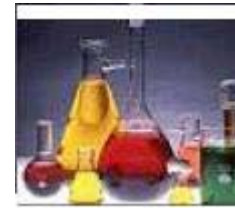


Gamma linolenic acid (GLA)

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Synonyms/Common Names/Related Substances:

- Blackcurrant berry, blackcurrant dried leaf, blackcurrant oil, blackcurrant seed oil, borage oil (*Borago officinalis*), borage seed oil, BSO, bugloss, burage, burrage, casis, cassis, cureall EPO, Efamol, European black currant, European blackcurrant, evening primrose oil, fever plant, fungal oil, king's grosellero negro, hempseed oil, huile de hourrache, huile d'onagre, n-6, n-6 essential fatty acids, night willow-herb (*Oenothera biennis*), omega 6, omega-6, omega-6 fatty acids, omega 6 oil, omega-6 oil, polyunsaturated fatty acid, primrose, PUFA, quinsy berries, ribes nero, ribes nigri folium (*Ribes nigrum*), scabish, *siyah frenkuzumu*, squinancy berries, starflower, starflower oil, sun drop, zwarte bes, (Z,Z,Z)-Octadeca-6,9,12-trienoic acid.

CLINICAL BOTTOM LINE/EFFECTIVENESS

Brief Background:

- Gamma linolenic acid (GLA) is a dietary omega-6 fatty acid found in many plant oil extracts. Commercial products are typically made from seed extracts from evening primrose (average oil content 7-14%), blackcurrant (15-20%), borage oil (20-27%) and fungal oil (25%). To a limited extent, GLA is found naturally in the diet in human breast milk, cold-water fish and in organ meats such as liver, but at very low concentrations (1-2%).
- GLA is available commonly as a dietary supplement and is sold over the counter in capsules or oil to treat a variety of conditions such as eczema, oral mucocoeles (mucus polyps), hyperlipidemia, depression, postpartum depression, chronic fatigue syndrome, psoriasis, muscle aches, and menopausal flushing.
- Some well-designed randomized clinical trials have found good evidence for GLA treatment in rheumatoid arthritis, acute respiratory distress syndrome, and diabetic neuropathy.
- Little or no effect has been found in treatment of atopic dermatitis, attention deficit hyperactivity disorder (ADHD), cancer prevention, menopausal flushing, systemic sclerosis, and hypertension.
- GLA is also used to help with the body's response to tamoxifen in breast cancer patients.

Scientific Evidence for Common/Studied Uses:

Indication	Evidence Grade	 GRADING SYSTEM LINK
Diabetic neuropathy	<u>B</u>	
Acute respiratory distress syndrome	<u>C</u>	
Atopic dermatitis	<u>C</u>	
Attention deficit hyperactivity disorder	<u>C</u>	
Blood pressure control	<u>C</u>	
Cancer treatment (adjunct)	<u>C</u>	
Immune enhancement	<u>C</u>	

Mastalgia	C
Menopausal hot flashes	C
Migraine	C
Osteoporosis	C
Pre-eclampsia	C
Premenstrual syndrome	C
Pruritis	C
Rheumatoid arthritis	C
Sjogren's syndrome	C
Ulcerative colitis	C

Historical or Theoretical Uses which Lack Sufficient Evidence:

- Cancer ([1;2](#)), cystic fibrosis ([3](#)), hypertension (arterial) ([4](#)), red blood cell aplasia ([5](#)), systemic sclerosis ([6](#)), venous disorders ([7](#)).

Expert Opinion and Folkloric Precedent:

- GLA is not found in high levels in the diet. It has been suggested that some individuals may not convert the omega-6 fatty acid linoleic acid to longer chain derivatives, such as GLA, efficiently. Thus, supplementation with GLA-containing oils, such as borage oil and evening primrose oil, is occasionally recommended to increase GLA levels in the body.

Brief Safety Summary:

- **Likely Safe:** When used orally and short-term (up to 12 months) in recommended doses, GLA has been found to be nontoxic ([8;9](#)).
- **Possibly Safe:** When used longer term (up to 36 months) at recommended doses, some studies recommended taking GLA with another dietary supplement, eicosapentaenoic acid (EPA) ([10;11](#)).
- **Note:** Studies following patients taking large doses, for example, 1.4g to 2.8g per day for up to one year in randomized, placebo-controlled studies have found GLA to be non-toxic ([8;9](#)).

DOSING/TOXICOLOGY

General:

- Recommended doses are based on those most commonly used in available trials, or on historical practice. However, with natural products it is often not clear what the optimal doses are to balance efficacy and safety. Preparation of products may vary in concentration of GLA from manufacturer to manufacturer, and from batch to batch within one manufacturer. Because it is often not clear what additional components are packaged in combination with GLA (e.g., vitamins, antioxidant agents, etc.), standardization based on commercial preparations may not be possible, and the clinical effects of different brands may not be comparable.

Standardization:

- Capsules are usually sold with stated GLA content, for example, Efamast® Evening Primrose Oil 1,300mg states that it contains GLA 10% or 130mg, Cardiovascular Research Ltd. Borage Oil GLA-

240™ contains 240mg of GLA.

- Evening primrose or borage oil extract (in liquid form) is usually sold with stated GLA concentration.

MECHANISM OF ACTION

Pharmacology:

- Constituents:** GLA is a long-chain omega-6 polyunsaturated fatty acid, known by its chemical structure as 18:3 n-6. It is not commonly found in the diet, but is formed in the body from linoleic acid by the action of the delta-6-desaturase enzyme. When ingested as a dietary supplement, GLA increases the content of its elongase product, dihomo-gamma-linolenic acid (DGLA), within cell membranes such as in tissue phospholipids and triacylglycerols. DGLA is the precursor to anti-inflammatory and vasodilatory eicosanoids that can be converted by inflammatory cells into 15(S)-hydroxy-8,11,13-eicosatrienoic acid and prostaglandin E1. As an essential fatty acid, GLA is an important constituent of membrane phospholipids where it plays a role in membrane integrity and fluidity.

HISTORY

- Research in the early 1970s into potential outcomes in humans of GLA deficiency led to ventures for the production and sale of GLA dietary supplements. Dr. John Williams founded Bio-Oils Research Ltd; Dr. David Horrobin founded Efamol Ltd (now Scotia Holdings plc). Both experimented with chemical synthesis, which produced very low yields. They looked at extracting oils from several plants - evening primrose, borage, black currant, and red currant-and narrowed the sources to evening primrose and borage oil.
- Efamol (Scotia Holdings plc) licensed two pharmaceutical products in the United Kingdom, developed from evening primrose oil, for eczema and mastalgia.
- Today, production and extraction of oil from evening primrose and borage is done by companies primarily in China, New Zealand, and England. Pharmaceutical licensing for GLA oil products has had only limited success worldwide.

EVIDENCE TABLE

Condition	Study Design	Author, Year	N	Statistically Significant?	Quality of Study 0-2=poor 3-4=good 5=excellent	Magnitude of Benefit	ARR	NNT	Comments
Diabetic neuropathy	Randomized clinical trial	Keen, 1993	111	Yes	5	High	NA	NA	480mg daily for over 1 year.
Diabetic neuropathy	Randomized clinical trial	Jamal, 1986	22	Yes	4	Medium	NA	NA	360mg daily for 6 months.
Acute respiratory distress syndrome (ARDS)	Randomized clinical trial	Pacht, 2003	43	Yes	5	Medium	NA	NA	Enteral feeding of GLA + EPA or an isonitrogenous, isocaloric standard diet through for 4 to 7 days at a minimum caloric delivery of 75% of basal energy expenditure x 1.3.
Acute respiratory	Randomized clinical trial	Gadek, 1999	98	Yes	4	Medium	NA	NA	EPA+GLA or an isonitrogenous.

distress syndrome (ARDS)									isocaloric standard diet at a minimum caloric delivery of 75% of basal energy expenditure x 1.3 for at least 4-7 days.
Acute respiratory distress syndrome (ARDS)	Randomized clinical trial	Nelson, 2003	98	No	3	NA	NA	NA	Same study subjects as Pacht, 2003 with focus on oxidative stress. Enteral feeding of GLA + EPA or an isonitrogenous, isocaloric standard diet through for 4 to 7 days at a minimum caloric delivery of 75% of basal energy expenditure x 1.3.
Atopic dermatitis	Meta-analysis	Van Gool, 2004	>745	No	NA	NA	NA	NA	19 trials; 11 used to calculate overall severity; trials limited by methodology.
Atopic dermatitis	Randomized clinical trial	van Gool, 2003	118	No	5	NA	NA	NA	100mg daily GLA for 6 months.
Atopic dermatitis	Randomized clinical trial	Takwale, 2003	140	No	4	NA	NA	NA	920mg daily for adults, 460 mg daily for children.
Atopic dermatitis	Randomized single-blind clinical trial	Callaway, 2005	20	No	3	NA	NA	NA	Hempseed oil; amount based on dietary incorporation.
Atopic dermatitis	Case series	Fiocchi, 1994	P	Yes	2	Small	NA	NA	3g daily for 28 days in infants.
Attention deficit hyperactivity disorder	Double crossover, randomized - sequence, placebo controlled trial	Arnold, 1989	18	No	2	NA	NA	NA	360mg daily vs. D-amphetamine vs. placebo.
Attention deficit hyperactivity disorder	Randomized clinical trial	Stevens, 2003	50	Yes	P	Small	NA	NA	In children, a combination of DHA, EPA, AA and GLA for 4 months was investigated.
Blood pressure control	Randomized clinical trial	Deferne, 1996	27	Yes	P	P	P	P	Amt GLA as blackcurrant seed oil.
Blood pressure control	Randomized clinical trial	Mills, 1989	30	Yes	P	P	P	P	Amt GLA as borage oil.
Blood pressure control	Randomized clinical trial	Leng, 1998	120	Yes	5	Medium	NA	NA	280mg GLA plus 45mg EPA.
Blood pressure control	Randomized clinical trial	Deferne, 1992	18	Yes	P	P	P	P	4g oil rich in GLA, EPA and DHA
Cancer treatment (adjunct)	Randomized clinical trial	McIlmurray, 1987	54	No	4	NA	NA	NA	500mg GLA and 10mg Vitamin E daily for 44 months; colorectal

									cancer patients.
Cancer treatment (adjunct)	Randomized clinical trial	van der Merwe, 1987	62	No	4	NA	NA	NA	1.44g daily for up to 7 months; hepatic cancer patients.
Cancer treatment (adjunct)	Equivalence trial	Kenny, 2000	38 + 47 comparison patients	No	0	NA	NA	NA	2.8 g GLA daily in addition to tamoxifen 20mg daily; breast cancer patients.
Immune enhancement	Randomized clinical trial	Wu, 1999	40	Yes	3	Small	NA	NA	675mg GLA as blackcurrant seed oil.
Immune enhancement	Randomized clinical trial	Miles, 2004	74	Yes	0	Small	NA	NA	2g GLA as compared with EPA, stearidonic acid or blends; Small changes in natural killer cell count and plasma IgE only.
Mastalgia	Randomized clinical trial	Goyal, 2005	555	No	3	NA	NA	NA	4g evening primrose oil (320mg GLA) daily.
Mastalgia	Case series	Cheung, 1999	66	NA	0	Medium	NA	NA	Gamolenic acid provided in evening primrose oil.
Menopausal hot flashes	Randomized clinical trial	Chenoy, 1994	56	No	3	NA	NA	NA	GLA as 4g evening primrose oil
Migraine	Open label	Wagner, 1997	168	Yes	NA	Large	NA	NA	1800mg GLA and alpha-linolenic acid
Osteoporosis	Randomized clinical trial	Kruger, 1998	65	No	3	NA	NA	NA	GLA+EPA and calcium 600mg daily for 18 months and 36 months.
Pre-eclampsia	Randomized clinical trial	D'Almeida, 1992	P	Yes	P	P	NA	NA	GLA as evening primrose oil plus fish oil
Premenstrual syndrome	Randomized clinical trial	Puolakka, 1985	30	Yes	P	Small	NA	NA	Efamol.
Pruritis	Randomized clinical trial	Yoshimoto-Furuie, 1999	16	No	P	NA	NA	NA	GLA as 2g evening primrose oil.
Rheumatoid arthritis	Randomized clinical trial	Belch, 1988	49	Yes	P	P	NA	NA	540mg GLA (as EPO) or 450mg GLA (as EPO) plus fish oil versus placebo.
Rheumatoid arthritis	Randomized clinical trial	Brzeski, 1991	40	No	P	P	NA	NA	540mg GLA per day for 6 months versus olive oil.
Rheumatoid arthritis	Randomized clinical trial	Leventhal, 1993	37	Yes	4	Medium	NA	NA	1.4g daily.
Rheumatoid arthritis	Randomized clinical trial	Leventhal, 1993	P	Yes	P	P	P	P	GLA as blackcurrant seed oil.
Rheumatoid arthritis	Randomized clinical trial	Zurier, 1996	56	Yes	4	Medium	NA	NA	2.8g daily of GLA for 6 - 12 months.
Rheumatoid arthritis	Randomized clinical trial	Remans, 2004	66	No	P	NA	NA	NA	EPA, DHA and GLA for 4 months showed no improvements.

Rheumatoid arthritis	Case series	Hansen, 1983	20	No	NA	NA	NA	NA	GLA and Efavit® for 12 weeks showed no effect on swollen joints, duration of morning stiffness, or patient's estimation of pain.
Sjogren's syndrome	Randomized controlled trial	Theander, 2002	90	No	3	NA	NA	NA	800mg or 1600mg GLA isolated from evening primrose oil.
Sjogren's syndrome	Randomized crossover controlled trial	Manthorpe, 1984	36	Yes	P	Small	NA	NA	GLA as 3g Efamol.
Ulcerative colitis	Randomized controlled trial	Middleton, 2002	63	No	3	NA	NA	NA	1.6g GLA plus 270mg EPA plus 45mg DHA.

EVIDENCE DISCUSSION

Mastalgia

- Summary:** Cyclical mastalgia is breast pain experienced by women and typically associated with the menstrual cycle. The pain can vary in severity and usually occurs between ovulation and menstruation. Evidence for efficacy of GLA treatment is very limited, although since the 1990s, GLA has been recommended historically as a therapy.
- Evidence:** Goyal et al. ([91](#)) conducted a randomized, double-blind, parallel group multicenter study in 555 women with moderate to severe mastalgia. Subjects received GLA alone (320mg GLA as 4g evening primrose oil per day), GLA plus antioxidants, antioxidants alone or placebo for four menstrual cycles. This was followed by a further eight menstrual cycles of open treatment in which all patients received GLA, but continued to be randomized to antioxidants or antioxidant placebo. Diary pain cards and linear analog charts were used for assessment of response. A reduction in breast pain was seen in all four treatment groups during the blinded treatment phase. This study showed that GLA (Efamast) efficacy did not differ from that of placebo fatty acids, regardless of whether or not antioxidant vitamins were present. This study was adequately powered, but did not discuss whether placebo and treatment capsules were identical or the reason for dropouts.
- Cheung et al. conducted a case series with 66 women of Asian origin ([92](#)). The data were based on patient responses at 3 and 6 months. Response rate was stated to be 97% at the end of the study, however the study design was not rigorous, for example, no placebo control or blinding was incorporated.

Menopausal hot flashes

- Summary:** One study has examined the effect of GLA (as evening primrose oil) on menopausal flushing, in a randomized, double-blind clinical trial. No improvement in the number of flushes was noted as compared with placebo. More clinical trials are needed before recommendations can be made in this area.
- Evidence:** Chenoy et al. ([93](#)) conducted a randomized, double-blind, parallel group study in 56 menopausal women suffering from hot flashes. Subjects received GLA (2000mg evening primrose oil twice per day) or placebo for six months. There was no effect on the number of flushes as compared with placebo.

Migraine

- **Summary:** One open-label, uncontrolled study has examined the effect of fatty acids, including GLA, on severity, frequency and duration of migraine attacks. Better-designed clinical trials are required before recommendations can be made.
- **Evidence:** Wagner et al. (94) conducted an open-label, uncontrolled study in 129 patients with regular migraine headaches. Subjects received a fatty acid formulation containing 1,800mg total (GLA plus alpha-linolenic acid) for six months. Eighty-six percent of patients experienced a reduction in the severity, frequency and duration of migraine attacks, while 90% of patients had reduced nausea and vomiting. A placebo-controlled group was lacking in this study.

Osteoporosis

- **Summary:** Some evidence from a clinical trial and observations of clinicians and dieticians has suggested that GLA and eicosapentaenoic acid (EPA) enhance the effects of calcium supplementation in elderly patients with senile osteoporosis. More clinical studies are required to produce results to determine efficacy in diverse elderly and middle-age populations.
- **Combination:** Kruger conducted a randomized, placebo controlled study of a combination of GLA, eicosapentaenoic acid (EPA) and calcium in 65 women (mean age 79.5 years) over 36 months (10). Both the treatment group and the placebo control group were given 680mg daily of calcium. This study is one of the longest-term GLA supplementations recorded and safety of GLA in combination with EPA was suggested. The study focused on calcium absorption, deposition and excretion (bone turnover). Benefits to the GLA+EPA group were noted, but were not statistically significant. More stratification of patients in different phases of osteoporosis or age groups may help further investigate GLA efficacy.

Premenstrual syndrome

- **Summary:** One placebo-controlled study using Efamol (containing GLA) suggests there may be benefit in terms of premenstrual syndrome symptoms. More information is needed in this area before recommendations can be made.
- **Evidence:** Puolakka et al. (22) conducted a placebo-controlled study in 30 women with severe premenstrual syndrome. Subjects received Efamol (GLA plus linoleic acid). Efamol treatment alleviated symptoms and depression better than placebo. However, there was no effect on the levels of various hormones, such as FSH, LH, prolactin, progesterone, estradiol and testosterone. Further studies are required in this area using adequate numbers of study subjects.

PRODUCTS STUDIED

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- **Blinded Peer-Review:** Natural Standard Editorial Board.

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