has been associated with low respiratory rates (at times requiring intubation), coma and death. Over 145 cases of GHB poisoning, including eight deaths, have been reported. Typically, those involved were other CNS-depressant agents such as alcohol along with GHB. These reports include ingestions of substances such as gamma-butylrolactone (GB) and 1,4 butanediol, both of which are converted to GHB in the body.

**DOSAGE AND ADMINISTRATION**

It is illegal to use or possess GHB except if enrolled in certain FDA-allowed clinical trials or for the FDA-approved indication of narcolepsy.

**LITERATURE**


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**Gamma-Linolenic Acid (GLA)**

**DESCRIPTION**

Gamma-linolenic acid or GLA is an n-6 (omega-6) polyunsaturated fatty acid. It is comprised of 18 carbon atoms and three double bonds. GLA is an all-cis n-6 polyunsaturated fatty acid also known as GLA, 18:3n-6; 6,9,12-octadecatrienoic acid; (Z, Z, Z)- 6,9,12-octadecatrienoic acid; cis-6, cis-9, cis-12-octadecatrienoic acid, and gamolenic acid. The structural formula of GLA is:

![GLA structural formula](image)

GLA (gamma-linolenic acid)

GLA is found naturally to varying extents in the fatty acid fraction of some plant seed oils. In evening primrose seed oil, it is present in concentrations of 7 to 14% of total fatty acids; in borage seed oil, 20 to 27%; and in blackcurrant seed oil, 15 to 20%. GLA is also found in some fungal sources. GLA is produced naturally in the body as the delta 6-desaturase metabolite of the essential fatty acid linoleic acid. Under certain conditions, e.g. decreased activity of the delta-6 desaturase enzyme, GLA may become a conditionally essential fatty acid. GLA is present naturally in the form of triacylglycerols (TAGs). The stereospecificity of GLA varies among different oil sources. GLA is concentrated in the sn-3 position of evening primrose seed oil and blackcurrant seed oil and in the sn-2 position in borage seed oil. GLA is concentrated evenly in both the sn-2 and sn-3 positions of fungal oil.

**ACTIONS AND PHARMACOLOGY**

**ACTIONS**

GLA may have anti-inflammatory and antithrombotic actions. It may also have lipid-lowering activity.

**MECHANISM OF ACTION**

The anti-inflammatory and anti-aggregatory actions can be accounted for by reviewing its role in eicosanoid biosynthesis. GLA is a precursor in the synthesis of prostaglandin E1 (PGE1) as well as the series-3 prostaglandins. It also serves as a precursor in the synthesis of eicosapentaenoic acid (EPA). EPA is a precursor of the series-3 prostaglandins, the series-5 leukotrienes and the series-3 thromboxanes. These eicosanoids have anti-thrombogenic, anti-inflammatory and anti-atherogenic properties. PGE1 inhibits platelet aggregation and has a vasodilation action. The incorporation of GLA and it metabolites in cell membranes may also play a role in the possible anti-inflammatory and anti-proliferative actions of GLA.

**PHARMACOKINETICS**

GLA-laden triacylglycerols (TAGs) following ingestion undergo hydrolysis via lipases to form monoglycerides and free fatty acids. Once formed, the monoglycerides and free fatty acids are absorbed by the enterocytes. In the enterocytes, a reacylation takes place reforming TAGs that are then
assembled with phospholipids, cholesterol and apoproteins into chylomicrons. The chylomicrons are released into the lymphatics from whence they are transported to the systemic circulation. In the circulation, the chylomicrons are degraded by lipoprotein lipase and the fatty acids including GLA are distributed to various tissues in the body.

GLA is metabolized to the 20 carbon polyunsaturated fatty acid, dihomo-gamma-linolenic acid (DHLA) or eicosatrienonic acid (ETA), which is converted to prostaglandin E1 (PGE1). It is also metabolized to eicosapentaenoic acid (EPA). GLA and DHLA are normally not found in the free state in the cell to any appreciable degree but occur as components of phospholipids, neutral lipids and cholesterol esters, mainly in cell membranes. PGE1 is metabolized to smaller prostaglandin remnants, which are primarily polar dicarboxylic acids. Most of the metabolites are excreted in the urine.

INDICATIONS AND USAGE
GLA appears to be effective in some cases of rheumatoid arthritis and may be indicated in some other inflammatory disorders, such as Sjogren’s syndrome and ulcerative colitis. Possible other indications include diabetic neuropathy, acute respiratory distress syndrome, hypertension and elevated serum lipids. GLA has been used with some success in some cancers, principally cerebral gliomas. It has not proved useful for tardive dyskinesia, premenstrual syndrome or menopausal flushing. It may be indicated in some cases for atopic eczema and atopic dermatitis, particularly to help with itching, as well as for uremic skin conditions in hemodialysis patients. It should probably not be used in efforts to enhance immunity as it may be immunosuppressive.

RESEARCH SUMMARY
GLA, supplied in the form of evening primrose oil or borage seed oil, has been studied for many years for its possible effects in arthritis and other inflammatory processes. This is not surprising given its ability to modulate the pathways toward an anti-inflammatory state. It has been shown to suppress inflammation and reduce joint tissue injury in many animal models. Since an early double-blind study demonstrated significant improvement in sufferers of rheumatoid arthritis (RA) who received 540 milligrams of GLA per day for a year (relapsing when switched to placebo for three months), several other clinical studies have followed. These have yielded some encouraging results.

In a randomized double-blind, placebo-controlled study of RA sufferers, those receiving 1.4 grams of GLA in borage seed oil daily experienced significant relief. GLA reduced the number of tender joints 36% and the swollen joint count by 28%. Those on placebo experienced no significant improvement or declined in condition. The dose used in this study was much higher than in most other studies. Other recent studies similarly suggest that GLA is an effective treatment option for some with RA, particularly given its safety profile.

There is preliminary evidence that GLA might also be useful in Sjogren’s syndrome and perhaps some other rheumatological disorder. It may be helpful for various dry-eye conditions. Recent animal work suggests GLA may enhance calcium absorption, reduce calcium excretion and increase calcium deposition in bone and thus play a therapeutic role in managing and preventing osteoporosis. A clinical pilot study noted encouraging results in elderly women given supplements of GLA, eicosapentaenoic acid (EPA) along with calcium carbonate. Those treated experienced increased lumbar and femoral bone mineral density over 36 months.

There is some evidence that prolonged use of GLA may result in reduced blood pressure in some hypertensive individuals, as well as fewer coronary events. These effects warrant further investigation.

There is some evidence that higher doses of GLA than typically used may improve blood lipids. In a small study, 17 subjects were assigned to two groups. One group of eight received 2 grams daily of GLA for six weeks, the other group received 500 milligrams daily for the same length of time. At the end of six weeks, the group that received 2 grams of GLA had a 37% lowering of their triglycerides and a 13% lowering of cholesterol. The lower dose showed no triglyceride or cholesterol-lowering activity. Unfortunately, there are no followup studies.

With respect to cancer, GLA has been shown to selectively kill 40 different human cancer cell lines in tissue culture without harm to normal cells. GLA appears to induce apoptotic death of tumor cells or, in various other ways, to suppress oncogene expression, at least in tissue culture. While the clinical use of GLA in cancer is only beginning, there is early encouraging news that it can help regress cerebral gliomas by 1 to 2 years. Other preliminary studies indicate GLA, alone or in combination with other substances, may be of some benefit in the treatment of pancreatic cancer, a finding that certainly warrants followup.

GLA’s role in treating some skin disorders has focused primarily on atopic eczema, where the results continue to be mixed after years of study. In one of the best double-blind, multicenter studies to date, 160 patients with eczema of moderate severity were randomized to receive 500 milligrams of borage oil or placebo daily for a 24-week period. Various improvements were noted using GLA, and these reached statistical significance in one of the studies’ subgroups. GLA has also been shown to have some efficacy in treating atopic dermatitis in both infant and adults, though...
here, too, results are mixed. GLA seems to have a positive effect on itching. One recent study showed that oral GLA supplementation can significantly relieve multiple uremic skin symptoms in hemodialysis patients.

GLA is being used to help ameliorate diabetic neuropathy with some encouraging results. In one multi-center randomized, double-blind, placebo-controlled study, those patients given 480 milligrams of GLA per day improved by all test parameters (at a level of statistical significance for 13 of the 16 parameters) over a one-year period. However, not all studies have been positive. There may be subgroups with diabetic neuropathy who could benefit from GLA. In a recent meta-analysis of treatments for tardive dyskinesia, no support was found for the use of GLA in this disorder. It has been suggested that GLA may be helpful in ulcerative colitis, but more research is needed to determine its role.

Treatment with GLA and EPA in the form of borage seed oil and fish oil significantly reduced the need for ventilatory support in 150 patients with acute respiratory distress syndrome. Patients thus treated were confined to intensive care an average of 12.8 days versus 17.5 days for controls.

Claims that GLA is useful in treating premenstrual syndrome (PMS) have not been supported by research findings, and GLA was found to be no better than placebo in preventing/treating menopausal flushing.

As an immune-modulator, GLA may primarily be an immune dampener rather than enhancer. Its ability to dampen some immune functions may make it useful in fighting some auto-immune disorders.

**CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS**

**CONTRAINDICATIONS**

Known hypersensitivity to a GLA-containing product.

**PRECAUTIONS**

GLA should not be used by pregnant women and nursing mothers unless recommended by a physician. Because of possible antithrombotic activity, those who take warfarin and hemophiliacs should exercise caution in its use. GLA should not be used before surgery.

**ADVERSE REACTIONS**

There have been no reports of serious adverse events in those taking GLA supplements. GLA is usually tolerated very well with no significant adverse effects.

**INTERACTIONS**

No interactions between GLA and aspirin, other NSAIDs, or herbs, such as Allium sativum (garlic) or Ginkgo biloba (Ginkgo), have been reported. Such interactions, if they were to occur, might be manifested by nosebleeds and/or increased susceptibility to bruising. If this does occur, GLA intake should be lowered or stopped.

**OVERDOSE**

No overdosing has been reported.

**DOSAGE AND ADMINISTRATION**

There are several forms of GLA supplements. A concentrated form of GLA is available. GLA is also available as evening primrose oil, borage seed oil and blackcurrant seed oil. Doses tried for rheumatoid arthritis and other conditions range from about 360 milligrams to 2.8 grams daily in divided doses and usually with meals. Doses of up to 2 grams daily may be helpful in those with elevated triglycerides. The concentrations of GLA varies in the different oil preparations and, depending on the concentration, the number of capsules daily may be smaller or larger in order to make up the desired dose.

**LITERATURE**


Hrelia S, Bordoni A, Biagi P, et al. gamma-Linoleic supplementation can affect cancer cell proliferation via
there are no credible studies demonstrating anabolic activity for this plant product.

Gamma-oryzanol is not just one substance, but a mixture of ferulic acid esters of ten triterpene alcohols: delta7-stigmastenyl ferulate, stigmasteryl ferulate, cycloartenyl ferulate, 24-methylenecycloartenyl ferulate, delta7-campestenyl ferulate, campesterol ferulate, delta7-sitostenyl ferulate, sitosteryl ferulate, compastanyl ferulate and sitostanyl ferulate. Cycloartenyl ferulate, 24-methylenecycloartanyl ferulate, and campesterol ferulate are the three major components of gamma-oryzanol. The fundamental structure of gamma-oryzanol is the ferulic acid aromatic nucleus esterified to cyclopentanoperhydrophenanthrene (see accompanying figures). The fundamental structure can be chemically described as (3beta)-9,19-cycloanost-24-en-3-ol-3-(4-hydroxy-3-methoxyphenyl)-propenoate. It is also called cycloartenyl ferulate. Its CAS Registry number is 21238-33-5, its empirical formula is C_{48}H_{58}O_{4} and its molecular weight is 602.88. The chemical structures below are described within this monograph.

\[
\text{MeO} \quad \text{HO} \\
\text{Oryzanol—Fundamental Structure} \\
\text{Ferulic Acid}
\]

**Gamma-Oryzanol**

**DESCRIPTION**

Gamma-oryzanol, a phytosterol derived from rice bran oil, is comprised of a mixture of plant sterols esterified to the phenol, ferulic acid. Rice bran oil is the richest source of gamma-oryzanol, but it is also found in corn, barley and other food oils, and in rye and wheat bran. Phytosterols play a number of roles in plants, including in growth and development, for membrane fluidity and as antioxidants. Rice bran oil also contains tocotrienols, members of the vitamin E family. The gamma-oryzanol concentration of rice bran oil is variable. High gamma-oryzanol rice bran oil contains about 1% or 10 mg per gram. Crude rice bran oil contains about 1.5%. (See Phytosterols and Phytostanols.)

Gamma-oryzanol was first isolated by the Japanese in the 1950s and has been used by the Japanese as a medicine for the treatment of anxiety, menopausal symptoms, peptic ulcers, gastritis and elevated lipids. It is a popular substance among bodybuilders for its supposed anabolic effects. It is also often used in cosmetics as a sunscreen, demulcent, lightener and brightener.

Studies have shown that gamma-oryzanol has antioxidant, anti-inflammatory and lipid-lowering activities. However,