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Feature

Ahiflower oil: A novel non-GM plant-based omega-3+6 source

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Summary

Ahiflower oil, a novel and proprietary dietary oil with the richest effective combined essential fatty acids from a single non-GM plant, has been developed agronomically in a unique vertically integrated "soil to oil" model at commercial scale by Nature's Crops International. Ahiflower oil helps resolve a persistent dilemma in sustainable global omega-3 nutrition from marine sources while dramatically improving dietary omega-3 EPA conversion from plant sources and while supplying beneficial anti-inflammatory GLA not found in fish or algal oils. Having achieved key regulatory clearances in the US and EU, Ahiflower oil is launching in the latter half of 2015 in supplements and foods.

High omega-3 demand triggers a dilemma

There is generally consensus among health experts that increasing daily dietary intakes of omega-3 fatty acids leads to a variety of health benefits. Cardiovascular and early childhood cognitive health benefits in particular are now well associated with consuming long-chain polyunsaturated fatty acids like EPA and/or DHA from marine or algal sources. Recent peer-reviewed studies have also shown certain cardio-protective benefits (e.g., reduced blood pressure) from increased daily intakes of plant-derived oils such as flaxseed oil rich in the essential fatty acid alpha linolenic acid (ALA). Recognizing these benefits, governmental regulatory bodies in the EU and USA have allowed nutrient content and qualified health claims to be made for foods and dietary supplements that supply safe intake levels of these omega-3 fatty acids (**Table 1a** and **1b**).

Table 1a. Allowed nutrient claims for ALA, EPA & DHA.

Allowed Nutrient Claims	ALA Amount	EPA+DHA Amount
EU (Article 8(1) of EC No 1924/2006		
"Source of Omega-3 Fatty Acids"	≥ 300 mg per 100 g and per 100 kcal	≥ 40 mg per 100 g and per 100 kcal
"High Omega-3 Fatty Acids"	≥ 600 mg per 100 g and per 100 kcal	≥ 80 mg per 100 g and per 100 kcal
FDA per *Federal Register* Final Ruling 04/28/2014		
"More"	≥ 160 mg more per RACC than ref. food (≥ 10% of 1.6 g/day)	Not allowed
"Good Source"	≥ 160 mg per RACC* (≥ 10% of 1.6 g/day)	Not allowed
"High"	≥ 320 mg per RACC (≥ 20% of 1.6 g/day)	Not allowed

* Reference Amount Customarily Consumed

Table 1b. Allowed qualified health claims for ALA, EPA & DHA.

Allowed Qualified Health Claims	Nutrient intake
EU Article 13(1)	
"ALA contributes to the maintenance of normal blood cholesterol levels"	2 g/day
"DHA contributes to maintenance of normal brain function"	250 mg/day
"DHA contributes to maintenance of normal vision"	250 mg/day
"DHA contributes to maintenance of normal blood triglyceride levels"	2 g/day (≤5 g/day)
"DHA and EPA contribute to the maintenance of normal blood pressure"	3 g/day (≤5 g/day)
"DHA and EPA contribute to the maintenance of normal blood triglyceride levels"	2 g/day (≤5 g/day)
"EPA and DHA contribute to the normal function of the heart"	250 mg/day
"Can maintain normal brain function, vision, and blood triglyceride levels"	DHA only
EU Article 14(1)(b)	
"DHA intake contributes to the normal visual development of infants up to 12 month of age"	100 mg
"DHA maternal intake contributes to normal development of the eye/normal brain development of the fetus and of breastfed infants"	200 mg in addition to 250 mg EPA+DHA
US FDA	
"Consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease"	2 g/day

However, a pervasive global dilemma is emerging: How to supply adequate omega-3 daily intakes to humans and farmed animals in a manner that is sustainable ecologically, scalable in annual oil volumes exceeding tens of thousands of metric tons, and appealing to consumers? With recent anchovy and sardine fishery closures in Peru and the US Pacific coast making headlines, consumers are becoming more concerned about long-term sustainability of marine omega-3 sources. The industry trade group GOED has reported that over 220 million consumers in 12 industrialized countries have self-selected away from consuming marine omega-3 products [Global Organization for EPA and DHA Omega 3s, *Seminar on MSC Certification of the Peruvian Anchoveta Fisheries (September 18, 2013)*, p. 22. Cited based on GOED proprietary consumer surveys]. Even so, for the remaining marine (and many algal) omega-3 oil consumers, a well-known challenge is that they have the characteristic "fishy" taste, odor, and "burp" reflux that many consumers find unappealing.

Algal oil sources of EPA and DHA, while helping to resolve marine omega-3 sustainability issues, have inherent scalability challenges and relatively high costs of production. Finished refined algal oils can cost from 8–12 times the price of regular fish oils (See **Table 2**).

Being produced in a relatively few commercial locations, algal sources are also susceptible to asset concentration risks, as occurred in the recent flooding of the Qualitas Almega PL production facility in West Texas, which impaired production of this EPA algal product for the remainder of 2015 [http://www.nutraingredients-usa.com/Suppliers2/Texas-storms-disrupt-Qualitas-algal-production-It-s-a-setback-but-we-re-still-in-a-unique-position-says-CEO].

Among leading plant-derived omega-3 sources – flax, chia, perilla, sacha inchi, and hemp seed oils – the inherent challenges are not supply chain sustainability and scalability, but rather metabolic conversion of ALA in tissues to longer-chain fatty acids like EPA and DHA. Due to the rate-limiting step involving the hepatic enzyme delta-6 desaturase (Δ6D), most humans convert ALA very poorly (<6%) to EPA, although some research suggests that vegetarians and vegans have a higher conversion capacity [1]. People therefore have to consume much higher daily amounts of these plant-derived oils to achieve the minimum omega-3 intake levels recommended by recognized authorities at 200–250 mg/day EPA equivalent or greater. For example, at a 3–6% ALA → EPA conversion rate in flaxseed oil (max 60% ALA), achieving 200 mg/day EPA equivalent would require taking 5.6 to 11.2 grams flaxseed oil vs. about 1 gram regular fish oil (18% EPA).

Practitioners and health-conscious consumers are seeking effective, appealing, and convenient solutions to providing minimum-recommended daily omega-3 intakes in formats that people will literally find easier to swallow – without compromising marine ecosystems. The latest industry market research shows the global demand for omega-3 supplements growing to $ 4.48 billion by 2020 with a 13.1% annual growth rate [http://newhope360.com/breaking-news/omega-sales-44-billion-2020]. Industry trend spotters are also identifying vegan products among the emerging wave that appeal not only to people concerned about animal welfare, but also to "flexitarians" – millenials and baby boomers who are consciously reducing their meat consumption and shifting to vegan or vegetarian products because of perceived health and eco-social benefits [http://www.foodnavigator-usa.com/Markets/Vegan-is-going-mainstream-trend-data-suggests].

Table 2. Omega-3 PUFA pricing by ingredient type, Global, 2013.

Ingredient	Mfr Avg Price ($/kg)
Microalgal DHA	$ 72.39
Microalgal EPA	$ 94.74
Cod Liver Oil	$ 10.08
Natural Fish Oil (18/12)	$ 8.12
Fish Oil Concentrates (40–50%)	$ 18.02
Fish Oil Concentrates (60–70%)	$ 39.88
Fish Oil Concentrates (85–95%)	$ 183.65
Krill Oil	$ 115.51

[Shanahan, Chris, *The State and Future of the Global Omega-3 Industry through 2020*. Frost & Sullivan (2014). Presentation delivered 7 Oct 2014 at Supply Side West.]

SDA: A game-changer in long-chain omega-3 nutrition from plants?

Stearidonic acid (n-3, C18 : 4), or "SDA", is the first metabolite in the conversion of the essential fatty acid ALA to EPA (**Figure 1**). When humans ingest ALA from principal sources such as nuts, seeds, and seed oils like flax or chia, it is initially converted to SDA in the liver using the often sub-optimally performing Δ6D enzyme. Consuming SDA directly effectively removes this initial step in EPA synthesis, resulting in a far more effective accumulation of EPA from SDA consumption compared to ALA consumption. This means that people seeking a plant-derived omega-3 source can obtain far higher effective omega-3 intakes using dietary oils that contain SDA.

Existing commercially-available examples include hemp (~1–3% SDA), black currant (~3% SDA), and echium (~12–14% SDA) seed oils. On the biotech side, Monsanto developed a genetically modified (GM) soya oil with a high SDA content, but this product was acquired by DSM in 2013 and does not appear to be commercially available as of this writing. SDA-rich soya oil faces labeling and regulatory challenges associated with GM food ingredients. Other microbially-generated SDA or EPA sources have been reported in research literature [2, 3], for example in trans-genic yeasts like *Saccharomyces cerevisiae* and *Yarrowia lipolytica*, but these

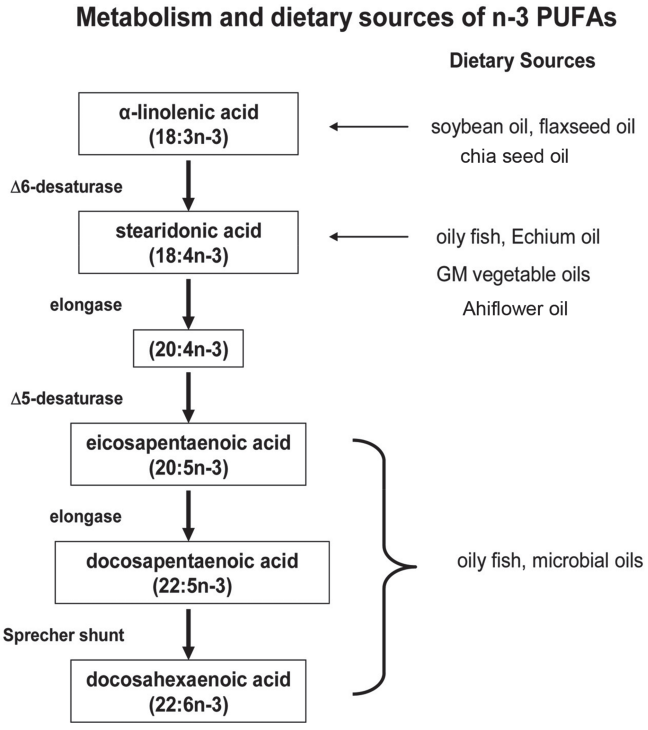

Figure 1. Omega-3 metabolism chart. Modified from Coupland K, *Lipid Technology 2008, 20, 152*.

products are likely many years away from commercialization and high-volume production, notwithstanding their GM status and potentially high manufacturing costs.

SDA's potential for dramatically improving bioavailability of long-chain omega-3 fatty acids in human nutrition led our company to seek a more sustainable, scalable, and unique plant-derived solution that addresses rapidly-growing global needs.

Enter Ahiflower® Oil: The richest effective combined omega-3+6 source

Agronomy. Ahiflower is Nature's Crops International's trademarked name for the products and proprietary intellectual property comprised by the cultivars, seeds, oils, and oil fractions from *Buglossoides arvensis* (L.) I.M. Johnst. (Corn Gromwell, Field Gromwell, Bastard Alkanet), a member of the *Boraginaceae* family. This small annual is a native species in northern temperate regions of Europe and Asia. It occurs as an introduced weed species in much of North America, Australia, and South America where wheat farming has occurred. It can be grown in colder temperate regions or at higher elevations in temperate regions in either hemisphere. It prefers neutral to slightly alkaline moist well-drained soils, however it does not require mechanical irrigation.

Ahiflower has been developed through patient natural selection and plant breeding techniques without genetic modification over the past 12 years. The result has been the agronomic development of internationally protected, elite, and robust cultivars that produce a high-yielding oilseed crop with the richest SDA content (18–20%) of any commercially-available plant. In its natural state as a wild-type variety, *B. arvensis* contains less SDA, typically 14% [4]. It also has a therapeutically significant omega-6 gamma linolenic acid (GLA) content, typically 5–6%, which is more than half the GLA content of evening primrose oil (8–10%). Further horticultural development is planned to further improve agronomic yield (kilograms of oilseed per hectare) as well as bio-marker yield (mg SDA+ALA+GLA per gram of refined oil).

In 2015, Ahiflower is being grown commercially on over 1,000 hectares in the UK on farms ranging from East Sussex to the Black Isle in Scotland, in both winter and spring crop varieties. It is propagated by seed using conventional seed drills and harvested using conventional combines. Individual farm crop yields of mature seeds in excess of 1 metric tons per hectare are occurring, with an overall average of 650–750 kg per hectare. Crop yields are improving steadily each year.

Commercially-available Ahiflower oil results from the expeller pressed, extracted, and refined oil from the seeds of this diminutive plant. Ahiflower seeds have a 19–21% oil content typically. The typical fatty acid content and purity specifications are provided in **Tables 3a** and **3b**. Prone neither to natural herbivory or insect pests, the plant has not been used nutritionally in Western diets. It has a neutral, clean aroma and flavor. Its aerial parts have had some folkloric and traditional uses in Asian countries like Japan and Korea, but the oil's potential role in human and animal omega-3+6 nutrition has not been explored until recently. Immediate potential applications include foods, beverages, dietary supplements, natural body care, and pet and equine feeds. Pharmaceuticals represent future promise in cardiovascular, immune, and cancer therapeutics.

Operations and quality control. Rather uniquely among commodity plant-derived omega-3 oils, Ahiflower oil's production is controlled completely – from soil to oil – under a proprietary (Crops Assured 365®) identity, quality, and purity system. At no point do the seed, the crops, or the bulk refined Ahiflower oil leave the chain of custody and every master batch of refined oil bears a Crop Assured 365® certificate attesting to its conformance to strict compositional and purity limits meeting both US and EU requirements. All microbial, heavy metal, pesticide, and PCB/PAH limits are tested and verified at the master batch level using recognized third party testing laboratories that follow peer-reviewed published analytical methods and/or national pharmacopeia methods. Since

Table 3a. Ahiflower oil fatty acid composition.

Analyte*	Specification
Stearidonic Acid Ω-3 C18 : 4 (SDA)	17–21%
Gamma Linolenic Acid Ω-6 C18 : 3 (GLA)	4.5–8%
Alpha-Linolenic Acid Ω-3 C18 : 3 (ALA)	42–48%
Linoleic Acid Ω-6 C18 : 2 (LA)	9–15%
Oleic Acid Ω-9 C18 : 1 (OA)	6–14%
Palmitic Acid C16 : 0	4–7%
Unsaponifiable Matter	<1.5%
Erucic Acid	<1%
Free Fatty Acid	<0.3%

* Method: AOCS Ce 1h-05

Table 3b. Ahiflower oil key quality parameters.

Analyte	Specification	Method
Peroxide Value (mEq/kg)	<5	AOCS Cd 8-53
p-Anisidine Value	<15	AOCS Cd 18-90
Pyrollizidine Alkaloids (μg/kg)	<1	HP/LC-MS; Cramer et al., J Am Oil Chem Soc (2014) 91: 721–731
Arsenic (mg/kg)	<0.1	ICP-MS; AOAC 993.14
Cadmium (mg/kg)	<0.1	ICP-MS; AOAC 993.14
Lead (mg/kg)	<0.1	ICP-MS; AOAC 993.14
Mercury (mg/kg)	<0.1	ICP-MS; AOAC 993.14
Pesticide Residues	ND	Per European Pharmacopeia
Sum of Dioxins (pg/g)	<0.75	per EC 1881/2006 sec 5.12
Dioxins and Furans, Dioxin-Like PCBs (pg/g)	<1.25	per EC 1881/2006 sec 5.12
PCBs (mg/kg) (209 congeners)	<0.09	US EPA 1668, CA Proposition 65
PCB 6-ICES Congeners (ng/g)	<40	Sum of congeners 28, 52, 101, 138, 153, and 180
Polycyclic Aromatic Hydrocarbons (PAHs)	<2.0 μg/kg benzo(a)pyrene, <10.0 μg/kg total PAH	per EC 1881/2006 sec 6.1.1

the source crop is in the Borage family, refined Ahiflower oil must also be tested to contain no unsafe pyrollizidine alkaloid (PA) levels. The recognized limit for this naturally occurring contaminant is 4 ppb (μg per kg) in the EU. However, Ahiflower oil is third-party tested to comply with a <1 ppb PA limit using a proprietary method developed from a peer-reviewed publication specializing in PA quantitation that follows a more sensitive LC-MS/MS method.

Further, each Ahiflower oil master batch is fully traceable back to the original farms on which the seed was grown. For the 2014 and 2015 crops, all commercial Ahiflower oil has been grown under contract by small independent farmers in strategic production locations. By comparison with other plant-derived omega-rich oils, the finished refined oil may have changed hands many times between primary crude oil producers and the finished branded ingredients. Oils are frequently combined from disparate regions like China, the EU, and Latin America in order to achieve targeted bio-marker levels, yet resulting in traceability back through the supply chain being either lost or muddled.

Clinical science. Because Ahiflower oil is novel, its animal and human clinical trial history is brief. However, analogous dietary oils (SDA soya oil and echium) composed of the same fatty acids have been tested extensively and there is an established peer-reviewed published record of safe outcomes. All of the clinical science conducted thus far confirms that SDA converts readily to EPA (n-3, C20 : 5) and DPA (n-3, C22 : 5) in circulating cells in humans and in hepatic, intestine, and brain tissues (in mice) far more efficiently than ALA. In essence, the empirical data confirms the theoretical data pertaining to EPA and DPA accrual resulting from SDA consumption over relatively short trial durations (up to 16 weeks). On the other hand, no significant DHA (n-3, C22 : 6) accrual in circulating cells or in tissues has yet been associated with dietary SDA consumption.

In 2014, Dr. Marc Surette and his researchers at the University of Moncton conducted the first randomized double-blinded placebo-controlled human clinical trial with Ahiflower oil. The results of this study were presented at the 2015 Experimental Biology Symposium in Boston in March [6]. The peer-reviewed publication of the results is forthcoming. In essence, this 28-day interventional study involved healthy human adults (n = 16 or 17 per study arm) consuming 10 ml either of refined flaxseed oil (as placebo) or Ahiflower oil. Blood draws were taken at day 0, day 14, and day 28. Fatty acid profiles were measured in a variety of circulating cells (plasma, red blood cells (RBCs), monocytes, and neutrophils) after each blood draw. The results after 28 days were significant ($p < .001$) and showed EPA accruals 2.2 to 4.0 ($\mu = 3.0$) times greater from Ahiflower oil over flaxseed oil.

RBCs are typically not the best measure to see the greatest physiological impact from omega-3 consumption. Clinical trials have shown that plasma omega-3 PUFA are more associated with cardiovascular end points than that of RBCs because they are a better measure of cellular tissue accrual. Furthermore, plasma gets more enriched than do RBCs when a person ingests SDA or EPA, suggesting the efficacious dose of Ahiflower oil could be considerably lower than indicated by RBC accrual alone. This is supported by data from the Ahiflower clinical trial which indicated approximately 16% greater increase in omega-3 levels in plasma versus RBCs.

This translates to an efficacious Ahiflower oil dose of approximately 2.3 to 3 grams per day, providing the internationally recommended 200–250 mg EPA minimum daily equivalent. This is considerably less than 5.6–11.2 grams of flaxseed (or chia) oil, and manageably close to 1 to 1.4 grams of standard fish oil – without the ecological down sides. Ahiflower oil is simply a superior dietary oil for people seeking more efficacious omega-3 plant nutrition. Plus, Ahiflower oil's naturally occurring omega-6 GLA content, commonly used for its anti-inflammatory prostaglandin-1 series inhibition benefits in women's reproductive, skin, and joint health, combines with omega-6 linolenic acid (LA) to comprise a 15–18% overall omega-6 content. Ahiflower oil's combined omega 3-6-9 content is therefore over 90%, making it the new go-to plant-derived omega-rich oil backed by human clinical research.

Regulatory and market status

Key regulatory filings in the USA, European Union, and Canada have been made for Ahiflower. A self-determined Generally Recognized As Safe (GRAS) notification for refined *Buglossoides* oil via an independent expert review panel was made in August 2013. FDA's Office of Food Additive Safety concluded its review of the self-determined GRAS status with no objections as of December 2014. This means that Ahiflower oil can be sold as an ingredient in foods and beverages in the United States within daily intake levels up to 2.25 grams SDA per day, or about 11–12 grams Ahiflower oil per day. Further, FDA's guidance regarding New Dietary Ingredients (NDI) allows for an exemption from making NDI notifications for dietary supplement uses if the "dietary supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered." [FDC Act §§ 413(a) (1)–(2), 402(f). See *NDI Draft Guidance* availabile via 76 Fed. Reg. 39111 (July 5, 2011)] Ahiflower oil has already met this criterion as of March 2015, so it is fully commercially available to branded dietary supplement manufacturers marketing products in the USA.

In the European Union, Technology Crops LLC originally filed a Novel Foods application for refined *Buglossoides* oil in June 2013. This application received a favorable scientific opinion of "safety" under intended uses from the European Food Safety Authority in February 2015. A final decision granting EU Novel Foods status was published in the *EU Journal* in July 2015. Ahiflower oil may now be used in food supplements, dairy products and analogues, cheese and cheese products, butter and other fat and oil emulsions including spreads (not for cooking or frying purposes), and breakfast cereals, among other approved uses in the European Union. However approved uses limit the daily intake in dietary supplements to 500 mg SDA or about 2.5 grams Ahiflower oil, with allowances for higher intakes in various foods.

As of July 2015, Ahiflower oil is fully commercialized with co-branding partners in functional foods and dietary supplements market channels. The initial focus is on the US and EU markets with next-phase launches planned in Canada, Korea, Australia, and New Zealand once the underlying regulatory approvals are secured. Consumers in the US will start seeing food and dietary supplement brands incorporating or featuring Ahiflower oil in the latter half of 2015.

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