Echium oil: A valuable source of n-3 and n-6 fatty acids

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Abstract: *Echium oil is a vegetable oil of non-GMO plant origin extracted from the seeds of Echium plantagineum containing significant amounts of omega-3 fatty acid Stearidonic Acid (SDA) and omega-6 acid γ-linolenic acid (GLA). Typical fatty acid composition of Echium oil is: Oleic acid (18:1 n-9) 16%, Linoleic acid (LA, 18:2 n-6) 19%, γ-linolenic acid (GLA, 18:3 n-6)10%, α-linolenic acid (ALA, 18:3 n-3) 30% and Stearidonic acid (SDA, 18:4 n-3) 13%. This natural ratio of fatty acids, trough their metabolism, deliver enhanced plasma concentrations of eicosapentaenoic (EPA, 20:5 n-3), docosapentaenoic (DPA, 22:5 n-3) and dihomo-γ-linolenic (DGLA, 20:3 n-6) acids without increasing the concentrations of arachidonic acid (AA, 20:4 n-6). GLA is commonly associated with the anti-inflammatory effects of oils such as evening primrose oil and borage oil. Supplementation with GLA can markedly increase serum AA with subsequent pro-inflammatory effects. The presence of stearidonic acid in echium oil prevents the accumulation of serum AA and AA-derived eicosanoids without preventing the accumulation of DGLA which is the real n-6 precursor of anti-inflammatory eicosanoids. SDA is an intermediate in the biosynthetic conversion of ALA to EPA. As SDA is the product of the rate-limiting Δ6-desaturase step and due the efficiency of the elongase and Δ5-desaturase steps, SDA is readily converted to EPA. SDA has the physiologic benefits of EPA, for instance, lowering the serum triglycerides in hypertriglyceridemic subjects. Therefore echium oil is a true alternative for vegetarians or those who do not eat fish, to benefit from the anti-inflammatory effects of omega-3 and omega-6 long chain polyunsaturated fatty acids.*

Key words: *echium oil, vegetable oil, omega-3, omega-6, stearidonic, gamma-linolenic*

The knowledge on the beneficial effect of effects of omega-3 long chain polyunsaturated fatty acids (LCPUFA's) on inflammatory and autoimmune diseases like atherosclerosis, cancer, rheumatoid arthritis, asthma, Alzheimer's disease and others has increased dramatically during recent years [1-4]. Amongst those probably cardiovascular disease is the area where the benefits are most recognised specially since 2004 when the US FDA issued a Qualified Health Claim on omega-3 fatty acids and Coronary Heart Disease [5-10]. Recently, the nutritional requirements for n-3 fatty acids have shifted to their adequate intake to reduce disease risk rather than that to correct or prevent nutritional deficiency [11]. Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) are the most beneficial n-3 LCPUFA and can be obtained from marine rich diet. Also omega-6 LCPUFA's, in particular γ-linolenic (GLA) which is present in plant oils like evening primrose oil and borage oil have anti-inflammatory and immunomodulating effects trough the conversion to dihomo-γ-linolenic (DGLA) [12-14].

Unfortunately high concerns exist about the long-term sustainability of global fisheries and although aquaculture is a growing source of fish, the requirements of omega-3 containing farmed fish for EPA and DHA requires fish meal and fish oil to be provided in their diets.

This has made that research is looking at plant-based sources of omega-3 fatty acids. The most abundant LCPUFA in plant oils are either omega-3 α-Linolenic Acid (ALA) which is found in high concentrations in flax seed oil or omega-6 Linoleic (LA) which is present on oils like evening primrose oil and borage oil *(table 1)*. Nevertheless the bioconversion of LA and ALA to their respective longer omega-6 and omega-3 LC PUFA's is not an efficient process because on the fatty acid metabolic pathway which consist of several elongation and desaturation steps *(figure 1)* the first step in the pathway, the Δ-6 desaturate step, is the rate limiting in humans [15, 16].

As previously mentioned long-chain polyunsaturated fatty acids, in particular EPA, DHA and DGLA, amongst other functions, are precursors of eicosanoids and docosanoids which have critical roles on inflammation and the immune system. As shown of *figure 1* as a general rule we can state that EPA and DGLA produce anti-inflammatory eicosanoids (series 3 and series 1 prostaglandins and thromboxanes and series 5 and 3 leukotrienes, respectively) whereas arachidoic acid (AA) produces pro-inflammatory eicosanoids (series 2 prostaglandins and thromboxanes and series 4 leukotrienes). DHA produces anti-inflammatory docosanoids [17]. Therefore dietary sources of LCPUFA's should contain these fatty acids or efficient precursors. Blends of omega-3 and omega-6 fatty acids or natural oils containing both may offer synergistic health protection against inflammatory chronic diseases.

Combinations of omega-3's and omega-6's

Although most of the studies on LC-PUFA's have been focused on either marine omega-3 FA on one side or on vegetable omega-6 FA on the other, recently there has also been studies showing the benefits of blends of omega-3 and omega-6 fatty acids in several areas like cardiovascular diseases, asthma or maternal supplementation.

Fatty acids compete for space in cell membranes and supplementation with a single fatty acid can exacerbate depletion of the other fatty acids which are also necessary. Thus supplementation with fish oil omega-3 can lead to a reduction in DGLA and a reduction of the beneficial eicosanoids derived from DGLA. Supplementation with omega-6 oils (*i.e.*, GLA rich oils) may cause a reduction in EPA and a potentially

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Table 1. *Typical fatty acid content of echium oil and other plant oils.*

	Echium oil	Flaxseed oil	Blackcurrent oil	Borage oil	Evening primorose oil
LA (18:2 n-6)	19%	14%	45%	39%	70%
LA (18:3 n-6)	10%	-	16%	21%	10%
ALA (18:3 n-3)	30%	58%	11%	1%	-
SDA (18:4 n-3)	13%	-	3%	0.1%	-

harmful increase in AA unless EPA/DHA are supplemented along with such omega-6 oils [18, 19]. A combination of omega-3 and omega-6 fatty acids may act synergistically ([20] and references therein) increasing the levels of omega-3 and at the same time maintaining the levels of AA. A recent review [8] concluded that "n-6 fatty acids do not inhibit the beneficial effects of n-3 fatty acids and that, in fact, a combination of both types of fatty acid may be associated with the lowest risk of cardiovascular disease".

Laidlaw and Holub [21] established that daily supplementation with 4 g EPA/DHA and 2 g GLA lowered patients risk of having a hearth attack within the next ten years by 43%, even more effectively than EPA/DHA alone. Blood level of triglycerides decreased by 35% and the LDL-cholesterol, *i.e.* the "bad cholesterol", was reduced by 11.3% although it is known that fish oil supplementation alone typically has no effect, or a slight elevating effect on LDL-cholesterol levels.

Chilton *et al.* [22] showed in a randomized, double-blind, placebo-controlled, parallel-group, prospective trial in patients with mild to moderate atopic asthma that daily consumption of dietary GLA and EPA in a novel emulsion formulation inhibited leukotriene LTB_4 biosynthesis. Leukotriene inhibitors and leukotriene-receptor antagonists are effective in the treatment of asthma and therefore potentially useful in such population.

Current recommendation for pregnant and lactating women is that they should aim to achieve an average daily intake of at least 200 mg DHA [23]. Fish oil supplementation during pregnancy not only improves maternal and neonatal DHA status, but often reduces GLA, DGLA and AA levels also, which may compromise foetal and infant development. Controlled studies of supplementation with highly purified DHA have showed increases on DHA by approximately 150% in both plasma and platelet phospholipids and decreased n-3 DPA by approximately 50%. At the same time, EPA increased approximately 50% and 100 % in plasma and platelet phospholipids respectively demonstrating retro-conversion of DHA to EPA with no accumulation of n-3 DPA ([9] and references therein). Besides DHA and AA, n-3 DPA is also an important fatty acid in human milk phospholipids and triglycerides [24, 25]. In fact in a recent study of supplementation of infants with breast milk or infant formulas, lower levels of nervonic, n-3 DPA and DHA were found in all plasma lipid fractions from infants fed formula compared to those in the human milk-fed infants (the diets used in the study were designed to be as similar as possible in fatty acid composition). The authors conclude that levels of nervonic acid, n-3 DPA and DHA in formulas for full-term infants should be increased [26].

Recently, Koletzko *et al.* [27] have proposed a blend of a DHA concentrate and evening primrose oil (rich in GLA) for maternal supplementation. In women of childbearing age the tested blend was well tolerated and appeared safe. It increased plasma GLA, DGLA, and DHA levels without impairing AA status. As we will see later in the text, echium oil is able to increase plasma levels of n-3 DPA and therefore

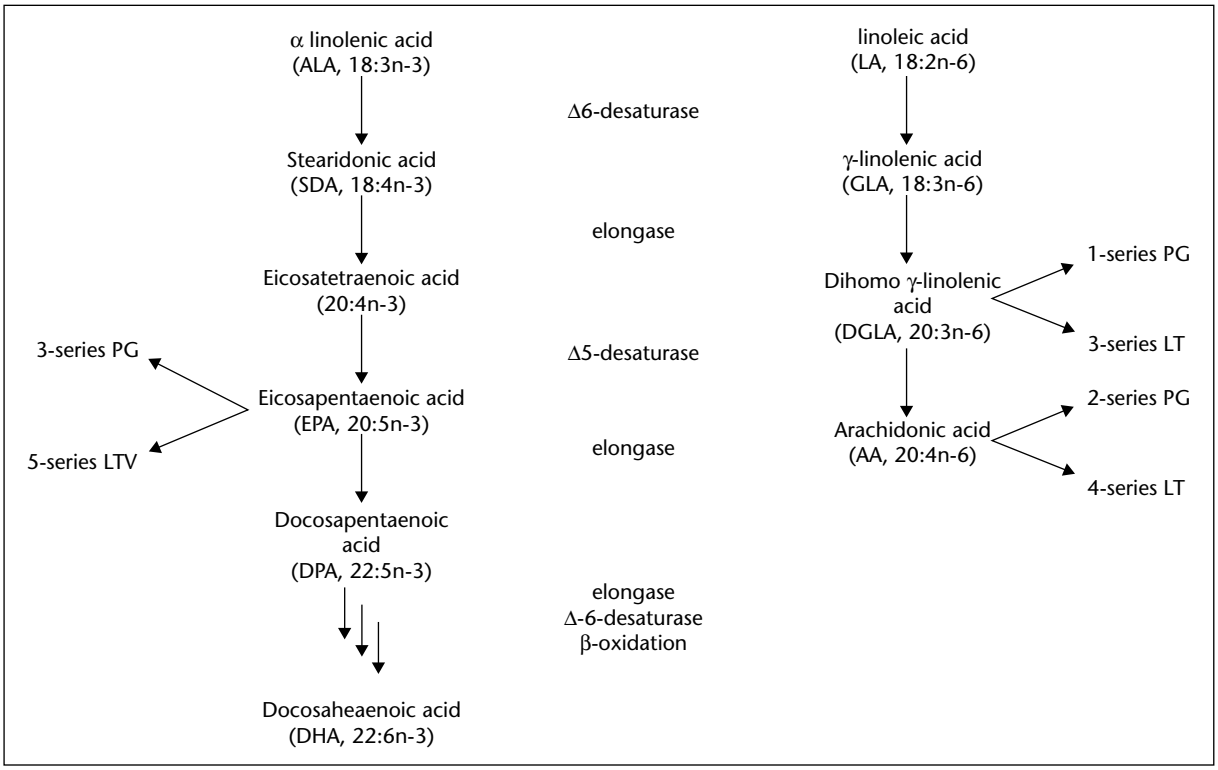

Figure 1. *Metabolic pathway of omega-3 and omega-6 polyunsaturated fatty acids and derived eicosanoids.*

a blend of a DHA concentrate and echium oil might be useful for maternal supplementation.

Echium oil

Echium oil is a vegetable oil of non-GMO plant origin extracted from the seeds of *Echium plantagineum* containing significant amounts of omega-3 fatty acid Stearidonic Acid (SDA) and omega-6 acid γ-linolenic acid (GLA). Both SDA and GLA are the immediate products of the rate-limiting Δ6-desaturase step and due the efficiency of the elongase and Δ5-desaturase steps, are readily converted to the longer PUFA's.

Echium oil contains a unique combination of omega-3 and omega-6 fatty acids. It contains significant quantities (more than 10%) of four different PUFA's, SDA and ALA omega-3 PUFA's and GLA and LA omega-6 PUFA's. A shown on *table 1* this is quite unusual as plant oils rich on omega-3's like flaxseed besides ALA only contains LA in significant amounts and plant oils rich on omega-6's like borage oil, evening primrose oil or blackcurrant oil only contain very minor quantities of omega-3's.

Telpner and Holub [28] compared in humans the supplementation during 28 days of a blend of flax seed and borage oil *vs* echium oil. Both supplementation treatments had equivalent amounts of omega-3 (ALA + SDA) and omega-6 (GLA). They measured the levels of the fatty acids in serum phospholipids. They concluded that SDA supplementation is 3 times more efficient that ALA for producing elevations of EPA+n-3 DPA, that SDA supplementation is 3.6 times more efficient that ALA for producing elevations of n-3 DPA, that DHA levels did not change during the study in both cases and that echium oil supplementation showed a significant rise in EPA and DGLA but not rise on AA. It is worth to note that EPA supplementation has also little effect if any on DHA levels.

Chilton *et al.* [29] studied the effect of supplementation of echium oil on subjects with mild-to-moderate hypertriglyceridemia during four weeks. The plasma concentration of omega-3 fatty acids ALA, SDA and n-3 DPA increased during the study whereas there was no change in plasma DHA. The plasma concentration of omega-6 fatty acids GLA and DGLA also increased during the supplementation period. In addition the changes on the fatty acid profile were associated with a significant decrease on circulating triglyceride concentration on hypertriglyceridemic subjects. This was observed at SDA supplementation levels of 2 g/d which is within the dose range of omega-3 LC PUFA's from fish oil required to decrease circulating TG concentrations.

The mechanism of TG reduction by echium oil has been recently studied in apoB100-only LDL receptor knockout mice [30].

The qualitative changes of the omega-3 fatty acid profiles on subjects supplemented with omega-3 (raise on n-3 DPA and EPA but not on DHA) is similar to those observed in people consuming EPA and is due to the presence of SDA in echium oil. SDA has various physiological functions in the human body [31-37].

Thus Harris *et al.* [38] have recently studied the effect of supplementation of SDA (76% as ethyl ester) in dogs and shown that it caused an increase of EPA and n-3 DPA in red blood cells and heart with no changes on DHA. They have estimated than SDA was 20-23% efficient compared with dietary EPA in raising tissue EPA levels.

James *et al.* [39] studied the metabolism of SDA in humans in comparison with ALA and EPA in a diet with low LA intake. Dietary SDA increased EPA and n-3 DPA concentrations but not DHA concentrations in erythrocyte and in plasma phospholipids. The relative effectiveness of the tested dietary fatty acids in increasing tissue EPA was 1:0.3:0.07 for EPA:SDA:ALA. Thus, SDA is 30% efficient compared to EPA to increase EPA concentration and is about 4.3 times more efficient than ALA. The authors concluded that vegetable oils containing SDA could be a dietary source of n-3 fatty acids that would be more effective in increasing tissue EPA concentrations than are current ALA-containing vegetable oils.

It is worth to note that all studies on SDA supplementation show, in addition to an increase on EPA levels, an increase also on the levels of n-3 DPA. The role of this fatty acid in cardiovascular disease risk is currently not fully understood although there is epidemiological and *in vitro* studies which suggest beneficial effects [40-44].

In addition to the cardiovascular area there are others areas like skin inflammation caused by UV radiation, asthma or acne in which echium oil may be beneficial.

UV radiation cause sunburn (erythrema, pain swelling and blistering) and induces the release of pro-inflammatory prostaglandin PGE_2. In a study by Coupland *et al.* [45] using several vegetable oils on artificial skin grown from human fibroplasts exposed to UVB irradiation, echium oil was the most effective on reducing the release of PGE_2 as shown on *figure 2*.

Studies in progress by Chilton and co-workers [46] shows than supplementation with echium oil and borage oil inhibits the generation of LTB_4 thus confirming the potential utility of this approach for inhibiting leukotriene generation in asthma patients.

Acne patients have low levels of linoleic acid in their skin surface lipids. Topically applied linoleic was shown to induce an almost 25% reduction in the overall size of microcomedones, the initial development step of acne lesions, over a 1-month treatment period in acne-prone patients [47]. Therefore echium oil which besides SDA and GLA also contains linoleic acid may be an interesting product for acne treatment. In fact in a recent review on SDA [31], the benefits of SDA, GLA and other PUFA's (GLA>DHA=SA=AA=ALA>LA) have been proposed in regulating androgen action in target cells that could attenuate disorders linked to a high 5α-reductase activity which, specially in women, are associated with the presence of acne. On the other hand, recently an article [48] has shown that inflammatory mediators (LTB_4, PGE_2) are implicated in the initiation of acne lesions and that are present in sebaceous glands of acne-involved facial skin. A study demonstrated that a LTB_4 blocker led to a 70% reduction in inflammatory acne lesions [49]. Being echium oil able to inhibit the release of

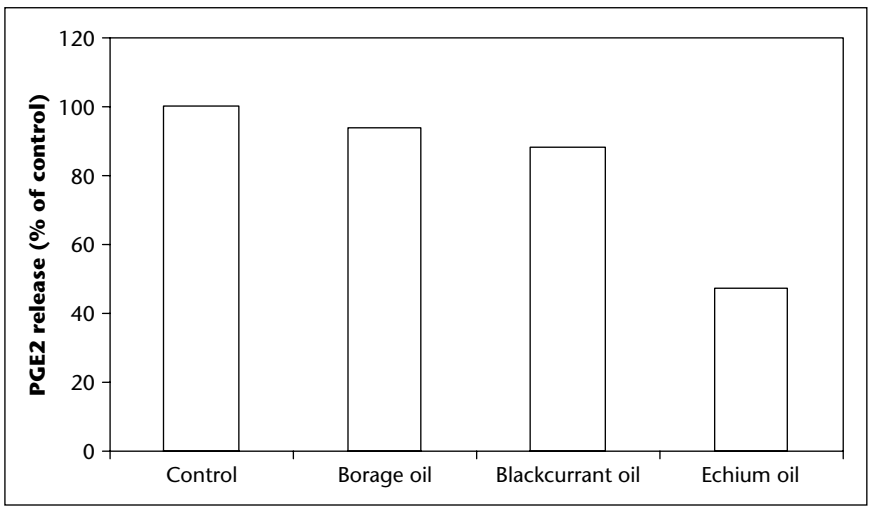

Figure 2. *PEG2 release (% of control) after UVB irradiation of synthetic human skin.*

LTB_4 and PGE_2 it might be useful in treating acne.

Conclusion

Echium oil is a potent natural non-GMO vegetable source of GLA and SDA and after ingestion of their respective metabolites DGLA, EPA and n-3 DPA. It is a true alternative for vegetarians or those who do not eat fish, to benefit from the anti-inflammatory effects of omega-3 and omega-6 long chain polyunsaturated fatty acids[1].

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