oils containing relatively high levels of SDA using this type of technology has a number of advantages compared with more highly unsaturated fatty acids from fish. Generating a stable terrestrial crop whose oil is rich in a highly unsaturated (n-3) PUFA is sustainable and cost effective. Regarding structural benefits, oxidation potential is linearly proportional to the number of methylene-interrupted double bonds in a fatty acid (20). SDA has 4 double bonds compared with 5 and 6 for EPA and DHA, respectively. The lower unsaturation index of SDA greatly enhances stability and shelf life with a concomitant reduction in off flavors and odors that result from the generation of oxidative products.

According to the FAO of the United Nations, world captures fisheries production has declined since 1989, while the world aquaculture production has dramatically increased since 1970 (21). The major commercial use of fish oil is for aquaculture, where 87% of the world's fish oil is used in fish feed (22–24). Only 6% is used for human consumption and the rest is used in animal feed (6%) and industrial uses (1%) (22,23,25). Substitution of SDA for EPA/DHA could alleviate some of the commercial pressures on fish oil and problems associated with over-fishing, particularly if dietary SDA can be converted to EPA and/or DHA.

Metabolism of dietary SDA and other (n-3) PUFA

Synthesis. SDA is formed directly from ALA (Fig. 1). ALA is the simplest (n-3) PUFA from which all other (n-3) PUFA are metabolically derived (Fig. 1) and when consumed, it is converted to SDA via $\Delta 6$ desaturase, the rate-limiting enzyme in the pathway. Dietary ALA can be converted to SDA and then EPA and DHA following consumption in response to inadequate tissue levels of DHA; however, the extent of this conversion appears to be minimal when supplemented to a typical Western diet (26–29). Similarly, when evaluating changes in plasma phospholipid SDA, EPA, and DHA levels, supplementation of ALA to the typical diet has little impact (26,30–33). In fact, the major metabolic fate of supplemented ALA appears to be oxidation (27,28), not conversion to or through SDA. When tissues become adequately enriched with DHA, feedback-inhibition of $\Delta 6$ desaturase occurs by inhibiting the rate of transcription via a mechanism involving PPARα (34).

Downstream metabolism of SDA. Tissue phospholipids typically contain negligible levels of SDA. When SDA enters the metabolic pathway after the $\Delta 6$ desaturase step, it is rapidly converted to EPA. Following consumption of SDA, EPA levels in plasma, neutrophil, heart, and erythrocyte phospholipids increase up to 5 times the initial value (10,30,35,36), and thus SDA is considered a "pro-EPA" fatty acid. When compared with dietary EPA, dietary SDA is ~17–30% as effective in humans at raising EPA levels in RBC and in plasma phospholipids (30,37). Some studies suggest similar efficacy, although these studies used less controlled blends of oils containing SDA for comparison (36,38). Similar effects are observed in dogs supplemented with SDA vs. EPA, with 20–26% efficiency of incorporation of EPA into erythrocytes by dietary SDA as compared with dietary EPA (**Fig. 2**) (35). When modifying tissue DHA composition in humans consuming a typical Western diet, none of the precursor (n-3) PUFA (i.e. ALA, SDA, or EPA) have an effect, indicating dietary supplementation of preformed DHA is the only way to effectively modify tissue levels of DHA (10,26,30,32,33).

Rodents vs. humans. The extent of the metabolism of SDA is different in experimental rodent models compared with humans. The ability to desaturate and elongate precursor PUFA in rodents is much more pronounced and, as such, one has to interpret these data cautiously when trying to extrapolate to humans (39). It should be remembered that the typical Western diet already contains appreciable amounts of (n-3) PUFA (ALA, EPA, DPA, and DHA). However, it is common in studies using experimental rodent models to use background diets completely devoid of (n-3) PUFA (i.e. corn oil), resulting in an exaggerated response when (n-3) PUFA are supplemented (40). If ALA is part of the background rodent diet, changes in tissue EPA levels are significantly reduced (41). Nevertheless, all of these effects are

far greater than that observed in humans where dietary ALA does not significantly change and SDA almost doubles tissue EPA levels (10,30,33). Similar concerns exist if the (n-3) PUFA content of cultured cells is low prior to the addition of exogenous (n-3) PUFA. Thus, if rodent diets and cell culture experiments are not designed appropriately, results generated under these preclinical experimental conditions may not accurately reflect the biological impact of these PUFA if a comparison to humans is desired (42).

Physiological effects of SDA vs. other (n-3) PUFA. A number of review articles have established a relationship between (n-3) PUFA and the reduction of risk for cardiovascular disease (43–48). These effects appear to be clearer for the (n-3) LCPUFA than for ALA. A number of mechanisms have been proposed, i.e. their effects on fibrinolysis and reductions in circulating triacylglycerols levels (49), platelet activation (50), coagulation (49), and the expression of vascular adhesion molecules (47,51). However, these beneficial effects may not be dependent upon (n-3) fats containing both EPA and DHA. The Japanese EPA Lipid Study, with 18,640 subjects consuming background diets relatively rich in EPA and DHA, demonstrated that long-term supplementation of pure EPA significantly reduced major coronary events in the absence of supplemental DHA in patients with a history of coronary heart disease (48). Therefore, as a metabolic surrogate for EPA, SDA has the potential to augment health promotion and mimic disease reduction observed with (n-3) LCPUFA.

Plasma lipids. Dietary EPA and DHA have distinct effects on plasma lipids with beneficial outcomes for cardiovascular diseases not shared by ALA (45,52). In hyperlipidemics, (n-3) LCPUFA are potently hypotriglyceridemic, and in general, raise HDL and LDL cholesterol levels (if at all), but LDL cholesterol is in a form that is larger and less atherogenic (53). Only 3 clinical trials involving SDA and plasma lipids have been reported in the literature (10,30,37). When mildly hypertriglyceridemic subjects were provided SDA in the form of echium oil (1.88 g/d SDA), serum triacylglycerol levels were significantly reduced by 22% with no other reported changes in the lipid profile, but this was only a preliminary open-labeled study without a parallel control group and the results are difficult to interpret (10). In contrast, when normolipidemics were provided SDA (0.75–3.7 g/d) there were no significant changes in triacylglycerols or other plasma lipids (total, HDL or LDL cholesterol) compared with groups supplemented with ALA or EPA (37,54).

Omega-3 index. Recently, a new clinical biomarker for cardiovascular disease has been proposed called the omega-3 index, the sum of EPA+DHA in erythrocyte membranes expressed as a percentage of total erythrocyte fatty acids (55). The omega-3 index correlates very well with risk for a variety of cardiovascular disease endpoints and is as good or better than other traditional circulating risk factors (i.e. C-reactive protein, LDL cholesterol, total cholesterol:HDL cholesterol ratio, etc.) for relative risk of sudden cardiac death (33). In a side-by-side experiment evaluating the impact of supplemental ALA, SDA, or EPA on changes to the omega-3 index, SDA and EPA were more effective than ALA ($P = 0.0005$ and $P = 0.0001$, respectively), which had no effect (33). Relative to each other, SDA was 17% as effective as EPA.

Inflammation and inflammatory disorders. (n-3) LCPUFA have been reported to favorably affect inflammation and inflammatory disorders (2). They have been shown to decrease the production of cytokines, adhesion molecules, reactive oxygen species, and proinflammatory eicosanoids (2). Furthermore, they appear to be important in the resolution of the inflammatory response via the formation of the newly discovered E and D series resolvins (56,57).

Only a few studies have directly compared SDA with other (n-3) PUFA on indices of inflammation. When SDA, ALA, or EPA were provided to healthy subjects, ex vivo inflammatory cytokine production [interleukin (IL)-1β and tumor necrosis factor-α] in whole blood or peripheral blood monocytes were unaffected by diet (30,38). SDA-containing echium oil or EPA supplementation did not affect phagocytosis by neutrophils and monocytes, lymphocyte proliferation, and delayed-type hypersensitivity (38). The only variables that were affected by the supplemented oils were the Ig. SDA-containing echium oil and EPA decreased IgE levels, whereas Ig-γ G_2 concentrations increased only with EPA supplementation (38). The results of this study demonstrated that although dietary SDA significantly increased leukocyte EPA levels (125%), it did not affect indices of immune function at a dose of 1 g/d and these overall limited effects mimicked, for the most part, those observed with EPA+DHA. On the other hand, supplementation of SDA (0.13 g/d) to subjects in the form of blackcurrant seed oil (6.3 g/d) increased lymphocyte proliferation and delayed-type hypersensitivity, with no changes in IL-1β and IL-2 production (in stimulated peripheral blood monocytes) (58). It is, however, unclear whether these beneficial effects are due to the SDA. When purified ALA, SDA, or EPA were fed to Balb/c mice at a dose of 1% by weight, tumor necrosis factor production from stimulated whole blood (reduction) or production by splenocytes (no effect) were similar regardless of the type of (n-3) PUFA provided (59). Using a mouse ear inflammation model, SDA and EPA demonstrated similar efficacy (reductions in edema, erythema, and blood flow) (9). In summary, the effects of SDA on inflammatory mediators mimic those of EPA, but more studies investigating the comparative effects of SDA and other (n-3) LCPUFA are needed.

Cancers. (n-3) LCPUFA have been shown to have some beneficial effects on cancer, either by reducing risk, inhibiting tumor growth, or enhancing tumor sensitivity to radiation or chemotherapy or palliatively by reducing the symptoms of unwanted side effects to these treatments (60,61). These effects may be related to their ability to inhibit eicosanoid formation as indicated by similar effects with cyclooxygenase inhibitors (62–64).

When dietary SDA was tested side-by-side against ALA, EPA, and DHA in an experimental animal model of colorectal cancer that spontaneously develops intestinal tumors, SDA reduced tumor number by >46% (**Fig. 3**) (41). This effect was as good as or better than dietary EPA or DHA. Dietary ALA did not affect lowering tumor number, suggesting the importance of (n-3) PUFA with 4 or more double bonds. In another study, a xenograft model for the recurrence of prostate cancer, the proliferation index of Los Angeles Prostate Cancer-4 (LAPC-4) cells was lower and the apoptotic index higher in recurring prostate tumors with SDA-treated animals (compared with a linoleic acid control) and SDA appeared to have a protective effect because of a fewer number of animals with recurrent tumors (65). These results are very promising, because dietary (n-3) LCPUFA, but not ALA, appear to reduce risk of metastatic prostate cancer (66). Similar results were observed in NIH-3T3 cells, where cell proliferation was significantly inhibited by the addition of SDA, but not by ALA (67). In contrast, using MDA-MB-231 cells in culture, an estrogen-independent human breast cancer cell line, the effects of SDA and ALA were not much different (68), possibly due to

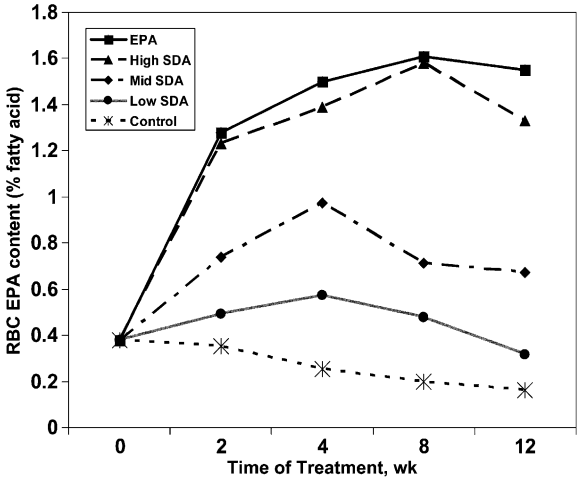

FIGURE 2 The effects of dietary SDA (21.4, 64.2, and 192.9 mg/kg body weight) compared with EPA (42.9 mg/kg body weight) and sunflower oil (control) in dogs on tissue EPA content (percent of total fatty acids). Values are means derived from 5 animals at each time point and dose. Overall effects across all time points were significant ($P < 0.001$) from baseline. Reproduced and slightly modified from (35) with permission from the corresponding author and publisher.

their inability to effectively reduce prostaglandin E_2 (PGE_2) formation, a known tumor promoter (62). However, the expression of cyclooxygenase-2 protein was significantly reduced in those cells treated by SDA, but not ALA (68). The cyclooxygenase-2 pathway is important in maintaining tumor integrity, enhancing proliferation and angiogenesis, and inhibiting apoptosis (62,69). These results are encouraging, because a number of studies have reported inverse relationships of dietary (n-3) LCPUFA and cancer risk in humans (3,4,70,71) and these effects were linked to inhibition of the arachidonic acid cascade (3); however, a number of systematic reviews did not show efficacy with (n-3) PUFA on incidence (72,73).

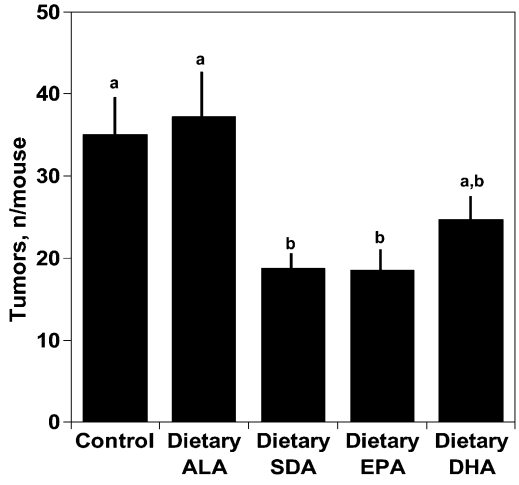

FIGURE 3 Effect of dietary supplementation of various (n-3) PUFA on spontaneous tumor formation (tumor number) in $Apc^{Min/+}$ mice. Mice were supplemented (n-3) PUFA (3% by weight) for 7 wk on top of a background diet designed to mimic a Western diet. Values are means ± SEM, $n = 9$–10 animals/group. Bars without a common superscript differ, $P < 0.05$. Adapted from tumor number data presented in (41) with permission from the corresponding author and publisher.

Eicosanoids. Only 3 known human studies involving SDA and eicosanoid production have been published, 2 involving fatty acids added exogenously to isolated cells (platelets or polymorphonuclear leukocytes) and another study investigating peripheral blood mononuclear cells from subjects given SDA-containing blackcurrant seed oil (58,74,75). In the latter study, human subjects were provided 131 mg SDA for 2 mo as part of a capsule containing blackcurrant seed oil (750 mg) (58). PGE_2 formation was reduced by 24 and 47% when isolated peripheral blood mononuclear cells were stimulated with the mitogens. With regards to the in vitro studies, preincubation of isolated human platelets with physiologically relevant levels of SDA (5 μmol/L) or EPA (5 μmol/L) significantly reduced eicosanoid formation (12-L-hydroxy-5,8,10-heptadecatrienoic acid and 12-hydroxyeicosatetraenoic acid) by 24–28% and 39–47%, respectively, following stimulation (75). When human polymorphonuclear leukocytes were incubated with elevated levels of SDA (20 μmol/L) or EPA (20 μmol/L) in the presence of arachidonic acid (20 μmol/L), metabolites of the 5-lipoxygenase pathway (5-hydroxyeicosatetraenoic acid, leukotriene B_4, and leukotriene B_4 nonenzymatic isomers) were consistently reduced 40–50% by both fatty acids (74).

In $Apc^{Min/+}$ mice fed ethyl esters of various (n-3) PUFA (ALA, SDA, EPA, and DHA at 3% by weight) for 7 wk on a background diet already containing human equivalent doses of ALA (~0.7% by energy), intestinal prostaglandin formation (PGE_2 and 6-keto-prostaglandin $F_{1\alpha}$) was significantly lower (~50%) in all groups compared with controls and these changes coincided with reduced tissue arachidonic acid content (41). SDA and EPA were the dietary fatty acids associated with the lowest prostaglandin levels. Similarly, Ishihara et al. (59) fed Balb/c mice diets containing ALA, SDA, or EPA (1% by weight) and measured PGE formation in stimulated whole blood or isolated splenocytes. PGE levels were equivalently reduced by ~50% irrespective of the (n-3) PUFA provided.

The impact of SDA compared with other (n-3) PUFA on eicosanoid formation in cultured cells is difficult to interpret because of a lack of physiological relevance. When MDA-MB-231 human mammary tumor cells were treated with ALA or SDA at levels of 50 or 200 μmol/L, PGE_2 levels did not change, results consistent with minimal changes in arachidonic acid content (68). Nevertheless, the addition of fatty acids to cells in culture has a number of problems. Most cells grown in vitro are typically low in (n-3) PUFA compared with their in situ counterparts. The levels of exogenous fatty acids used are typically considerably greater than physiological levels (~5 μmol/L) and when nonphysiologic levels are used, there is redirection of exogenous fatty acids into a dramatically expanded triglyceride pool, the impact of which is unclear but could be a contributing factor to observed results (67).

Platelet function. In a study investigating the exogenous treatments of SDA on platelet aggregation (human), SDA (0.5–4.0 μmol/L) inhibited platelet aggregation at a dose of 2 μmol/L in the presence of collagen or arachidonic acid when added simultaneously, but the presence of U46619, an analogue of prostaglandin H_2, did not differ (75). However, if platelets were preincubated with SDA or EPA in a comparison experiment, platelet aggregation was significantly impaired with either fatty acid regardless of the type of agonist used (collagen, arachidonic acid, U46619, or thrombin). In humans fed SDA, ALA, or EPA, function was not affected in any group (33). These results suggest that SDA and EPA do not differ in platelet function modification.

In summary, (n-3) LCPUFA appear to have the greatest efficacy (compared with ALA) in prevention and/or treatment of

various chronic and acute diseases; however, we are faced with the following dilemma. Although the scientific community recognizes the health promotion and disease prevention benefits of (n-3) LCPUFA, convincing people to consume fish products is challenging because of the negative aspects (real or imaginary) associated with the consumption of fish and fish oils, i.e. concerns regarding safety, shelf life (oxidizability), and palatability ("fishy" smell and taste). Furthermore, ALA is poorly converted to the biologically active EPA and DHA. This creates additional problems for many vegetarians who avoid animal products (76). Increasing development and commercialization of nontraditional foods containing (n-3) LCPUFA underscore the public's desire to include these healthy nutrients in their daily dietary regimens (6). Generating plant sources rich in LCPUFA is another mechanism to help achieve dietary recommendations for (n-3) LCPUFA without having to consume seafood.

SDA favorably compares with dietary EPA in side-by-side experiments in a limited number of studies. Similar effects were observed with the inhibition of tumorigenesis in a rodent model of colorectal cancer, in ex vivo platelet aggregation studies, changes in tissue arachidonic acid content and eicosanoid formation, similarities on biomarkers of inflammation and modification of plasma lipid profiles. However, compared with EPA, it was significantly less effective in modifying tissue EPA levels and the omega-3 index. Currently, the data justifying the use of SDA as a surrogate for EPA is promising, but not all the effects were significant. SDA appeared to be as safe as other (n-3) LCPUFA. Only 1 paper has reported self-reported adverse events, but this was with echium oil and these adverse events were no different from what was reported in the control and EPA groups (77). These data suggest that SDA may be a surrogate for EPA for health promotion and disease prevention, but more comparative studies are needed to more confidently establish dose-response parameters.

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