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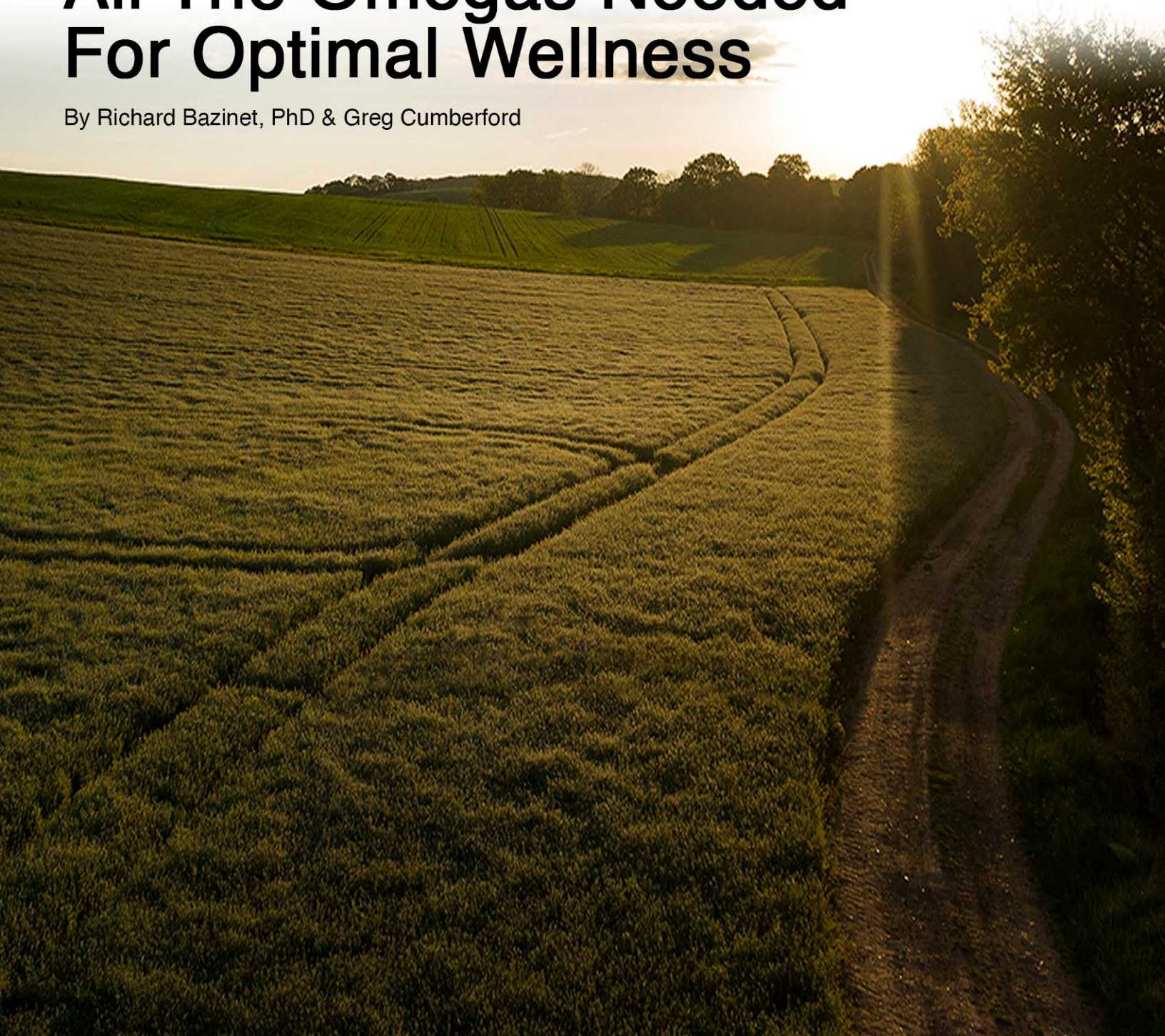

Plant-Based Dietary Sources Can Supply All The Omegas Needed For Optimal Wellness

By Richard Bazinet, PhD[a] & Greg Cumberford[b]

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Take-Away Points • *2 minute read*

- Emerging preclinical and clinical science indicates that plant-based ALA and SDA intakes convert to circulating DHA relatively rapidly and achieve adequate brain DHA levels, while significantly elevating circulating EPA levels especially from higher omega-3 SDA intakes. This challenges the accepted consensus that plant-based omega-3 sources don't convert to DHA 'efficiently'.

- Increasing circulating EPA/DHA levels through omega-3 supplementation correlates with a number of wellness endpoints, but new research is differentiating the respective roles and benefits of elevated EPA vs DHA and their ratios.

- Recently published large cohort clinical trials and meta-analyses highlight the value of elevating EPA vs DHA levels in preventing cardiovascular adverse events and improving cognitive performance in average adults. The role of elevating EPA levels and ratios deserves more scrutiny and opens up legitimate inquiry as to whether focusing on high preformed DHA intakes is necessary in most adults.

- Achieving adequate omega-3 and omega-6 dietary intake goals globally from omega-rich plant-based sources matches human genomic dietary requirements. Such sources can be a rallying point for championing regenerative omega-3 supply chains vs degrading ocean health to meet global demand.

- Ahiflower® oil is a plant-based omega source that supplies higher levels of immediate omega-3 precursors to EPA and DHA due to its exceptionally high ALA and SDA content, increases circulating EPA and anti-inflammatory GLA levels, and has new preliminary evidence of relatively rapid DHA turnover.

- SDA is the most efficient plant-based omega-3 fatty acid precursor for EPA and DHA synthesis, converting up to 4 times the rate of ALA into EPA. Ahiflower is the richest non-GM plant-derived source of SDA.

Introduction

Recent science is upending much of what many industry stakeholders and health care professionals have been told about omega fatty acid metabolism and their sources.

2021 marks the 50th anniversary of the beginning of the omega-3 revolution, where today a $5.2 billion global omega-3 nutraceutical marketplace[1] is a leading dietary supplement industry segment, but one that faces increasing ecological sustainability challenges.[2],[3] For many years, the research community has known that if recommended dietary EPA/DHA intakes actually occurred globally from marine omega sources,[4] the added pressure on exponentially increasing fish stock collapses would be unsustainable.[5],[6] Also, the marine omega-3 reduction and purification process is not efficient ecologically. For every metric tonne of fish biomass harvested only 10 kilograms of commercial EPA/DHA oil is produced.[7],[8] Other EPA/DHA sources do exist, including some genetically modified oilseed crops, biotech algal oils, and aquaculture fish like salmon. But the latter relies on wild-harvested fish meals and therefore exacerbates the EPA/DHA supply sustainability challenge. By contrast, the equivalent amount of naturally synthesized EPA/DHA can be produced competitively from only 1/10th a hectare of non-GM, regeneratively cultivated farmland.

This paper questions the notion that humans have somehow evolved with an innate inefficiency at converting essential fatty acids to their longer chain, downstream metabolites.

Humans have well understood and genetically determined metabolic pathways for converting plant-based omega-3 and omega-6 fatty acid intakes from essential ALA and LA—or their elongated metabolites SDA and GLA—to longer chain fatty acids (Fig. 1).[9] A recently launched new oilseed source derived from what was considered a diminutive weed species (Buglossoides arvensis) has the highest naturally occurring ALA, SDA and GLA levels. It reframes the debate on optimal and most sustainable dietary omega sources. This paper highlights new clinical and dietary intervention research yielding important insights indicating that optimally balanced omega fatty acid intakes can be derived from non-GM terrestrial plant-based dietary sources which convert readily and adequately to circulating EPA and DHA. It questions the notion that humans have somehow evolved with an innate inefficiency at converting essential fatty acids to their longer chain, downstream metabolites. It concludes that existing, readily scalable and regeneratively grown plant-based sources can meaningfully address clinical wellness endpoints, while alleviating global pressure on ocean ecosystems that the dominant sourcing of omega-3 oil causes.

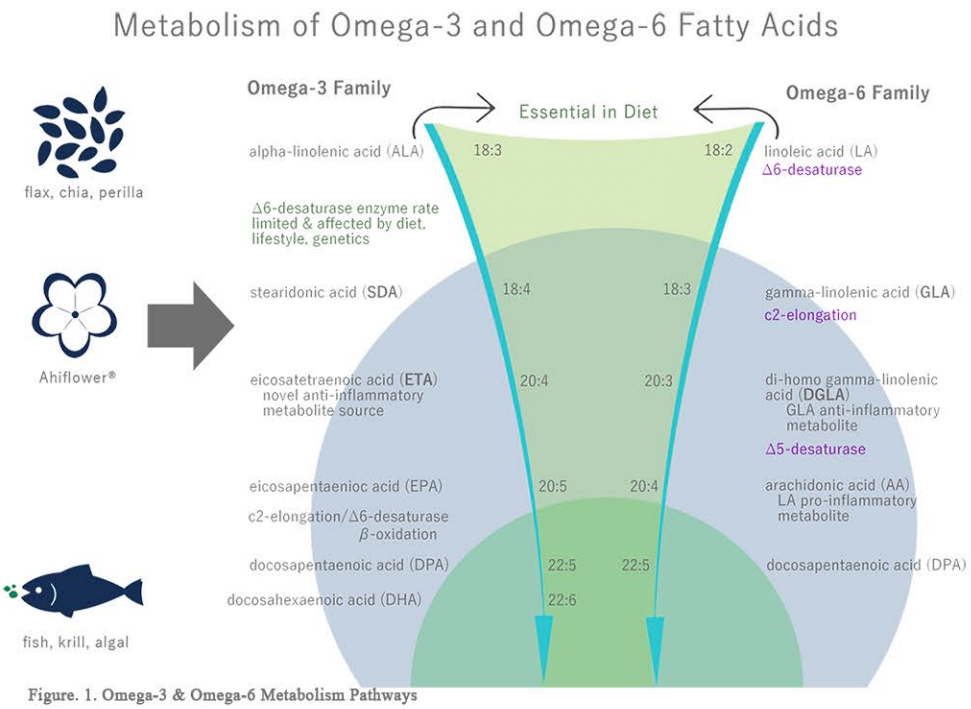

Figure. 1. Omega-3 & Omega-6 Metabolism Pathways

How Much EPA & DHA Is Enough?

In 1971, the journal *Lancet* published the seminal study by Danish researchers Bang and Dyerberg[10] linking the near absence of ischemic heart failure and diabetes in Western Greenland Inuits to elevated polyunsaturated fatty acid levels from seal and fish oil heavy diets, and then specifically to elevated EPA/DHA levels. The ensuing 5 decades have led to over 31,000 clinical research publications[11] on omega-3 fatty acid metabolism carried out all over the world. It is now a common medical and nutritional practice to recommend that people consume more oily fish (salmon, sardines, anchovies) or more omega-3 EPA/DHA supplements to boost circulating long-chain polyunsaturated fatty acid (LC-PUFA) levels. This has been shown to provide various cardiovascular, neurological, mood, skin, and immune support benefits, including for prenatal development, neonatal brain health (ie in breast milk or infant formula), and for traumatic brain injury.[12]

A cascade of clinical research and literature reviews[13] into the effects of omega-3 supplementation has occurred. Numerous findings at the cellular membrane interface and in metabolism have uncovered the mechanisms and activities by which omega-3 lipids and their metabolites influence membrane permeability, combat oxidative stress, mediate eicosanoid and prostaglandin inflammation response, and regulate key signaling functions in various cells and tissues.[14]

To the frustration of many health professionals and researchers who ask “How much circulating EPA/DHA is enough for an average adult to experience optimal wellness?” answers remain elusive.

As a result, clinical science generally supports expectations of improved health outcomes, increased longevity and reduced risk of incidences of major adverse cardiological events (MACE) under diets that contribute to elevated circulating EPA/DHA. Evidence also supports the anti-inflammatory, pro-resolving, neuro-protective, mental wellness, and immune-modulatory benefits of elevated LC-PUFA levels. However conclusive support of these linkages from randomized controlled human clinical trials is still controversial. The only two positive randomized controlled trials (RCTs) showing benefits in cardiovascular outcomes in humans this century used EPA sources.[15],[16]

Several recently reported large cohort clinical trials underscore potentially important clinical differences between elevating EPA *versus* elevating DHA. This has major consequences for how people can achieve optimal health outcomes via supplementation. Mounting evidence shows that plant-based omega-3 intakes are completely adequate for DHA uptake in key tissues.

To the frustration of many health professionals and researchers who ask “How much circulating EPA/DHA is enough for an average adult to experience optimal wellness?” answers remain elusive. While it is possible for physicians and nutritionists to correlate high preformed marine EPA/DHA or algal DHA intakes with elevated Omega-3 Index levels, it is much less clear how the background diet—especially when it is high in omega-6 linoleic acid (LA)—impacts EPA/DHA conversion efficiencies. With human clinical evidence of ALA-to-DHA synthesis occurring as needed from adipose tissue stores, we question whether humans are inherently inefficient converters of plant-based omega-3 fatty acids. The high level of LA intakes from modern industrialized background diets clearly plays a role.[17],[18],[19]

Further, several recently reported large cohort clinical trials underscore potentially important clinical differences between elevating EPA *versus* elevating DHA. This has major consequences for how people can achieve optimal health outcomes via supplementation. It further opens legitimate inquiry as to whether focusing on high-preformed DHA intakes (and DHA’s proportionately high role in the Omega-3 Index) is necessary for most healthy adults, since mounting evidence shows that plant-based omega-3 intakes are completely adequate for DHA uptake in key tissues.

The Challenge in Agreeing on Omega-3 & Omega-6 Intake Requirements, Balance & Sources

The medical and omega-3 research community has been largely biased against advocating for plant-based omega-3 ALA and SDA intakes, even though these fats are essential to the human diet. This is primarily due to the fact that average people consuming them—setting aside pregnant women, vegans or vegetarians[20],[21]—fail to raise circulating LC-PUFA levels as efficiently as from animal or algal sources while barely elevating circulating DHA levels at all. By conventional consensus, since we are 'poor converters' of plant-based omega-3 fatty acids, preformed sources rich in EPA/DHA are viewed as 'better'. This despite the Institute of Medicine not having a formal intake requirement for EPA/DHA.[22]

> Even though our biological requirements for balanced omega-3 and omega-6 intakes have not changed since pre-industrial times, our modern Western industrialized diets have changed dramatically.

Yet this consensus is yielding to new insights instigated by novel analytical techniques, genomics, and intervention studies separating EPA and DHA effects. Importantly, typical omega-3 ALA intakes in the modern Western diet are cited as dropping to only 1:20 vs omega-6 LA, far out of balance with the historic 1:1 to 1:4 ratio from which most human diets evolved.[23] So even though our biological requirements for balanced omega-3 and omega-6 intakes have not changed since pre-industrial times, our modern Western industrialized diets have changed dramatically.

Research has evaluated whether excess LA intakes competitively impair omega-3 ALA's hepatic enzymatic conversion to longer-chain EPA and DHA. When LA levels are high, competition occurs between available hepatic Δ6-desaturase enzymes required for ALA-to-DHA synthesis.[24] The University of Toronto's Department of Nutritional Sciences is investigating whether varying proportions of plant-based LA in the diet is indeed a principal cause of ALA's supposedly 'inefficient' synthesis onward to DHA.

Recent research by this group shows that although there is a negative correlation between LA intake and DHA levels, the mechanisms behind this effect involve more than LA's hepatic enzyme competition with ALA. In effect, humans are not actually inefficient converters, rather they convert what is available, proportionately, relative to abundance in the diet.

Despite understanding that dietary preformed DHA intakes raise Omega-3 Index levels, we are learning how and whether excessive LA intakes (at up to 10% total energy) may impact DHA synthesis from plant-based omega-3 fatty acids. Background dietary intake patterns (vegan, meat eating, fish eating) and sex matter,[25] likely setting up enzymatic and hormonal response capacities attuned to accustomed diets. We are also learning how and whether high levels of preformed DHA intakes impair the activity of various enzymes that most human genotypes possess naturally for the purpose of synthesizing DHA from plant-based omega-3 sources. Existing evidence favors that high preformed DHA intakes suppress natural EPA-to-DHA biosynthesis.[26] Both these influences must be factored into any assessment of the supposed 'inefficiency' of plant-based omega sources.

> In effect, humans are not actually inefficient converters, rather they convert what is available, proportionately, relative to abundance in the diet.

Certain indicative effects have been seen as a result of high preformed DHA in circulation, including non-competitive impairment of the binding capacity of elongase 2 enzymes.[27] Further, dietary ALA appears necessary for efficient synthesis of circulating unesterified EPA stores, which form a very good source for regular brain tissue DHA maintenance even in the presence of dietary preformed DHA. Moreover plant-based omega-3 fatty acids in the diet are seen to contribute to the majority of noted EPA pooling in circulating cells, as opposed to so-called DHA 'retroconversion'.[28],[29]

Using specialized carbon isotope ratio mass spectroscopy, preliminary evidence in mice shows that plant-based dietary ALA and SDA sources[30](flax and Ahiflower oil) convert to circulating plasma DHA at relatively efficient turnover rates compared to a fish oil based DHA source, with Ahiflower oil converting to DHA more efficiently than flaxseed oil due to Ahiflower oil's SDA content.[31] Mice consuming preformed DHA also demonstrated declines in circulating EPA levels from a pre-equilibrated baseline. Whereas the plant-based Ahiflower oil elevated and flax sources maintained circulating EPA from baseline.[32]

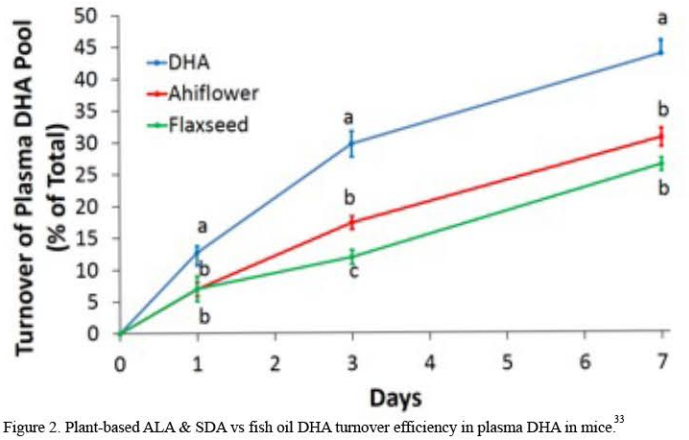

Figure 2. Plant-based ALA & SDA vs fish oil DHA turnover efficiency in plasma DHA in mice.[33]

These new findings underscore that while mammals are capable of efficiently and even preferentially metabolizing preformed sources of DHA, when these sources are unavailable they are actually genetically predisposed to readily biosynthesizing plant-based omega-3 sources. To date, our team's research in rodents and humans is showing that the simplistic rubric of mammals being 'poor' or 'inefficient' DHA synthesizers is simply not correct.

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Clinical Evidence of EPA's Understudied Significance

Since elevated DHA intakes are universally recommended by physicians and nutritionists to support cardiovascular and cognitive wellness (including mental health), it is important to note recent scientific findings that call into question whether high DHA intakes are always necessary to achieve desired clinical endpoints

In a 2019 review of the longitudinal Multi-Ethnic Study of Atherosclerosis (MESA) cohort study of over 6800 US adults, the authors found that elevated plasma EPA was significantly associated with reduced risk for heart failure.[34] Further, a new meta-regression analysis in 2021 of 92 controlled human clinical trials investigating EPA and DHA supplementation on markers of coronary heart disease risk found that a higher EPA/DHA ratio correlated with lower inflammatory C-reactive protein levels. The researchers found that higher EPA vs. DHA levels associated with higher systolic blood pressure, but only in studies giving considerably high 2-6 gram/day levels of combined EPA and DHA.[35] This is the first meta-analysis to examine the effects of the EPA/DHA ratio on cardiovascular clinical endpoints.

In a new 2021 study reported at the American College of Cardiology's annual symposium[36], higher circulating EPA levels, but not DHA levels, correlated with reductions in major adverse cardiac events (MACE) including all-cause death, myocardial infarction, stroke, heart failure hospitalization in seniors at higher risk for cardiovascular disease. This was based on a 10-year look-back analysis of 987 individuals based on primary analysis of plasma EPA and DHA levels. The study found that lower, not higher, DHA levels correlated with lower MACE event likelihood. This supports the findings of the 2018 large cohort ANCHOR trial in patients with cardiovascular disease (CVD) that concluded that a high 4 g/day EPA ethyl ester intake drives modest but significant reductions in MACE, but in which subsequent analysis also showed no significant increases in circulating DHA.[37]

However, it is important to note that a broad evaluation of 17 prospective studies demonstrated that blood EPA, DHA and EPA+DHA were associated with a lower risk of premature death, including from cardiovascular disease, and that EPA+DHA were not additive.

Also in 2021, on the cognitive wellness front, in the first placebo-controlled human cognitive performance study of its kind[38], University of Northumbria researchers looked specifically at the respective roles of EPA vs. DHA supplementation. Key measures looked at changes in overall standard cognitive performance scores. Surprisingly only EPA-dominant supplementation boosted global memory accuracy and global speed scores over 6 months, but not DHA-dominant supplementation. In this trial, the DHA cohort performed worse vs. placebo and experienced lower accuracy of memory scores vs baseline. Daily dosing levels in the active groups contained 900 mg EPA or DHA, respectively.

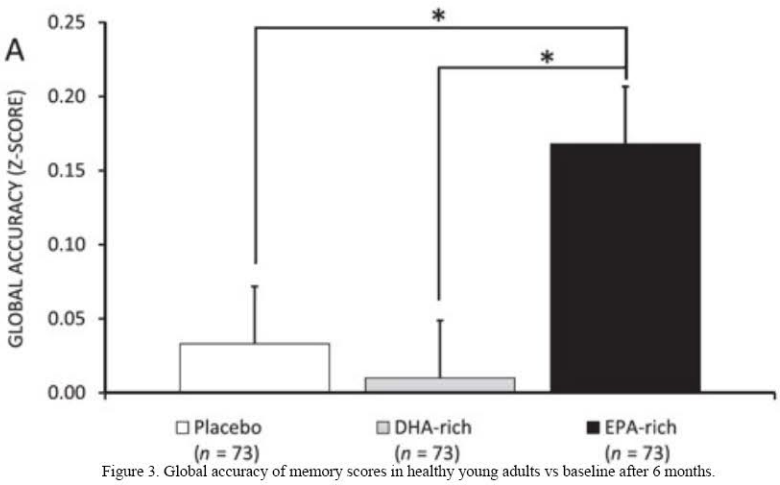

Figure 3. Global accuracy of memory scores in healthy young adults vs baseline after 6 months.

While the study from Northumbria might seem at odds with other randomized controlled trials of DHA and cognition, it is important to consider that most studies of DHA and cognition are null, especially when preregistered primary outcomes are considered.

Clearly circulating EPA plays an important role physiologically despite its proportionately smaller levels vs DHA in the body and brain.

The emerging picture is that the body gives top metabolic priority to maintaining brain tissue DHA needs and will do so from *any* omega-3 dietary source, preferentially from preformed DHA sources when available.

Research has shown that when not needed for DHA synthesis, dietary ALA and SDA will form myriad omega-3 metabolites and tissue structures that cannot form adequately from dietary DHA via 'retro-conversion'.

However, excess DHA pooling in circulating cells or 'packing up' in various organs besides the brain may interfere with, and possibly suppress, endogenous biosynthesis pathways for required essential omega-3 and omega-6 PUFA.[39] As noted, endogenously formed (unesterified) plasma EPA-to-DHA biosynthesis is a major source of brain tissue DHA accrual, even when supplemental DHA is present.[40] Further, a new finding presented in 2021 shows that the omega-3 composition of the brain's microglial cells—immune macrophage cells that combat invading pathogens and a range of inflammatory stressors in the brain—is surprisingly high in EPA and low in DHA compared to the whole brain.[41],[42] This despite the brain's overall gray matter having almost negligible EPA content. Clearly circulating EPA plays an important role physiologically despite its proportionately smaller levels vs DHA in the body and brain.

These findings support that plant-based omega-3 sources are necessary to maintaining the body's natural metabolic priority and affinity for fluxing EPA metabolites into critical tissues, as and when needed. Mammals appear 'hard-wired' to convert plant-based sources onward to brain tissue EPA and then DHA. Research has shown that when not needed for DHA synthesis, dietary ALA and SDA will form myriad omega-3 metabolites and tissue structures that cannot form adequately from dietary DHA via 'retro-conversion'.[43] Thus, maintaining proper omega-3:6 balance from the richest-available plant-based sources in the diet is paramount and, between endogenously synthesized EPA and DHA, favoring elevated EPA accrual in the balance of circulating LC-PUFA appears to be optimal.

General brain tissue DHA levels do not increase linearly beyond homeostasis requirements with increasing omega-3 intakes from any dietary source, including preformed DHA. Rather, the brain only requires so much precursor omega-3 substrate or preformed DHA at a time to maintain a dynamic needs-based equilibrium. Minimum corresponding 'healthy DHA' levels in circulating plasma or blood are still unknown, and indeed this will vary greatly by genetics, sex, age, environmental and dietary stressors, and background dietary omega-6 LA imbalance factors.

Where questions about the role of omega-3 fatty acids in attaining or modulating a desired health endpoint included a capacity to separate out EPA vs DHA intake levels or ratios—findings indicate that the simple rubric of 'more DHA is better' deserves more scrutiny.

The DHA requirement for a normal human brain is understood to be only about 3.8 mg/day. This can be easily achieved through biosynthesis of plant-based ALA[44] and even more so with SDA. Individual genetics and phenotypic enzymatic FADS2 and ELOVL suites in particular appear to play a crucial[45] role and strike against taking a 'one size fits all' approach to recommended routine intakes of preformed DHA.

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Do Healthy Adults Require High Preformed DHA Intakes? Supply Chain Implications

An alternative and provable hypothesis is that biologically, humans and mammals that evolved with diets dominantly coming from plants, do not actually require supplemental preformed DHA except in clear medically established cases such as in prenatal development, post-natal breastfeeding, and post-traumatic brain injury.

Most people simply require a natural, pre-industrial balance of plant-based essential omega-3 and omega-6 fatty acids in their diets.

Plant-based omega-3 fatty acids will naturally and efficiently biosynthesize and accrue as circulating stores of EPA, which will then be deployed dynamically onwards to tissue DHA forms as needed. Emerging science indicates that the human body will successfully manage a dynamically changing, constantly optimized omega-3:6 flux endogenously from plant-based sources.

The most biologically advanced plant-based omega-3 fatty acid sources will be those with the richest levels of omega-3 SDA (which enable more efficient EPA conversion) and omega-6 GLA because both these fatty acids bypass the first rate-limiting Δ6-desaturase step (per Fig 1). In omega metabolism, the most effective sources for facilitating a dietary 'rebalance' of omega-3 and -6 PUFA intakes—closer to pre-industrial levels—will have the highest omega-3:6 ratio.

Ahiflower oil leads—both compositionally and environmentally—compared to genetically modified SDA-enriched soya (not grown regeneratively) as well as vs. echium, hemp, and black currant seed oils that also contain measurable SDA levels (Chart 1.) SDA is the most efficient plant-based omega-3 fatty acid precursor for EPA and DHA synthesis, converting up to 4 times the rate of ALA into EPA. Ahiflower is the richest non-GM plant-derived source of SDA.[46] No other commercial dietary SDA sources exist.

Chart 1. Highest SDA-Containing Plant-Based Dietary Oils

Key Fatty Acids	Ahiflower (%)	GMO SDA Soya* (%)[47]	Echium(%)[48]	Hemp (%)[49]	Black Currant (%)[50]
ALA (c18:3, n-3)	42-48	11	30	18-21	10-12
SDA (c18:4, n-3)	19-22	21	11-13	1-2	2-4
LA (c18:2, n-6)	9-15	25	19	48-52	38-40
GLA (c18:3, n-6)	5-8	6	9-11	3-4	15
Total Omega-3	60-65	32	40-43	20-23	12-16
Total Omega-6	14-33	31	29	51-56	53-55
Typical SDA:GLA Ratio	3.5:1	3.5:1	1:1	0.5:1	0.2:1
Typical Omega-3:6 Ratio	**4:1**	**1:1**	**1.5:1**	**0.4-0.45**	**0.2-0.3**

Note: Conventional plant-based omega-3 oil sources flaxseed, chia, and perilla seed contain only ALA and LA.
**GMO SDA Soya oil is presently not in commerce in human nutrition in North America, Europe, or the UK.*

Bringing Regenerative Sourcing to Omegas

Among commercially-available plant-based omega sources, the most environmentally responsive oilseed supplies will be those that fit well within local and regional soil, pollinator, and rural farmland biodiversity schemes now coming under regenerative farming, soil health, and carbon-capture protocols.[51],[52] Total omega-rich oil yield per hectare has to be a consideration. Ahiflower yields more SDA+ALA+GLA per hectare than any other oilseed crop and requires significantly less fertilizer or chemical inputs than most other farmed commodity crops.

Conclusion

Significant accumulating evidence supports human health improvements accruing from elevated plant-based omega-3 intakes. More credence should be given to them—notably to SDA and the highest SDA-containing sources like Ahiflower oil.

Farmed non-GM plant-based omega-3 sources do not contain preformed EPA/DHA. Instead they rely on an innate human genomic capacity to convert plant-based essential and post-Δ6-desaturase fatty acids efficiently. These sources sidestep the unintended outcomes attributable to excess preformed DHA intakes and ratios. Their use can strongly support the ecological abundance and biodiversity of our oceans. Most healthy adults can meet all their EPA/DHA synthesis requirements from regeneratively grown plant-based SDA-rich sources—led by Ahiflower oil.

The implication of recognizing that most humans are naturally efficient plant-based omega-3 converters is profound. It could shift the present global reliance on wild-harvested forage fish oil to regeneratively farmed sources. Practically every temperate climate country around the world could participate in their production. Accumulating soil restoration and regenerative ecological effects on millions of acres would convert global omega-3 nutrition from slowly degrading to truly championing broad-based sustainability.

For inquiries, please contact: info@ahiflower.com

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