GLA: Uses and new sources

Frank J. Flider


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A flowering, mature safflower in controlled growth conditions.

Perceptions concerning the benefits and function of fats and fatty acids in human nutrition have gone through a series of rather dramatic changes over the past several years. Not too long ago, fats of all types were reviled by the consuming public as witnessed by the numerous low-fat and no-fat diets that were once in vogue. More recently, the pendulum has swung the other way, as high fat and high protein diets became the rage.

Today, the tendency is to moderate our total fat intake, focusing our attention on increasing intake of monounsaturates and omega-3 (n-3) oils, while reducing or eliminating saturates, *trans*- fats and omega-6's (n-6) from our diets. While consumer understanding of the roles of fats and fatty acids in our diet is improving, the mass media's tendency to over simplify and gloss over complex issues continues to result in misconceptions and misperceptions.

Among these misconceptions is a general belief that all n-6 fatty acids are undesirable and unhealthy. One nutritionally important n-6 fatty acid is gamma linolenic acid (C18:3n-6), commonly known as GLA. GLA is a key component of evening primrose oil (EPO), borage oil (BO) and black currant oil (BCO), all of which are popular dietary supplements.

Also known as γ-linolenic acid and gamolenic acid, the nutritional and health benefits of GLA are becoming increasingly more recognized and understood. Despite our growing body of information, our knowledge of GLA pales in comparison to what is known about the n-3 rich fish oils.


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An Arcadia employee checking flower formation on safflower seedlings

GLA in the PUFA pathway

GLA is manufactured in the human body by the action of the D-6 desaturase enzyme on linoleic acid (C18:2n-6). The basic polyunsaturated fatty acid (PUFA) pathway is shown in Figure 1. Like α-linolenic acid (C18:3n-3 or ALA), linoleic acid cannot be synthesized by mammals and must be obtained from the diet.

Although the typical Western diet is plentiful in linoleic acid, the activity of the D-6 desaturase enzyme is often impaired, resulting in lower than desirable production of GLA. Factors believed to impair the human D-6 desaturase enzyme include aging, stress, diabetes, alcohol, smoking, cholesterol, *trans*- and saturated fatty acid consumption, n-3 fatty acid deficiency and vitamin and mineral deficiencies. Because human D-6 desaturase also converts linolenic acid to stearidonic acid (C18:4n-3 or SDA) and generally favors the n-3 pathway, impaired enzyme activity makes GLA synthesis even more problematic.

Once GLA has been synthesized, it is very rapidly elongated to dihomo-γ-linolenic acid (C20:3n-6), also known as DGLA. DGLA is a precursor to prostaglandin PGE1

and 15-OH-DGLA, two important substances with a wide range of desirable benefits. PGE1 inhibits platelet aggregation and inflammation, produces vasodilation, inhibits cholesterol biosynthesis, regulates immune responses and reduces blood pressure. 15-OH-DGLA inhibits 5- and 12-lipoxygenases, therefore inhibiting the formation of proinflammatory compounds from arachidonic acid (C20:4n-6 or ARA) such as PGE2 and 4-series leukotrienes. Many of the positive effects attributed to GLA supplementation may be due to the positive effects of GLA's derivatives.

By the action of human D-5 desaturase, DGLA is converted to ARA. Although DGLA is the precursor for ARA production, consumption of high levels of GLA does not result in the accumulation of high levels of ARA. Like human D-6 desaturase, human D-5 desaturase has limited activity. As a result, production of PGE1 and 15-OH-DGLA from DGLA is preferred over ARA production.

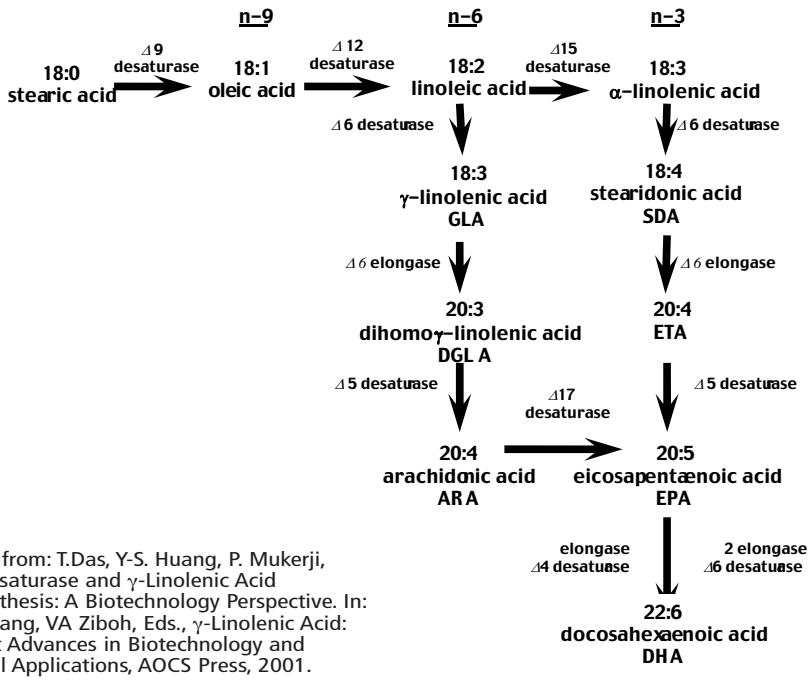

Figure from: T.Das, Y-S. Huang, P. Mukerji, ω6-Desaturase and γ-Linolenic Acid Biosynthesis: A Biotechnology Perspective. In: Y-S Huang, VA Ziboh, Eds., γ-Linolenic Acid: Recent Advances in Biotechnology and Clinical Applications, AOCS Press, 2001.

Figure 1. Basic PUFA pathway

GLA supplementation

Based upon the research and publicity given to n-3 fatty acids, there is a prevailing impression that they are metabolically and nutritionally more important than n-6 fatty acids. In fact, some health and nutritional professionals have suggested that n-6 fatty acids may be deleterious to health and should be avoided. In reality, it is important to maintain a balance of both n-3 and n-6 fatty acids. As n-6 and n-3 fatty acids are competitive inhibitors of each other's metabolism, particularly at the desaturase level, an imbalance of one type will interfere with the metabolism of the other. Like EPA and DHA supplementation, supplementation with GLA bypasses the rate limiting D-6 desaturase enzyme.

Although there are no established recommended daily intake levels for GLA, typical dietary supplement intake levels range between 90–270 mg of GLA, equating to two to six 500 mg capsules of evening primrose oil or one to three capsules of borage oil. Based upon a number of studies on evening primrose oil by the late David Horrobin and others at Efamol, therapeutic GLA levels may range between 100–500 mg daily. Horrobin suggested that daily supplementation of 500–2,000 mg of GLA may provide pharmacological benefits; at one time, two Efamol evening primrose products were approved as registered pharmaceuticals in the United Kingdom.

Table 1
Typical Fatty Acid Composition of GLA Oils (%)

Fatty Acid	Evening Primrose Oil	Borage Oil Black	Currant Oil
16:0	6.3	6.3	6-7
18:0	1.8	4.5	1-2
18:1	10.3	17.8	9-11
18:2	71.6	34.4	47-50
18:3 (GLA)	9.1	23.1	15-19
18:3 (ALA)	0.3	0.2	12-15
18:4	—	—	2-4
20:1	0.3	4.2	
22:1	—	2.8	
24:1	—	1.8	

GLA sources & issues

The two most important sources of dietary GLA in terms of market share are evening primrose oil and borage oil, with 10% and 20% GLA respectively. Consumption of black currant oil, which contains 15–20% GLA, is very limited due to supply restraints. Hemp seed oil, which contains up to 5% GLA, is also an excellent source of ALA. Typical compositions for EPO, BO and BCO are provided in Table 1.

Both evening primrose and borage are grown as identity-preserved specialty crops. Although yields and qualities of evening primrose and borage have been improved through limited breeding programs, production costs could still be 10 or more times higher than other oilseed crops. Intake of 100–500 mg of GLA would require two to ten 500 mg evening primrose capsules and a therapeutic dosage of 2,000 mg would require 40 capsules. Considering many consumers take a number of different vitamins and supplements in addition to GLA, daily consumption and the expense of such a large number of capsules is a commitment that is often difficult to make. Likewise, cost and low concentration make it difficult to incorporate efficacious levels of GLA in nutraceutical and functional food products.

Alternative GLA sources

As demonstrated by its lack of GLA, canola normally does not have any D-6 desaturase activity. In order to produce GLA more economically and to make it more readily available, Calgene developed transgenic canola oil varieties containing as much as 43% GLA. This was accomplished by introducing D-6 and D-12 desaturase genes from the fungus *Mortierella alpina* into canola cells. As demonstrated in Figure 1., this two enzyme system drives production of GLA in the normally high oleic canola background. It was necessary to utilize D-12 desaturase as well as D-6 desaturase, as D-6 alone resulted in development of significant quantities of C18:2n-9, a fatty acid not normally found in most vegetable oils. When D-12 desaturase was introduced along with the D-6, C18:2n-9 was converted to GLA. Despite the fact that Calgene conducted several generations of field trials on high GLA canola varieties, for reasons not made public the product was never commercially produced.

With a continuing demand for more concentrated and more economical sources of GLA, Arcadia Biosciences embarked upon a program to develop high GLA safflower varieties. For a number of economical, agronomic and compositional reasons, safflower is believed to be an ideal oilseed background for GLA. There are several defined growing regions throughout North America and since most safflower is already contract produced, identity preservation should be readily achievable. Safflower is basically self-pollinating, eliminating open pollination concerns sometimes expressed about canola.

One disadvantage of a canola background for GLA production is the presence of significant quantities of linolenic acid (C18:3n-3). Because linolenic acid competes with linoleic acid for D-6 desaturase activity, production of stearidonic acid (C18:4n-3), quite possibly at the expense of GLA, could result if canola is used. Unlike canola, safflower is essentially devoid of linolenic acid and as such, stearidonic acid formation will not be a factor.

In addition to the benefits of lower production costs and higher GLA concentrations than current commercial sources, safflower GLA oil should have other nutritional benefits. Borage oil contains approximately 10% C20, C22, and C24 fatty acids, including 2.5% erucic acid (C22:1n-9). High levels of very long chain fatty acids, particularly erucic acid, are not expected to be an issue with safflower oil derived GLA.

There are several safflower compositions that may be suited for GLA production. Native safflower oil, which contains over 75% linoleic acid, is an obvious target. There are also high oleic safflower varieties containing over 80% oleic acid (C18:1n-9) which may prove useful. Among the strategies being explored are the uses of D-6 and D-12 desaturases as described above.

As of this writing, we are awaiting analysis of our first generation of transformed safflower seeds, commonly known as the T1 generation. Through combinations of plant breeding, crossing and possibly additional transformation events, our objective is to produce hybrid safflower seeds containing an oil with at least 25% but hopefully 40+% GLA. This upper concentration represents a potential 4-fold increase over evening primrose oil and a 2-fold increase over borage and black currant oil GLA levels. Due to higher GLA concentration levels and reduced production costs, the market price per unit of GLA should be substantially lower than possible with current sources. It is believed that the combination of lower costs, increased GLA levels and predictable supplies will drive increased usage of GLA in supplements, nutraceuticals and functional foods.

GLA uses

There are a number of studies focused upon the efficacy of GLA in various conditions. However, compared to the body of knowledge surrounding n-3 fatty acids (ALA, EPA and DHA), there is a relative dearth of information about the effects of GLA. While there is conflicting evidence concerning GLA activity in some applications, the preponderance of uses and applications are based upon demonstrated anti-inflammatory effects and the general effects of its downstream products DGLA, PGE1 and 15-OH-DGLA. Areas where GLA may be beneficial include infant nutrition, atopic eczema, dermatitis, diabetic neuropathy, breast pain, premenstrual syndrome (PMS), rheumatoid arthritis, high blood pressure and general inflammation.

Nutritional supplements & pharmaceuticals

GLA oils are popular nutritional supplements. According to a July 2004 article in *The Natural Foods Merchandiser*, evening primrose oil is one of the 25 fastest growing nutritional supplements in the United States. Sold primarily in 500 and 1,000 mg soft-gel capsules, alone or in combination with other nutritional oils, this is the largest market sector for GLA oils.

One of the earliest uses for evening primrose was for the alleviation of PMS symptoms. Other uses include relief of arthritis pain, reduction of blood pressure and skin improvement. GLA oils may be considered to be among the first recognized cosmeceuticals, which are dietary supplements taken for the purpose of improved skin health.

Two evening primrose oil products were once licensed pharmaceuticals in the U.K. Efamast™ was indicated for relief of cyclical mastalgia and Epogam™ for treatment of atopic eczema. Because evening primrose oil is readily available in retail stores, it made no sense to continue its status as a prescription drug and as a result, these products have since been delisted.

Atopic eczema and dermatitis

Atopic eczema, also known as dermatitis, is a skin condition characterized by itching, rashes and lesions. It can start in early childhood and in some cases, can persist into adulthood. Several studies have demonstrated that atopic eczema patients tend to have elevated linoleic acid levels and lower than normal levels of GLA, DGLA and ARA. This profile has been shown to exist even prior to

information

Read more about GLA!

- *γ-Linolenic Acid: Recent Advances in Biotechnology and Clinical Applications*, Y-S Huang, VA Ziboh, ed., a monograph published by AOCS Press, contains papers presented at a symposium on γ-linolenic acid held during the 2000 AOCS Annual Meeting. Hardbound, 272 pages, cost: US $40. Log on to netlink: aocs.org/catalog or call +1-217-359-2344, ext. 148 to order your copy.

- P. Clough, Specialty Oils Containing Long-Chain PUFA. In: *Structured and Modified Lipids*; F.D. Gunstone, Ed.; Marcel Dekker, Inc., 2001, pp. 75-117.

emergence of skin lesions, indicating a causative effect rather than a result of the disease.

Studies have shown that GLA supplementation along with the use of topical steroids and emollients showed an improvement over traditional methods alone, but it usually takes several months before an improvement becomes apparent. More study is warranted, as there have been conflicting reports on the utility of GLA in this application.

Diabetic neuropathy

Diabetic neuropathy, which is a painful and debilitating neurological complication of diabetes, develops over time as a result of abnormally high levels of blood sugar. Fatty acid abnormalities have been demonstrated in diabetics, particularly low DGLA and ARA in nerve membranes and red blood cell membranes. Low DGLA levels result in reduced levels of PGE1 and prostacyclin, impairing circulation. Low PGE1 also increases phospholipase A2 (PLA2) activity, resulting in the release of ARA from membranes and increasing membrane stiffness. Free ARA forms vasoconstrictors, restricting circulation and, over time, a deterioration of motor and sensory nerves results. GLA in the form of evening primrose oil has repeatedly been shown to improve nerve conduction velocity (NCV) and improve established diabetic neuropathy symptoms.

Infant nutrition

The use of the long-chain PUFA arachidonic acid (ARA or C20:4n-6) and docosahexaenoic acid (DHA or C22:6n-3) in infant formulas has dramatically increased in recent years. As GLA is a metabolic precursor to ARA, it has been suggested that it may be safer to feed infants GLA rather than ARA. There have been a number of preterm and term GLA-containing infant formulas introduced in Europe and the Far East.

Cosmetics

In addition to their cosmeceutical value as dietary supplements, GLA oils have been used in a wide range of skin care products for their purported skin softening and moisturizing properties. Lower cost and higher concentration GLA oils should be attractive to this market, enabling the cost-effective use of functional levels of GLA.

Further down the pathway

Future possibilities for high n-6 oils include high DGLA and high ARA oils. Since DGLA is the precursor of desirable eicosanoids, high DGLA oils may represent the next generation of n-6 based oils. The production of high DGLA oil could involve the addition of an appropriate elongase gene to high GLA-producing safflower oil.

The further addition of the appropriate D5-desaturase may result in the production of ARA. While expression of large quantities of ARA has not been observed in oilseeds, ARA has been recently expressed in low concentrations in *Arabidopsis* leaves, tobacco and flaxseeds. Along with DHA, ARA supplementation has been shown to be beneficial in infant development and a plant source of ARA may be a cost effective alternative to the expensive fermentation sources of ARA currently available.

Frank J. Flider is director of business development, output traits for Arcadia Biosciences, Inc. Contact him at: 4455 E. Camelback Rd., Ste B200, Phoenix, AZ 85018 USA; phone: +1-602-474-3748; e-mail: fjflider@arcadiabio.com. ■