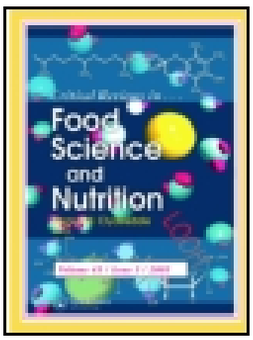

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REVIEW

Plant-based stearidonic acid as sustainable source of omega-3 fatty acid with functional outcomes on human health

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ABSTRACT

Dietary omega-3 long chain polyunsaturated fatty acids (n-3 LC-PUFA) like eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) are known to be potent biological regulators with therapeutic and preventive effects on human health. Many global health organizations have recommended consuming marine based omega-3 sources for neonatal brain development and reducing the risk of various chronic diseases. However, due to concerns regarding the origin, sustainable supply and safety of the marine sources, alternative n-3 PUFA sources are being explored. Recently, plant-based omega-3 sources are gaining much importance because of their sustainable supply and dietary acceptance. α-linolenic acid (ALA, 18:3n-3) rich seed oils are the major omega-3 fatty acid source available for human consumption. But, efficiency of conversion of ALA to n-3 LC-PUFAs in humans is limited due to a rate-limiting step in the n-3 pathway catalyzed by Δ6-desaturase. Botanical stearidonic acid (SDA, 18:4n-3) rich oils are emerging as a sustainable omega-3 source with efficient conversion rate to n-3 LC-PUFA especially to EPA, as it bypasses the Δ6-desaturase rate limiting step. Several recent studies have identified the major plant sources of SDA and explored its potential health benefits and preventive roles in inflammation, cardiovascular disease (CVD) and cancer. This systematic review summarizes the current state of knowledge on the sources, nutraceutical roles, food-based applications and the future perspectives of botanical SDA.

KEYWORDS

Nutraceuticals; omega-3-fatty acids; stearidonic acid; seed oils

Introduction

n-3 and n-6 fatty acids are the two major families of PUFAs whose balanced dietary intake has gained much attention in global nutrition because of their potential health benefits (Simopoulos 2010; Wijendran and Hayes 2004). Dietary PUFAs from n-3 family are α-linolenic acid (ALA; 18:3n-3), eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3), whereas linoleic acid (LA; 18:2n-6), γ-linolenic acid (GLA; 18:3n-6) and arachidonic acid (AA; 20:4n-6) are important dietary PUFAs from n-6 family. ALA and LA are essential fatty acids and precursors of long chain (C_{20-22}) n-3 and n-6 fatty acids, respectively (Simopoulos 2010). Among the two families, n-3 family has been known to reduce the risk of a number of chronic diseases and provide potential health benefits to humans (Whelan, Gouffon, and Zhao 2012).

EPA and DHA are more potent than ALA and SDA in reducing the risk of cardiovascular diseases (Whelan 2009), inflammation (Calder 2006), cancer (Hall et al. 2007) and neurological disorders (Walker et al. 2013) that have been well evidenced from large number of epidemiological studies and randomized controlled trials. In view of their potential health benefits, various health regulatory bodies have provided global dietary recommendations for EPA and DHA (Table 1). However, current daily dietary intakes of EPA and DHA are below the recommended levels in the United States and Europe (Mahaffey, Clickner, and Jeffries 2008; EFSA Panel on Dietetic Products, Nutrition, and Allergies, NDA 2010). For example, typical intakes in western countries are between 110 and 500 mg/day, with US consumption at the lower end on this scale (Whelan, Jahns, and Kavanagh 2009). Based on estimates from the US National Health and Nutrition Examination Survey 1999–2000, the average PUFA intake of men is 20 g/day and that of women is 16 g/day, coming mainly from LA. The dietary intake of very long chain PUFA is estimated to be between 100 and 170 mg/day. The ratio of n-6/n-3 suggested in the diet for meeting recommended levels of n-3 PUFA is 4:1 or 2:1 (Simopoulos 2003). Current n-6/n-3 ratio of typical Indian diet is 38:1 (Pella et al. 2003). Potential problem to meet the recommended values includes typical western diet and increased consumption of vegetable oils high in pro-inflammatory omega-6 fatty acids with less or no omega-3 fatty acids (Ruiz-López et al. 2009). Further, consumption of more n-6 PUFAs interferes with n-3 PUFA metabolism as both compete for the same desaturases and elongases. It is very likely that the present western diet rich

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Table 1. Recommended daily intakes of EPA and DHA.

Sl. no.	Organization	EPA + DHA recommendations	References
1	World Health Organization, WHO	1–2% of energy/day (for general adult population)	Expert consultation on diet et al. (2003)
2	European Food Safety Authority, EFSA	250 mg/day (for general adult population)	EFSA Panel on Dietetic Products, Nutrition, and Allergies, NDA) (2010)
3	International Society for the Study of Fatty Acids and Lipids, ISSFAL	500 mg/day (for general adult population)	Cunnane et al. (2004)
4	AFFSA-French Food Safety Agency	500 mg/day (for general adult population)	AFFSA (France)) (2010)
5	British Nutrition Foundation, UK	1.5 g/week (for general adult population)	British Nutrition Foundation (2000)
6	US National Academy of Science, Institute of Medicine	140 mg/day (for general adult population)	Institute of Medicine (U.S.) and Institute of Medicine (2005)
7	Food and Agricultural Organization, United Nations	300 mg/day for pregnant/lactating women, of which 200 mg/day should be DHA	(Joint F.A.O. 2010)
8	Food and Agricultural Organization, United Nations	100–150 mg (2–4 years) 150–200 (4–6 years) 200–250 (6–10 years)	(Joint F.A.O. 2010)

in n-6 PUFA may not supply required n-3 PUFA and contributes to ever-increasing levels of chronic diseases present in many populations, which in turn affect global healthcare system.

Major available sources of EPA and DHA include sea foods especially fish and algae. Health authorities have recommended consuming two fatty fishes per week, which is sufficient to provide 250–300 mg/day of EPA and DHA (Kris-Etherton, Harris, and Appel 2002; Scientific Advisory Committee on Nutrition, SACN 2004). However, in Western countries the amount consumed is inferior to the recommended levels. This might be due to their dietary preferences, barriers associated with sustainable fish supply, taste, fishy odor, methyl mercury and polychlorinated biphenyls contamination of marine environment, geographic reasons and economic status (Baker et al. 2016; Maki and Rains 2012). Further, the stability of fish oil is also a concern because of their high unsaturation index. Although marine algae are promising source of EPA and DHA, the inherent scalability, production and market price negate their supply (Cumberford and Hebard 2015). The species specificity, growth conditions, seasons, developmental stages and processing have shown a strong impact on the fatty acid composition of algae oil. These factors along with high unsaturation index limit their use only in infant food formulations and DHA supplements, not as edible oil. Also, the clinical studies examining the safety and overall health benefits of algal oils are limited (Guschina and Harwood 2006; Wells et al. 2017). Thus, plant-based sources emerge as economical, dietary acceptable and sustainable sources of omega-3 fatty acids. α-linolenic acid is the major n-3 PUFA in seed oils such as flax, chia, soybean, hemp, canola and walnut (Williams and Burdge 2006). However, ALA does not confer the health benefits similar to EPA and DHA (Swanson, Block, and Mousa 2012). The efficiency of bioconversion of ALA to n-3 LC-PUFAs is limited due to ALA to SDA rate-limiting step catalyzed by hepatic enzyme Δ6-desaturase. The rate of EPA to DHA conversion depends on the Δ6-desaturase gene activity and translocation of 22:4n-3 to peroxisomes. Further, ALA is more utilized in β-oxidation (Burdge and Calder 2005). The bioconversion rate of ALA to EPA is 0.2–10% and to DHA is less than 0.05–0.5% (Burdge 2004; 2006; Petrović-Oggiano et al. 2020; Plourde and Cunnane 2007). ALA to n-3 LC-PUFA conversion studies were carried out mainly using isotopically labeled ALA or ALA supplements. Similar conversion rates were observed under both the approaches (Plourde and Cunnane 2007). This conversion rate was influenced by sex and gene variants of desaturase and elongase enzymes (Minihane 2016). In men, the estimated mean net conversion rate of ALA to EPA was 8%, whereas in women it was 21% (Baker et al. 2016; Burdge 2004). In women of child bearing age, a higher proportion of ALA was converted to n-3 LC-PUFA and only a lower portion was enrouted for β-oxidation possibly by the influence of estrogen (Burdge 2004; Welch et al. 2010). Another study evaluated the endogenous synthesis of AA and DHA in two preterm infant groups - no-LC-PUFA fed group and LC-PUFA fed group (with ^{13}C labelling) by calculating the absolute and percentage LC-PUFA synthesis relative to dietary intake. AA and DHA synthesis dramatically decreased in 7 month old infants fed with LC-PUFA and AA synthesis was significantly higher than DHA synthesis (Carnielli et al. 2007). Given the above, there is an urgent need to identify and develop effective and viable alternate sources for meeting the increasing global demand of long chain omega-3 fatty acid supplements. Recently, consumption of seed oils rich in stearidonic acid is found to enhance the tissue levels of EPA better than ALA rich oil. SDA bypasses the rate limiting step in EPA synthesis, hence is an efficient alternate precursor for n-3 LC-PUFA synthesis (Lefort et al. 2016). The health promoting roles of botanical SDA in comparison to other n-3 fatty acids has also been recognized (Lefort, LeBlanc, and Surette 2017; Surette 2013; Whelan 2009). Hence, the current article summarizes the major plant sources of SDA and its potential health outcomes in preventing various chronic diseases.

Structure and metabolism of stearidonic acid

Stearidonic acid or all *cis*-6, 9, 12, 15- octadecatetraenoic acid or moroctic acid is an 18 carbon omega-3 poly unsaturated fatty acid with four *cis* double bonds in the acyl chain.

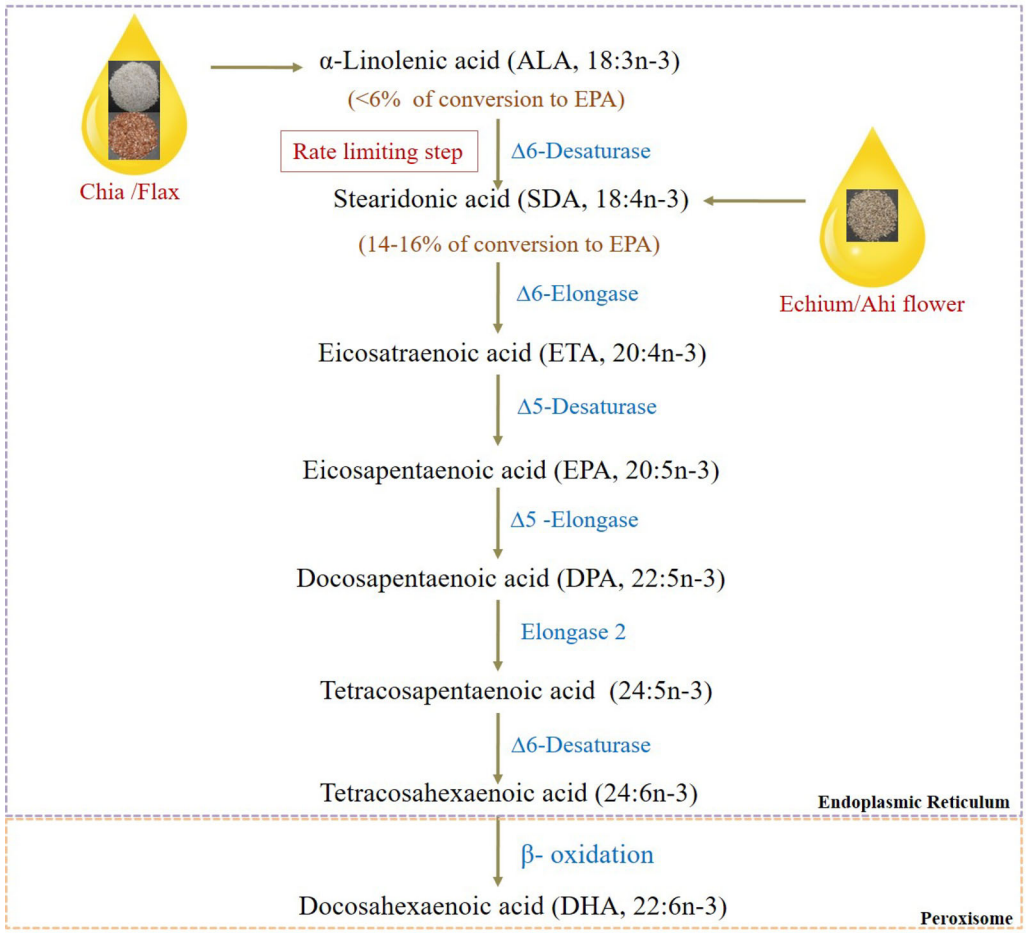

Figure 1. The biosynthetic pathway of n-3 fatty acids.

Molar mass of SDA is 276.4 g/mol and its molecular formula is $C_{18}H_{28}O_2$ (Akoh 2017; Ching Kuang 2008). Stability of SDA in comparison to EPA and DHA is high due to its less unsaturation index. SDA is the first intermediate metabolite in the biosynthesis of EPA in humans and is produced by the desaturation of α-linolenic acid by rate limiting enzyme Δ6-desaturase in the liver (Burdge, Jones, and Wootton 2002). Consumption of SDA effectively increases the tissue levels of EPA and DPA in comparison to dietary ALA (James, Ursin, and Cleland 2003; Kuhnt et al. 2016; Lemke et al. 2010; Surette et al. 2004), which involves a series of elongation and desaturation steps (Figure 1). However, its conversion to DHA is reported to be low (Dittrich et al. 2015; James, Ursin, and Cleland 2003; Kuhnt et al. 2014; Pieters and Mensink 2015) with few exceptions (Abeywardena et al. 2016; Lefort et al. 2016; Lemke et al. 2010; Miles, Banerjee, and Calder 2004; Surette 2013). The reasons include Δ6-desaturase gene variability, tissue type, age, hormonal effects, insulin resistance and transcriptional control via PPARα (Lefort et al. 2016; Merino et al. 2011; Tang et al. 2003). The downstream metabolic fate of SDA in the n-3 pathway is its rapid conversion to EPA followed by enrichment of the latter in the membrane phospholipids (James, Ursin, and Cleland 2003; Whelan 2009). Incorporation of long chain n-3 PUFA in membrane phospholipids has physiological effects on membrane functions and signaling molecules involved in number of chronic diseases like inflammation, CVD and cancer (Miles, Banerjee, and Calder 2004; Subedi et al. 2015; Surette et al. 2004). For example, metabolism of membrane EPA by cyclooxygenase or lipoxygenase produces less potent inflammatory eicosanoids such as Leukotriene B5 (LTB5), Leukotriene B5 (LTE6) 5-hydroxy EPA and cytokines than those formed by arachidonic acid (Calder 2006). Further, biological regulators like E- series resolvins and protectins are produced by the action of cyclooxygenase-2 and phospholipases on membrane EPA (Calder 2006; Serhan, Hong, and Lu 2006). Thus, consumption of SDA offers an alternate strategy to meet the recommended levels of health promoting long chain n-3 PUFA, especially EPA (Figure 1).

Plant sources of SDA

Plant seed oils are the richest source of C_{18} PUFA. This is because terrestrial plants lack fatty acid elongases and desaturases required for the biosynthesis of higher PUFAs like AA, EPA and DHA (Venegas-Calerón, Sayanova, and Napier 2010, Ruiz-Lopez et al. 2015). Hence, they accumulate C_{18} PUFAs like LA, ALA, GLA and SDA as terminal fatty acid metabolites. Among C_{18} rich plant seed oils, high amount of SDA is reported only in few species of following families: Boraginaceae (4–19%) (Kleiman et al. 1964; Miller

Table 2. The oil content of major SDA plants.

Plant	Family	Oil content (%)
Echium plantaginuem (Berti et al. 2007; Croda Chemicals Europe Ltd. Cowick Hall, Snaith, Goole, East Yorkshire, DN149A 2006)	Boraginaceae	20–30
Ribes nigrum (Black currant) (Šavikin et al. 2013)	Saxifragaceae	18.6–22.7
Cannabis sativa (Hemp) (Kriese et al. 2004)	Cannabinaceae	33–36
Buglossoides arvensis (Ahi flower) (Cumberford and Hebard 2015; Prasad et al. 2019)	Boraginaceae	16–19
Primula sikkimensis (Aitzetmüller and Werner 1991)	Primulaceae	18

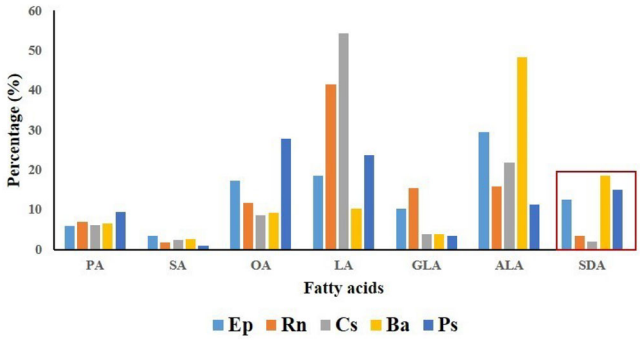

Figure 2. The fatty acid composition of major plant sources of SDA. The SDA content is shown in box. PA, palmitic acid; SA, stearic acid; OA, oleic acid; LA, linoleic acid; GLA, γ-linolenic acid; ALA, α-linolenic acid; SDA, stearidonic acid; Ep, *Echium plantaginuem*; Rn, *Ribes nigrum*; Cs, *Cannabis sativa*, Ba, *Buglossoides arvensis*; Ps, *Primula sikkimensis*. For references, refer to Table 2.

et al. 1968), Primulaceae (11–14%) (Aitzetmüller and Werner 1991), Saxifragaceae (3–4.5%) (Johansson, Laakso, and Kallio 1997; Turchini et al. 2011), Cannabinaceae (1–3%) (Callaway, Tennilä, and Pate 1996) and Loasaceae (2–8.5%) (Aitzetmüller, Brühl, and Weigend 2004) (Table 2; Figure 2). Most of the plant species from the above families are wild and not agronomically adapted. Although many other plant species are known to have SDA, their low levels are challenge for commercialization. This section aims to summarize in detail the major and commercially available plant seed oils rich in SDA with respect to their nutritional values, cultivation and commercialization. This may further help in addressing the potential challenges involved in establishing sustainable alternate sources of plant-based n-3 fatty acids.

Echium oil

Echium plantagineum seeds are natural source of SDA and GLA. This plant is an annual, invasive weed of Boraginaceae family. It is widely distributed in Australia and South America. Seed yield per hectare is approximately 250–425 kg and oil content is 200–250 g/kg seeds. Echium oil has a balanced composition of n-3 (ALA and SDA) and n-6 (LA and GLA) fatty acids. This is distinctive from the other oils like flax seed (n-3 oil) or borage oil (n-6 oil) (Mir 2008). The fatty acid profile of Echium oil (EO) is shown in Figure 2. The SDA and GLA content of Echium oil range from 12 to 15% and 10 to 13%, respectively. European commission has given novel food status for Echium oil and it is commercialized by Croda chemical Europe Limited (Turchini et al. 2011). Genetic diversity of Echium is a major obstacle for domestication of the crop, whereas seed yield, oil and SDA content per hectare may obstruct its commercialization (Coupland 2008). Adaptation of this crop to various geographical locations and selection of the stable lines for high seed yield, oil and SDA content by plant breeding programs is essential to establish it as a sustainable commercial oilseed crop.

Hemp oil

Hemp oil is extracted from the seeds of *Cannabis sativa* L., a member of Cannabinaceae family. It is an annual herbaceous plant rich in oil and fiber. Seed yield per hectare is 1000–1500 kg and oil content is 33–36%. Fatty acid profile of hemp seed oil is shown in Figure 2. SDA content of hemp seed oil is 1–3% (Kriese et al. 2004) and n3/n6 ratio is 2:3.1 (Hartsel et al. 2016). Consumption of hemp seed oil is limited in some countries due to the presence of psychoactive constituent delta-6 tetrahydrocannabinoid (THC) (Oomah et al. 2002). Further, low SDA content of hemp demands much higher daily intake of oil to meet the daily recommended levels of n-3 PUFA.

Blackcurrant oil

Blackcurrant (*Ribes nigrum)* is a hardy, woody shrub of Saxifragaceae family and is well known for its commercial applications in juice and food processing industries. Europe is the major producer of black currant oil (90%). Seed waste produced during berry juice processing is an excellent source of PUFA. Oil content of blackcurrant varieties range from 18.6% to 22.7% and SDA content ranges from 1 to 4% of total fatty acids. GLA content (10–15%) of black currant is higher than its SDA content (Šavikin et al. 2013). The n-3 to n-6 ratio is 1:4 or 1:5. In principle, this may affect the efficiency of EPA synthesis upon consumption as both GLA and SDA compete for the same metabolic pathway.

Buglossoides seed oil

Oil extracted from the seeds of *Buglossoides arvensis* is the known richest natural source of SDA in the plant kingdom. *B. arvensis* is an herbaceous, terrestrial, hardy annual weed of Boraginaceae family. It is native to northern temperate regions of the Europe and Asia. Seed yield per hectare is 650–750 kg and oil content is 19–21%. SDA content of *B. arvensis* seed oil ranges from 17 to 21% of total fatty acids (Cumberford and Hebard 2015; Prasad et al. 2019). Buglossoides oil is superior to Echium oil with respect to its yield, high SDA and low GLA content. Nature's Crop International (NCI), Canada has developed high yielding spring and winter crop varieties with high SDA content.

Table 3. Genetically modified plant sources of SDA.

GM crop	Genes introduced	SDA content of wild type plant seeds (% of total fatty acids)	SDA content of transgenic plant seeds (% of total fatty acids)
SDA-Canola (Ursin 2003)	*Mortierella alpina* Δ-6 and Δ-12 desaturase and Canola Δ-15 desaturase	0.0	23
SDA-Soyabean (Eckert et al. 2006)	Borage Δ-6 desaturase and Arabidopsis Δ-15 desaturase	0.0	29
SDA-Linseed (Ruiz-López et al. 2009)	*Primula vialli* Δ-6 desaturase	0.0	15.4
Monsanto SDA-Soybean (Harris 2012b; Lemke et al. 2010)	*Primula juliae* Δ-6 desaturase and *Neurospora crassa* Δ-15 desaturase	0.0	28
Perilla frutescens (Lee et al. 2019)	*Phytophthora citrophthora* Δ6 desaturase	0.0	13.8–21.5

Recently, Buglossoides oil/Ahiflower oil (NCI as Trade mark name) had received Generally Recognized As Safe (GRAS) approval from US Food and Drug Administration (FDA) and novel food status by European Food Safety Authority (EFSA). However, *B. arvensis* grows well in colder regions or at higher elevations in the temperate region (Cumberford and Hebard 2015). Thus, adaptation of this crop to different geographical locations and development of cultivars might be a potential strategy to replace the sustainability problems associated with fish oils and to meet the global omega-3 demand. Recently, our group assessed the adaptability and suitability of this plant as a commercial crop in tropical regions of India (Sreedhar et al. 2017).

Genetically modified SDA-rich plant oils

Genetic engineering of oil seed crops has opened door to the era of designer plant oils and provides an opportunity to modify the levels of fatty acids in plant seed oils or to produce nutritionally important non-native fatty acids (Damude and Kinney 2008). Oil seed crops like canola, soybean and linseed have been genetically modified by introducing specific desaturase to produce high amount of SDA (Eckert et al. 2006; Ruiz-López et al. 2009; Ursin 2003) (Table 3). Eckert et al. (2006) genetically modified the soybean plant by co-transforming borage Δ6 -desaturase and Arabidopsis Δ15-desaturase, which resulted in the increase of SDA content of the seed oil by 29%. In a recent study, transgenic expression of Δ6-desaturase from *Phytophthora citrophthora* in *Perilla frutescens* accumulated over 45% of SDA and GLA in T2 seeds (Lee et al. 2019). However, their commercial scale application ends with documented literature rather than to market.

Recently, transgenic SDA rich soybean crop was developed by introducing *Primula juliae* Δ6-desaturase and *Neurospora crassa fad3* (delta-15 desaturase) genes under the control of seed specific promoter (Harris 2012b). Temporal expression of *fad3* gene increases the flux of ALA to SDA and thus affects GLA synthesis. SDA content of GM soybean oil was 28% of total fatty acid (Lemke et al. 2010). US FDA has given GRAS status to Monsanto SDA omega-3 soybean oil and it also received positive scientific opinion from EFSA (Lemke et al. 2010). Application of transgenic technology to produce high SDA in already domesticated oil seed plants may provide an alternate strategy for sustainable supply of omega-3 fatty acids. However, marketing and usage of such oils in anti-GM countries is not possible (Table 3).

Potential health benefits

In vivo dietary effects of SDA rich plant oils on tissue n-3 LC-PUFA levels

Preventive and therapeutic relevance of dietary consumption of SDA relies mainly on its efficient conversion to EPA and DHA in human body. SDA is considered as 'pro-eicosapentaenoic acid' (Harris 2012a). Many supplementation studies and randomized clinical trials in humans and animal models indicate that consumption of SDA rich plant oils efficiently raised the levels of EPA in serum/plasma, red blood cells, polymorphonuclear cells and peripheral blood mononuclear cells in comparison to control/ALA rich diet (Tables 4 and 5). The relative efficiency of SDA to EPA conversion was estimated in few studies by comparing the raise in EPA levels (RBCs) following EPA rich diet or SDA rich diet, and then normalizing the values based on the dosage of each fatty acid. Harris et al. (2008) reported that SDA to EPA conversion efficiency relative to EPA rich diet was 16.6%, whereas 0.09% for ALA. Thus, an intake of 6 g/day of SDA produces the same effect as 1 g/day of EPA. Lemke et al. (2010) also observed similar results with a conversion efficiency of 17% relative to EPA (i.e., the ratio of SDA: EPA required to raise the tissue EPA levels to the same degree was 5.8:1) and suggested that a daily intake of ~1.5 g of SDA will be sufficient to meet the daily requirement of n-3 LC-PUFAs. In a phase 1 randomized clinical trials, Ahifower oil supplemented group (9.1 g/day) showed significant increase in the tissues levels of EPA and DPA compared to flax seed oil supplemented group (Lefort et al. 2016). None of the SDA supplementation studies (Table 4) showed significant increase in the SDA status of the tissues analyzed compared to baseline. This may be due to rapid conversion of SDA to EPA in the tissues, indicating that the activity of delta-5-desaturases and elongase in humans is sufficient for efficient metabolism of SDA (Harris et al. 2008; James, Ursin, and Cleland 2003; Lefort et al. 2016; Lemke et al. 2013; Miles, Banerjee, and Calder 2004).

However, most of the dietary SDA intervention studies were conducted for short duration on small populations and outcomes of these studies are not sufficient to address the health benefits attributed to EPA. Hence, daily intake amounts of SDA rich plant oils required to meet the

Table 4. Effect of SDA plant oils on tissue LC-PUFA levels in humans.

References	Subjects and duration of study	Intake, source of SDA oil, SDA percentage of oil	Tissue/cells analyzed	Effect of SDA-rich oil on tissue LC-PUFA levels (Fold change from control/ALA group) EPA DPA DHA
Lefort et al. (2016)	$n = 20$ humans Male 5 Female 12 (18–65 years) 28 days	Ahiflower oil 10ml/day, 20.1% SDA	Plasma Erythrocyte Polymorphonuclear cell Mononuclear cells	1.64* 1.06 1.00 1.25* 0.98 0.91 1.44* 0.98 0.91 1.77* 1.39 1.15
Kuhnt et al. (2016)	$n = 59$ humans, sex balanced 8 weeks	Echium oil 17g/day, 2g/day SDA	Plasma RBC Peripheral blood	2.50* 2.19* 0.27 2.65* 2.66* 0.4 2.15 1.55 1.3
Harris et al. (2008)	$n = 11$ Humans, both male and female (6–7) of ages 21–70 16 weeks	Genetically modified SDA soybean oil, 24 ml/day, 3.66g/day SDA	RBC	2.88** ND 1.00
Pieters and Mensink (2015)	$n = 32$ healthy overweight and slightly obese humans 917 men and 19 women, 4 people dropped out), 6 weeks	Echium oil 10g/day, 1.2g/day SDA	RBC	1.2** 1.09 0.96
Lemke et al. (2013)	$n = 50$ Humans, healthy men and women of age 21–65 years, 12 weeks	SDA soybean oil formulated baked bar/beverages 7g/day oil 1.5g/day SDA	RBC	1.73** 1.32** 0.97
Miles, Banerjee, and Calder (2004)	$n = 8$–12 healthy young males 12 weeks	Echium oil 9g oil/day SDA upto 1g/day	PMBC Plasma triacylglycerol	5.85** ND 2.05 0.66 ND 0.62

*Significantly different from ALA group.
**Significantly different from control group.

Table 5. Effect of SDA plant oils on tissue LC- PUFA levels in mice

References	Subject duration of the study	Intake, sources of SDA oil, SDA percentage of oil	Tissues/cells analyzed	Effects of SDA rich oil on tissue LC-PUFA levels (fold change from control/ALA group) EPA DPA DHA
Surette (2013)	$n = 5$ BALB/c mice 4 weeks	Ahiflower oil 1% of energy/day 1g/day SDA	Liver Intestine Brain	4.25** 2.5** 1.31** 2.2** 2** 1.07 ND 1.2 1
Abeywardena et al. (2016)	$n = 18$ Sprague–Dawley rats 12 weeks	Echium oil 5% (w/w)/day	Plasma phospholipids Heart phospholipids Liver phospholipids	6.5** ND 1 2** 3.18** 1.16** 1.6** 2** 0.62

**Significantly different from control group.

recommended EPA levels need to be addressed in long term clinical trials on larger population size. Tissue DPA levels were also found to increase following SDA consumption. However, significant impact of dietary SDA in enhancing tissue DHA levels was reported to be low (James, Ursin, and Cleland 2003; Kuhnt et al. 2014) with few exceptions (Abeywardena et al. 2016; Lefort et al. 2016; Lemke et al. 2010; Miles, Banerjee, and Calder 2004; Surette 2013). Generally, 22:5n-3 is elongated to 24:5n-3 which is desaturated to form 24:6n-3 by delta-6-desatuarse. 24:6n-3 is transported from endoplasmic reticulum to peroxisome where it undergoes β-oxidation to form 22:6n-3, DHA (Harmon et al. 2003; Li, Kaplan, and Hachey 2000). It is reported that the Δ6-deasturase can act on both n-3 (ALA) and n-6 (LA) pathways (Prasad and Sreedhar 2020) resulting in a potential competition for enzyme activity which may limit the conversion of 24:5n-3 to 24:6n-3 (D'Andrea et al. 2002; James, Ursin, and Cleland 2003; Voss et al. 1991). Another study showed that elongase 2 which converts 22:5n-3 to 24:5n-3 will be a check point since the absence of this enzyme in the heart tissue is believed to be the reason of low DHA synthesis in heart (Igarashi et al. 2008). Surette (2013) showed an increase in the content of liver DHA upon supplementation of Ahiflower oil (SDA rich) to BALB/c mice. Similarly, Abeywardena et al. (2016) also showed an increase in the DHA levels of heart phospholipids upon supplementation of Echium oil to Sprague–Dawley rats (Table 5). However, extrapolating this data to humans requires cautious interpretation of the data because the rate of desaturation and elongation in rodents is more pronounced compare to humans (Hulbert, Rana, and Couture 2002; Whelan 2009). DHA is essential for brain function and visual development (Deckelbaum and Torrejon 2012). SDA feeding studies have to be carried out to confirm the effects of SDA on DHA

synthesis. Further, RBC EPA + DHA content (Omega-3 index) is considered as a major risk factor for cardiovascular death (Lemke et al. 2010). Meeting the recommended levels of DHA probably requires consumption of DHA rich foods. However, Japan EPA lipid intervention study states that raise in tissue EPA levels has clinical benefits and lowers the risk of cardiac events irrespective of change in DHA level (Ohnishi and Saito 2013). Thus, dietary consumption of SDA rich plant oils can be an alternate strategy for enrichment of tissues with health promoting n-3 LC-PUFA.

In vivo dietary role of SDA rich plant oils in cancer

Mounting evidence from animal studies have solidified the view that long-chain n-3 PUFAs, especially EPA and DHA have preventive effects on cancer (Larsson et al. 2004). Specific anticancer benefits have been reported for n-3 LC-PUFA in terms of reducing the risk of tumor initiation, progression, and suppression. Further, it is reported to improve the efficacy of chemotherapy and radiotherapy (Hardman 2004). Consumption of SDA rich plant oils have been shown to raise tissue EPA levels. Increased EPA levels compete with arachidonic acid (AA) for COX enzyme and inhibit the AA derived proinflammatory and growth promoting eicosanoids synthesis (PGE2 series) in tumor cells (Larsson et al. 2004). Membrane phospholipid enrichment with EPA and DHA have shown to suppress the tumor growth by either CD95 induced apoptosis or by decreased NF-κb activation (Ewaschuk, Newell, and Field 2012; Sawyer and Field 2010).

Only a few studies have investigated the dietary impact of SDA rich plant oils on cancer. Recently, it has been reported that feeding *nu/nu* mice bearing human tumorigenic breast cells (MDA-MB-231, MCF-7) with SDA enriched flax seed oil reduce the growth of cancer. Supplementing SDA oil diet for 4 weeks enriched the membrane phospholipid classes (PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidyl inositol) with low levels of AA and high levels of EPA and DPA (Subedi et al. 2015). Changes in the fatty acid composition of PC, PE and PI with EPA and DPA have shown to reduce the tumor growth by various mechanisms like: changes in PE associated with CD95 translocation into lipid rafts in the membrane of tumor cells, changes in PC decrease cell proliferation and increase apoptosis in tumor cells and changes in PI produces apoptosis signaling molecules via protein kinase C (Calviello and Serini 2010). Similarly, SDA oil diet increased the total surface expression of CD95 and downstream signaling molecules like caspases-10 and Bad. Overall, changes in the n-3 LC-PUFA content following SO diet supplementation reduces the tumor growth by CD95 mediated apoptosis (Subedi et al. 2015).

In a double-blind clinical trial, it was shown that supplementation of echium oil to head and neck cancer patients for 7 weeks efficiently raised the tissue EPA and GLA levels, but failed to protect against radio/chemotherapy induced weight loss (Pottel et al. 2014). Synergistic effect of SDA and the chemotherapeutic agents, doxorubicin and docetaxel in two independent studies using prostate cancer cell lines was observed. These studies used commercial SDA. The combination reduced the dose of the drug needed and inhibited NF-κB and induced apoptotic pathway (Mansour et al. 2018).

Similar animal and clinical studies with SDA plant oils have to be carried out to have a better insight into the combinatorial effects of SDA and drugs. Thus, the dietary impact of SDA rich plant oils on cancer is less supportive of any beneficial claims attributed to EPA and DHA consumption, indicating that future studies are needed to strongly address this potential (Kawabata et al. 2013).

In vivo dietary impact of SDA rich plant oils on metabolic diseases

Globally, the prevalence of metabolic diseases and their complications are increasing at an alarming rate. They are now considered as major cause of mortality and morbidity. Preventive measures through dietary changes especially increased intake of n-3 fatty acids is of recent interest (Breslow 2006). Impact of dietary consumption of n-3 LC-PUFA in lowering risk of cardiovascular diseases has been evidenced from large number of clinical trials (Wang et al. 2006). Cardioprotective role of n-3 LC-PUFAs is due to the combination of various mechanisms including lowering triacylglycerol (TAG), antiarrhythmic, anti-thrombotic and hypotensive effects (Adkins and Kelley 2010). According to Japan EPA lipid intervention study, raise in tissue EPA content irrespective of DHA levels following EPA supplementation was shown to reduce the CVD risk by 19% (Ohnishi and Saito 2013). Hence, there is a great interest to investigate whether the tissue EPA enrichment by consumption of SDA rich vegetable oil will have similar effects on the risk of CVD. Studies in hyper triglyceridemic humans demonstrated that serum triacylglycerol levels decreased by 21% after 4 weeks of Echium oil (EO) supplementation ($\sim$2 g SDA/day) (Surette et al. 2004). In another study, EO supplementation significantly reduced the serum TAG cholesterol, low density cholesterol (LDL) and oxidized LDL levels irrespective of the age and body mass index whereas reduction in the TAG levels alone were observed following fish oil supplementation (Kuhnt et al. 2014). Further, EO provides ALA and GLA in addition to SDA. Hence, the observed TAG lowering effects of EO can possibly be due to the combined effects of SDA and other bioactive fatty acids. In a previous study, feeding male Wistar rats with SDA enriched soybean oil for 4 weeks was shown to decrease serum triacylglycerol by 18.5% and 32.5% in a dose dependent manner. Further, it is speculated that enrichment of serum and liver TAG with EPA upon SDA soybean oil consumption leads to increase in β-oxidation of TAG or decrease in the synthesis of TAG in the rat liver (Kawabata et al. 2013). The observed effects of EPA on β-oxidation and TAG synthesis are regulated at transcriptional levels via its interaction with peroxisome - proliferator activated receptors (PPAR) and sterol regulatory element binding proteins (SREBP) (Anderson and Ma 2009). In another study, therapeutic implications of SDA enriched soybean oil on obesity-related pathologies

were studied in obese and lean Zucker rats. Feeding SDA enriched soybean oil for 12 weeks reduced the levels of serum lipids and hepatic fat in obese Zucker rats. Omega-3 index (sum total of EPA and DHA of erythrocyte membrane) in SDA fed rats was found to be 2.4 times greater than control rats (Casey et al. 2013). It is also reported in a randomized, placebo-control, and double blind multicenter study that feeding overweight human subjects with SDA-soybean oil (4.2 g SDA/day) raised the omega-3 index by 1.16 fold compare to control (Lemke et al. 2010). However, none of the above studies showed the exact molecular mechanism underlying the therapeutic effects of SDA on metabolic diseases. Randomized double-blind clinical trial in hypertriglyceridemic subjects demonstrated that SDA rich Echium oil efficiently raised the tissue EPA levels compared to ALA fed group but failed to modify the blood lipid levels (Dittrich et al. 2015). Similar results were observed in another study with Echium oil as a source of SDA and healthy obese and overweight individuals as subjects (Pieters and Mensink 2015). This might be due to low dose of SDA used in those studies which is not sufficient to impart biological effect. In another study, EO was shown to improve circulating LC-PUFA levels, DGLA content and glucose tolerance in insulin resistant middle-aged to aged African green monkeys (Kavanagh et al. 2013). Further, reduction in the plasma TAG, VLDL and hepatic TAG levels were observed in mildly hypertriglyceridemic apoB100-only LDL receptor knockout mice upon EO supplementation (Zhang et al. 2008). n-3 LC-PUFAs such as EPA and DHA act as nutrient sensors in liver to determine the rate of lipogenesis and fatty acid oxidation. They play a major role in the hepatic lipid metabolism by down regulation of sterol regulatory element binding proteins 1c (SREBP-1c) and up-regulation of peroxisome proliferator-activated receptor α (PPAR-α), leading to depressed lipogenesis and increased fatty acid oxidation. Further, n-3 PUFAs act as ligand for PPAR-α that act as transcription factor and increase the expression of genes involved in fatty acid oxidation (Echeverría et al. 2016). However, the mechanism of SDA in controlling serum lipid levels and hepatic steatosis is different from those of EPA and DHA. Botelho et al. (2013) reported that EO was more efficient than marine oils in improving serum lipid profile and hepatic steatosis in high fat fed animals. The mechanism by which EO exerts these effects is by reduction of n-6/n-3 ratio in the liver and not by up-regulation of PPAR-α by n-3 PUFA. In general, other SDA sources like hemp seed oil and blackcurrant oil have also been reported to improve lipid profile (Schwab et al. 2006; Wu et al. 1999).

Most of the SDA intervention studies were carried out for short duration with small number of subjects and the outcome of these studies may not be sufficient to detect hypolipidemic, hypoglycemic and cardio protective effects. Obesity associated nonalcoholic fatty acid liver disease (NAFLD) is reported to cause about 50% reduction in EPA + DHA levels due to an impaired n6/n3 fatty acid intake, higher n-3 LC-PUFA peroxidation and a lower conversion of ALA to EPA by defective desaturases (Δ5/Δ6) activity. Depleted n-3 LC-PUFA levels lead to increased lipogenesis and decreased fatty acid oxidation, leading to hepatic steatosis (Clarke 2004; Valenzuela and Videla 2011). The effect of impaired desaturase activity may be ameliorated by SDA oil supplementation which eventually improve n-3 LC-PUFA levels. Further, long term clinical studies are required to elucidate the beneficial effects of SDA rich plant oils in reducing metabolic disorders such as obesity, hepatic steatosis and CVDs associated morbidity and mortality in both normal individuals and obese patients with NAFLD.

Role of SDA oils in inflammation and related complications

n-6/n-3 ratio is a key determinant of inflammation status. Studies have observed that high intake of n-6 PUFAs increase the risk of inflammation whereas n-3 PUFAs intake results in reduced inflammation. The consumption of EPA and DHA has shown to reduce the production of pro-inflammatory cytokines and eicosanoids from arachidonic acid and increase the production of resolvins which are anti-inflammatory molecules (Calder 2006). The impact of SDA rich dietary oils on the markers of inflammatory response are being recognized recently. In a double blind, placebo controlled 28 days study with 88 healthy human subjects, the effects of three different doses of Ahiflower oil (30%, 6% and 100%) on PUFA levels of plasma and mononuclear cells (MCs) and on the stimulated cytokine production were analyzed. Plasma and MC levels of ALA, SDA, EPA, eicosatetraenoic acid (ETA, 20:4n-3), and docosapentaenoic acid (DPA, 22:5n-3) increased whereas DHA level was unchanged. Also, the levels of the anti-inflammatory cytokine interleukin 10 significantly increased in the 100% Ahiflower fed group. This study indicates that a dose of 3 g of SDA-rich Ahiflower oil is sufficient to enrich plasma and MCs with n-3 PUFAs and to modulate immune response (Lefort, LeBlanc, and Surette 2017).

The therapeutic effect of SDA in human health is mostly due to it is readily conversion to n-3 LC-PUFAs, especially to EPA. However, SDA is also reported to play a direct role in attenuating inflammation by inhibiting 5-lipoxygenase which catalyzes the formation of inflammatory leukotrienes from arachidonic acid in a dose dependent manner comparable to the inhibition levels attained by EPA but less efficient than dichomo-γ-linolenic acid (20:3n-6) (Guichardant et al. 1993). In another study, SDA from echium oil repressed the nitric oxide production in lipopolysaccharide (LPS) induced RAW macrophages by inhibiting nitric oxide synthase (iNOS) protein, NF-Kb and suppressing the phosphorylation of mitogen-activated protein kinases (MAPK) pathway (Sung et al. 2017). Further, black currant oil consumption for two months decreased the prostaglandin E_2 production and moderately enhanced immunity in 40 healthy human subjects of age ≥65 years in a randomized, double blind, placebo controlled study (Wu et al. 1999). However, it is unclear that whether the observed effects were exerted by individual fatty acids (ALA, GLA and SDA) or by a combinatorial effect. In another controlled,

randomized single-blind crossover study of patients with atopic dermatitis, hemp oil consumption for a period of 20 weeks significantly reduced the skin dryness, itchiness and use of dermal medication, which indicates the wide potential of SDA rich oils in overall health (Callaway et al. 2005). However, detailed studies have to be undertaken to understand the molecular mechanism by which botanical SDA is exerting the anti-inflammatory response.

Potential applications of SDA oil in food industry

Botanical SDA oils are generally marketed in the form of oil capsules rather than as supplements/ingredient in food products. Their usage as cooking oil is limited due to high PUFA content. However, James, Ursin, and Cleland (2003) stated that SDA based food products can be an alternative to fish oil for enriching the tissues with n-3 LC-PUFAs. In their study, it was reported that incorporation of a vegetable oil with 10% SDA in food products like margarine, mayonnaise or in salad dressing resulted in SDA intake of >1.5 g/day which is sufficient enough to increase the tissue concentrations of EPA. Precisely, four servings of such foods per day with 187–375 mg SDA is known to meet the daily requirement of EPA (Decker, Akoh, and Wilkes 2012). In another study, Pande and Akoh (2012) have optimized the conditions for the production of *trans*-free structured margarine from SDA soybean and high stearate soybean oils with better stability and shelf life using enzymatic synthesis. Monsanto Company has developed and patented several functional food products (mayonnaise, mixed berry smoothies, soy milk and salad dressings) from their transgenic soybean oil enriched with SDA (Wikes 2009). They have also analyzed the shelf life of the products where SDA enriched oil based products showed an improved shelf life compared to other n-3 oils like flax oil and fish/algae oil (Wikes 2009). Due to less unsaturation and chain length compared to EPA or DHA, SDA based food products may have a better shelf life. The other reason for the high oxidative stability of the soybean SDA oil is the inherent antioxidant systems present in the soybean such as encapsulated oil bodies and high tocopherol levels (1100 μg/g of total tocopherols in SDA soybean oil) (Decker, Akoh, and Wilkes 2012). Whittinghill and Welsby (2010) studied the customer acceptance of several food products incorporated with SDA soybean oil such as bagels, breakfast bars, pastries, cookies, icings and chocolate coatings where the flavor, sensory and functional attributes were similar to that of regular soybean oil. In a similar study, several meat compositions were prepared with SDA soybean oil where the products had a favorable sensory and flavor attributes, better shelf life, minimal oxidation and better stability during extreme processing and reheating conditions (Lee, Lucak, and Orcutt 2012). In 2014, GRAS status was given to Buglossoides oil by FDA, allowing its usage in foods and beverages. It has also met the regulatory criteria for dietary supplement by FDA in 2015. The recommended daily intake of this oil in US is about 11–12 g/day which can provide up to 2.25 g SDA/day. In 2015, European Union granted Novel food status to Buglossoides oil which allows its use in food supplements and dairy products. The approved daily intake for this oil in the European Union is about 2.5 g/day which provide about 500 mg SDA (Cumberford and Hebard 2015). However, most of the studies were carried out with GM SDA enriched soybean oil. Similar studies with natural sources of SDA such as Ahiflower and Echium oils need to be carried out to meet the increasing demands for food-based SDA especially in the countries which are yet to accept GMO crops for food.

Conclusion and future perspectives

Preventive and therapeutic benefits of consuming long chain n-3 PUFA has been recommended by World Health Organization (WHO), American Heart Association (AHA) and other global health organizations. Use of marine based sources of EPA and DHA is reducing due to the concerns related to their non-vegetarian origin, sustainable supply, methyl mercury contamination, taste, odor and shelf-life. In order to meet their increasing global demand, alternative and sustainable sources of long chain omega-3 fatty acids need to be identified. One possible alternative is providing plant-based omega-3 fatty acids rich in n-3 LC-PUFA precursors like ALA and SDA. Stearidonic acid-rich plant oils are more efficient in raising tissue EPA status than ALA rich oils as SDA bypasses the rate limiting Δ6-desaturasation step for conversion to EPA. However, large scale cultivation and distribution of SDA rich crops is essential to meet the global omega-3 PUFA demand. *Buglossoides arvensis* is known to be the richest source of SDA in the plant kingdom and is being explored as a potential commercial alternative of omega-3 sources.

Although mounting evidence reveals that increasing intake of plant-based omega-3 fatty acids may be associated with the reducing risk of certain diseases and improving overall health, several key questions regarding the above require further studies. For example, dosage and daily intake of SDA required for providing overall health benefits across different populations? Optimal duration required for observing clinical benefits? If raise in tissue EPA level alone (through consumption of SDA rich oils) sufficient to provide health benefits? Recommended intake of SDA to manage cardiovascular and other metabolic diseases, for better brain development, better cognitive health? Future research addressing the above questions will help in utilizing plant-based SDA as a potential and efficient alternative source of sustainable omega-3 PUFA for human nutrition.

Methodology

Search engines such as NCBI, PubMed, Science Direct, Google Scholar and Web of science were used to extract the research articles using relevant key words such as n-3 and n-6 PUFA, stearidonic acid, omega-3 fatty acids, plant sources of stearidonic acid, health benefits of stearidonic acid, SDA based food products etc., Articles mainly focusing on plant sources of SDA, in vivo studies using SDA plant oils

and food based application of SDA are highlighted in the present review.

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Conflict of interest

The authors declare no conflict of interest.

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