Evening Primrose

Species (Family)

Oenothera species including *Oenothera biennis* L. (Onagraceae)

Synonym(s)

King's Cureall

Part(s) Used

Seed oil

Pharmacopoeial and Other Monographs

Martindale 32nd edition[G43]
Mills and Bone[G50]
PDR for Herbal Medicines 2nd edition[G36]

Legal Category (Licensed Products)

Evening primrose is not included in the GSL.[G37] Gamolenic acid is a prescription-only medicine.

Constituents

Fixed oils 14%. cis-Linoleic acid (LA) 72% (65–80%), cis-gammalinolenic acid (gamolenic acid, GLA) 2–16%, oleic acid 9%, palmitic acid 7% and stearic acid (3%).[1–5]

Food Use

Evening primrose root has been used as a vegetable with a peppery flavour.[5] The seed oil has been used as a food supplement for many years. LA and gamolenic acid are both essential fatty acids (EFAs), with LA representing the main EFA in the diet, whilst gamolenic acid is found in human milk, in oats and barley, and in small amounts in a wide variety of common foods.[4,5]

Herbal Use

An infusion of the whole plant is reputed to have sedative and astringent properties, and has traditionally been used for asthmatic coughs, gastrointestinal disorders, whooping cough and as a sedative painkiller.[5] Externally, poultices were reputed to ease bruises and to speed wound-healing.[5]

Evening primrose oil (EPO) is licensed for the treatment of atopic eczema, and cyclical and non-cyclical mastalgia. Other conditions in which evening primrose oil is used include premenstrual syndrome, psoriasis, multiple sclerosis, hypercholesterolaemia, rheumatoid arthritis, Raynaud's phenomenon, Sjögren's syndrome, postviral fatigue syndrome, asthma and diabetic neuropathy.[1–3,5]

Dosage

Recommended doses for evening primrose oil are specific to the condition being treated.

Daily doses for a licensed evening primrose oil product are 6–8 g (adults) and 2–4 g (children) in atopic eczema.[6] In cyclical and non-cyclical mastalgia, a daily dose of 3 to 4 g is recommended. These doses are based on a standardised gamolenic acid content of 8%. No special precautions are noted for the elderly. The oil may be swallowed directly, mixed with milk or another liquid, or taken with food.

A patient may need to receive evening primrose oil for a period of three months before a clinical response is observed.[3,6]

Pharmacological Actions

The pharmacological actions of evening primrose oil have been reviewed.[1–3,5]

The actions of evening primrose oil are attributable to the essential fatty acid content of the oil and to the involvement of these compounds in prostaglandin biosynthetic pathways.

Gamolenic acid and its metabolite dihomo-gamma-linolenic acid (DGLA) are precursors of both the inflammatory prostaglandin E_2 (PGE_2) series via arachidonic acid (AA), and of the less inflammatory prostaglandin E_1 (PGE_1) series. Actions attributed to PGE_1 include anti-inflammatory, immunoregulatory and vasodilatory properties, inhibition of platelet aggregation and cholesterol biosynthesis, hypotension and elevation of cyclic AMP (inhibits phospholipase A_2, *see below*).[1–3]

Dietary supplementation with gamolenic acid has been noted to have a favourable effect on the DGLA : AA ratio. Although an increase in arachidonic acid concentrations is also seen, this is much smaller and less consistent compared to the increase seen for DGLA.[3] Contributory factors to this nega-

tive effect on arachidonic acid are PGE_1 and 15-hydroxy-DGLA. The latter inhibits conversion of arachidonic acid to inflammatory lipoxygenase metabolites including leukotrienes, whilst PGE_1 inhibits the enzyme phospholipase A_2 which is required for the mobilisation of arachidonic acid from phospholipid membrane stores.[3] In addition, DGLA desaturation to arachidonic acid is a rate-limiting step in humans and proceeds very slowly.[3]

Gamolenic acid is not normally obtained directly from dietary sources and the body relies on metabolic conversion from dietary LA. This conversion is readily saturable and is considered to be the rate-limiting step in the production of gamolenic acid. A reduced rate of LA conversion to gamolenic acid has been observed in a number of clinical situations including ageing, diabetes, cardiovascular disorders and high cholesterol concentrations, high alcohol intake, viral infections, cancer, nutritional deficits, atopic eczema and premenstrual syndrome.[1–3] Direct dietary supplementation with gamolenic acid effectively bypasses this rate-limiting conversion step and has a beneficial effect on the ratio of inflammatory:non-inflammatory prostaglandin compounds.

Evening primrose oil represents a good source of both LA and, more importantly, of gamolenic acid. Numerous papers have been published on the biochemical rationale for the therapeutic uses of evening primrose oil and on its efficacy in various disease states associated with low concentrations of gamolenic acid. The use of evening primrose oil in various disease states which include atopic eczema, premenstrual syndrome including mastalgia, diabetic neuropathy, rheumatoid arthritis, Sjögren's syndrome, cardiovascular, renal, hepatic and gastrointestinal disorders, viral infections, endometriosis, schizophrenia, alcoholism, Alzheimer's disease and cancers has been reviewed.[3]

Atopic eczema An inherited slow rate of 6-desaturation (LA to gamolenic acid conversion) has been documented in this condition. Normal or elevated concentrations of LA are associated with reduced concentrations of their metabolites. Randomised, double-blind, placebo-controlled trials have shown gamolenic acid to produce a highly significant improvement in all features of atopic eczema, especially in itch.[1–3,7,8] The requirement for topical and oral steroids, histamines and antibiotics was also reduced.[3] However, attention has been drawn to the conflicting evidence of clinical trials on evening primrose oil. Two large trials have not shown evidence of benefit[10,11] whereas other trials have resulted in benefits, particularly for patients with moderate or severe eczema.[12,13] Adequate doses of evening primrose oil for treatment of atopic eczema are 160–320 mg of gamolenic acid daily in children aged 1–12 years and 320–480 mg in adults for three months.[9]

Cyclical/non-cyclical mastalgia PGE_1 is thought to modulate the action of prolactin. Abnormal concentrations may result in an excessive peripheral action of prolactin.[3]

Several placebo-controlled studies have demonstrated that gamolenic acid is better than placebo in the treatment of both premenstrual syndrome and breast pain.[1–3,14] Overall, cyclical mastalgia responds better than non-cyclical to all treatments (danazol, bromocriptine, evening primrose oil).

Premenstrual syndrome The use of evening primrose oil for the treatment of premenstrual syndrome has been rationalised on the grounds that hypersensitivity to prolactin is due to low levels of PGE_1.[15] High levels of linoleic acid and low levels of gamma-linolenic acid have been observed for patients with premenstrual syndrome. Several clinical studies have been reported and the conclusions vary from no beneficial effects being observed to marked improvements.[1–3,16]

Diabetic neuropathy Diabetes has been associated with reduced ability to desaturate essential fatty acids, with deficits resulting in abnormal neuronal membrane structure. Animal studies have shown that diabetic neuropathy can be either prevented or reversed by the provision of gamolenic acid as evening primrose oil. In humans, a double-blind, placebo-controlled trial has demonstrated reversal of diabetic neuropathy by gamolenic acid.[17]

Multiple sclerosis The results of clinical trials on the use of evening primrose oil for the treatment of multiple sclerosis are contradictory.[1,2] Patients with recent onset or less severe forms of the disease are more likely to respond. Linoleic acid may have a beneficial effect on the severity and duration of relapses and on the progression of the disease.[1] It is suggested that linoleic acid is involved in the immunosuppressive effect at the cellular level and may be of use when combined with a low animal fat/high polyunsaturated fat diet.[2]

Rheumatoid arthritis A randomised, double-blind trial has demonstrated a significant improvement in subjective symptoms of rheumatoid arthritis (RA) (indicated by a reduction in required non-steroidal anti-inflammatory drug treatment) in the active

group receiving evening primrose oil compared with the placebo group. However, no objective changes were observed in any of the biochemical indicators of RA.[1–3]

Sjögren's syndrome This disease is associated with the loss of secretions from exocrine glands throughout the body, but especially from the salivary and lacrimal glands. One of the features of EFA deficiency is exocrine gland atrophy. Placebo-controlled trials have shown a modest improvement in tear flow together with relief of lethargy, a prominent feature of the syndrome.[1,3]

Coronary heart disease Abnormal intake and metabolism of EFAs (both *n*-3 and *n*-6) are thought to be important risk factors for coronary heart disease (CHD), resulting in enhanced cholesterol and triglyceride biosynthesis, enhanced platelet aggregation and elevated blood pressure. Dietary supplementation with foods or oils rich in LA (*n*-6) or in marine (*n*-3) EFAs have been found to decrease significantly the risk of CHD, although it is considered that an optimum balance between *n*-3 and *n*-6 EFAs may well be important.[1–3,18] gamolenic acid has been reported to decrease blood pressure and platelet aggregation in both animal and human studies.[3]

Renal disease Renal tissue is especially rich in EFAs, and prostaglandins of the E series are believed to be important in maintaining adequate renal blood flow. Administration of gamolenic acid to animals has been reported to prevent or attenuate renal damage. A single placebo-controlled trial involving postrenal transplant patients demonstrated better graft survival rate for the group receiving evening primrose oil (45 patients) compared with the placebo group (44 patients).[3]

Liver disease PGE_1 has been administered to patients with liver failure, and has been observed to exert some cytoprotective effect and to maintain the normal function of the liver. There is little experience of gamolenic acid supplementation in liver disease.[17]

Gastrointestinal disorders A double-blind placebo-controlled crossover trial has indicated a beneficial effect of evening primrose oil on irritable bowel syndrome exacerbated by premenstrual syndrome. A beneficial effect superior to that of fish oil or placebo has been reported for evening primrose oil in ulcerative colitis. A protective effect of gamolenic acid against gastric ulceration has yet to be shown in humans.[3]

Viral infections/postviral fatigue A single placebo-controlled study has demonstrated significant beneficial effects in patients with well-defined postviral fatigue (PVF) receiving evening primrose oil compared with those receiving placebo. Symptoms arrested were muscle weakness, aches and pains, lack of concentration, exhaustion, memory loss, depression, dizziness and vertigo.[1,3]

Endometriosis A placebo-controlled trial has shown that gamolenic acid in combination with eicosapentaenoic acid (*n*-3 EFA metabolite) reduced symptoms of endometriosis in 90% women, whereas 90% of the placebo group reported no relief from symptoms.[3]

Schizophrenia It is believed that EFAs, in particular PGE_1, antagonise the excessive central dopaminergic activity that is thought to be a possible cause of schizophrenia. Low concentrations of LA in plasma phospholipids have been observed in populations of schizophrenics from Ireland, England, Scotland, Japan and the USA. It is thought that a poor recovery rate from the disease is associated with the presence of saturated fats in the diet, but not with unsaturated fats. Various open and placebo-controlled trials of gamolenic acid and DGLA supplementation have reportedly produced mixed results. Administration of evening primrose oil with co-factors known to be important in EFA metabolism (zinc, pyridoxine, niacin and vitamin C) enhanced the improvements in memory loss, schizophrenic symptoms and tardive dyskinesia that were observed in evening primrose oil-treated compared with placebo-treated patients.[1–3]

Alcoholism Evening primrose oil has been documented to reduce symptoms in the first three weeks of withdrawal, indicated by a reduced requirement for tranquillisers, and to significantly improve the rate of return to normal liver function. However, in the longer term, evening primrose did not affect the relapse rate.[3]

Dementia Alzheimer's disease and other forms of dementia are associated with low serum concentrations of EFAs. A single placebo-controlled trial in patients with Alzheimer's disease reported improvements in cerebral function in the evening primrose oil group compared with the placebo group.

Hyperactivity in children Hyperactive children tend to have abnormal levels of essential fatty acids. No improvements in behavioural patterns and no

changes in blood fatty acids were observed in one trial with evening primrose oil.[2]

Cancer *In vitro* studies have observed that malignant cells die following exposure to gamolenic acid and related fatty acids at concentrations that are non-lethal to normal cells. *In vitro* studies have shown gamolenic acid to inhibit the growth of various human cancer cell lines, and *in vivo* studies have described an inhibitory effect of gamolenic acid on tumour growth. Human studies are currently ongoing to assess the impact of gamolenic acid supplementation in various human cancers.[3]

Side-effects, Toxicity

Evening primrose oil appears to be well tolerated with very few side-effects reported, despite it being available for many years in a number of countries as a food supplement.[3] Mild gastrointestinal effects, indigestion, nausea and softening of stools and headache have occasionally occurred.[3,5] It has been noted that there may be an increased risk of temporal lobe epilepsy in schizophrenic patients being treated with epileptogenic drugs such as phenothiazines.[6] In cases of overdosage, symptoms of loose stools and abdominal pain have been noted. No special treatment is required.[6]

Toxicity studies have indicated evening primrose oil to be non-toxic.[3] The two principal components in evening primrose oil are LA and gamolenic acid. LA is commonly ingested as part of the diet. It has been estimated that the concentration of gamolenic acid provided by evening primrose oil is comparable to that metabolised in the body from normal dietary LA.[4] In addition, it has been calculated that a breastfed infant receives a higher proportion (mg/kg) of LA and gamolenic acid from human milk compared to that received from evening primrose oil.[4]

Contra-indications, Warnings

Evening primrose oil may have the potential to make manifest undiagnosed temporal lobe epilepsy, especially in schizophrenic patients and/or those who are already receiving known epileptogenic drugs such as phenothiazines.[6] No epileptic events have been reported in patients not being treated with phenothiazines.[6]

Pregnancy and lactation Animal studies have indicated evening primrose oil to be non-teratogenic.[6] However, data on the safety of evening primrose oil during human pregnancy are not available and therefore the risk of taking evening primrose oil during pregnancy should be carefully considered against the perceived benefit to the patient. Both LA and gamolenic acid are normally present in breast milk (*see* Side-effects, Toxicity) and therefore it is reasonable to assume that evening primrose oil may be taken while breast feeding.

Pharmaceutical Comment

Interest in the seed oil of the evening primrose plant lies in its essential fatty acid content, in particular in the linoleic acid (LA) and gamolenic acid (GLA) content. Both of these compounds are prostaglandin precursors and dietary gamolenic acid supplementation has been shown to increase the ratio of non-inflammatory to inflammatory prostaglandin compounds.

The use of evening primrose oil in various disease states associated with low gamolenic acid concentrations has been extensively investigated and a vast body of published literature is available. The beneficial effects of evening primrose oil in treating atopic eczema and mastalgia (cyclical/non-cyclical) have been recognised with product licences granted to evening primrose oil-containing preparations for these indications.[6] However, doubt has also been expressed over the effectiveness of evening primrose oil in eczema.[2,9,10,11,19] Alternative natural oil sources such as blackcurrant or borage (*see* Borage) that offer a higher gamolenic acid yield compared to evening primrose oil have been identified, although these oils have not been found to exhibit the same biological effects as those observed for evening primrose oil.[3]

Evening primrose oil is reported to be virtually non-toxic with only minor adverse effects such as headache and nausea occasionally associated with its use. The range of potential uses for evening primrose oil is extensive and results of further human studies are awaited to establish its efficacy in various therapeutic conditions.

References

See also General References G5, G29, G32, G36, G43, G50, G56 and G64.

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