

Evening Primrose Oil

Oenothera biennis L.

[Fam. *Onagraceae*]

OVERVIEW

Evening primrose is a plant native to North America, with its therapeutic use stemming from American indigenous medicine. Evening primrose oil (EPO) from the plant's seeds has been the subject of hundreds of scientific studies, which led to it becoming one of the most widely used botanical supplements today. EPO is sold in over 30 countries as a dietary supplement, drug, or food. In 2000, evening primrose oil ranked 10th of all herbal dietary supplements in U.S. food, drug, and mass-market retail outlets. Clinical studies have focused on its use in treating problems associated with essential fatty acid (EFA) deficiency: eczema, premenstrual syndrome (PMS), inflammation, and diabetic peripheral neuropathy. EPO is relatively high in EFAs, particularly gamma-linolenic acid (GLA) of which it contains 7–10%.

PRIMARY USES

- Atopic dermatitis
- Mastalgia, cyclical
- Lactation

OTHER POTENTIAL USES

- Atopic dermatitis in infants
- Diabetic neuropathy
- Dry eyes associated with Sjögren's syndrome
- Infant formula fortification
- Nutritional deficiencies (EFAs)
- Premenstrual syndrome symptoms
- Raynaud's disease
- Rheumatoid arthritis
- Seborrhoeic dermatitis (milk crust)
- Uremic skin symptoms

PHARMACOLOGICAL ACTIONS

Improves EFA composition of plasma, erythrocyte, and platelet lipids and α -tocopherol levels in non-diabetic persons and Type 1 diabetic patients; increases total fat and EFA content of mother's milk; affects fatty acid composition of serum lipids and adipose tissue in men with low dihomo-gamma-linolenic acid (DGLA) levels; helps maintain normal cellular structures; serves as prostaglandin precursor.

DOSAGE AND ADMINISTRATION

EPO is a long-term therapy, so immediate results should not be expected. A patient may need to use EPO regularly for up to four months before a clinical response is observed. EPO appears to be safe for long-term use of at least one year.

Internal

ATOPIC DERMATITIS: 4–6 capsules (500 mg) twice daily (40 mg GLA per capsule).

CYCLICAL MASTALGIA: 6 capsules (500 mg) daily (40 mg GLA per capsule) for 4–6 months.

DIABETIC NEUROPATHY: 8–12 capsules (500 mg) daily.

LACTATION AID: 4 capsules (500 mg) twice daily, morning and evening.

RHEUMATOID ARTHRITIS: 10–20 capsules (500 mg) daily.

UREMIC SKIN SYMPTOMS: 2 capsules (500 mg) twice daily (45 mg GLA per capsule).

NOTE: EPO may be swallowed directly or may be taken with milk, another liquid, or with food. EPO taken with food may minimize any potential gastrointestinal side effects. Concurrent ingestion of the antioxidant vitamin E will protect EFAs from free radical damage and also prevent creation of counterproductive substances. Concurrent ingestion of a daily multiple vitamin may also provide nutritional cofactors (e.g., B6 and magnesium) required for EFA metabolism.

External

ATOPIC DERMATITIS: Water-in-oil emulsion containing 20% EPO, twice daily, applied topically to affected area for at least four weeks.

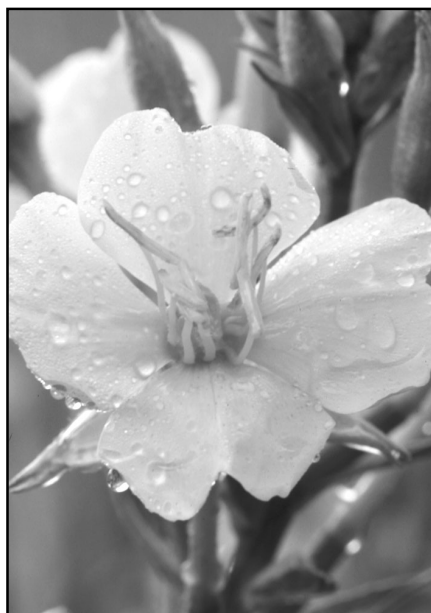


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CONTRAINDICATIONS

Previous reports suggested that patients diagnosed with schizophrenia and/or those already receiving epileptogenic drugs such as phenothiazines should consult a healthcare provider before using EPO. However, a recently published analysis of clinical trials involving polyunsaturated fatty acids in the treatment of schizophrenia did not indicate a clear therapeutic or adverse effect of EPO supplements on schizophrenic patients.

PREGNANCY AND LACTATION: There are no known restrictions. Because LA, GLA, and DGLA are important components of human breast milk, EPO presumably may be taken while nursing. According to the World Health Organization (WHO), pregnant or lactating women should get 5% of their total daily caloric intake from EFAs.

ADVERSE EFFECTS

Adverse effects are rare at recommended dosages, and are reported by less than 2% of people using EPO for extended periods of time. Occasional adverse effects include headache, mild nausea, and abdominal bloating. Overdose symptoms include loose stools and abdominal pain.

DRUG INTERACTIONS

GLA may exacerbate temporal lobe epilepsy in schizophrenic patients being treated with epileptogenic drugs such as phenothiazines (however, this effect has not been confirmed). Steroids and nonsteroidal anti-inflammatory drugs may interfere with GLA metabolism, though this theoretical concern has not been proven. Steroids have been reported to inhibit the D6D enzyme, whereby the metabolism of LA to GLA is inhibited. For patients taking steroidal drugs, supplementation with a source of GLA such as EPO, borage oil, or black current oil may be beneficial.

CLINICAL REVIEW

In 22 clinical studies on evening primrose with a total of 1,154 participants, all but six demonstrated positive effects for indications including PMS, dermatological conditions, diabetic neuropathy, and arthritis. Seven double-blind, placebo-controlled (DB, PC) studies investigated the use of EPO in dermatological conditions, including uremic skin symptoms, chronic hand dermatitis, atopic dermatitis, chronic stable-plaque psoriasis, and psoriatic arthritis (PsA). Treatment of PMS symptoms was the subject of two DB, PC studies. Other DB, PC studies evaluated the effects of EPO in the treatment of cyclic mastalgia, diabetic neuropathy, rheumatoid arthritis, and menopausal hot flashes. EPO also was evaluated for its effect on fat composition and the content of human milk as well as on the survival time of patients with primary liver cancer. A recent study on pregnant, low-risk, nulliparous women measured pregnancy length and active-phase labor outcomes. A meta-analysis of nine PC studies on atopic eczema correlated clinical improvement with a rise in plasma EFAs. Improvement in reported itching symptoms was highly significant ($p < 0.01$) compared to placebo. EPO showed a progressive effect, as well as a dose/response relationship in the 311 patients evaluated in the nine trials.

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OVERVIEW

Evening primrose is a plant native to North America, with its therapeutic use stemming from American indigenous medicine. Evening primrose oil (EPO) from the plant's seeds has been the subject of hundreds of scientific studies, which has led to it becoming one of the most widely prescribed botanical medicines. Evening primrose oil (EPO) is relatively high in essential fatty acids, which play a major role in its effectiveness. In 2000, evening primrose oil ranked 10th of all herbal dietary supplements in U.S. food, drug, and mass-market retail outlets.

USES

Atopic dermatitis; painful breasts during menstruation; lactation; uremic skin symptoms; nutritional deficiencies (essential fatty acids); atopic dermatitis in infants; seborrheic dermatitis (milk crust); infant formula fortification; dry eyes associated with Sjögren's syndrome; Raynaud's disease; PMS symptoms; diabetic neuropathy; rheumatoid arthritis.

DOSAGE

ATOPIC DERMATITIS: 4–6 capsules (500 mg) twice daily [containing 40 mg GLA (gamma-linolenic acid) per capsule].

BREAST PAIN RELATED TO MENSTRUAL CYCLE: 6 capsules (500 mg) daily for four to six months [40 mg GLA per capsule].

DIABETIC NEUROPATHY: 8–12 capsules (500 mg) daily.

LACTATION AID: 4 capsules (500 mg) twice daily.

RHEUMATOID ARTHRITIS: 10–20 capsules (500 mg) daily.

UREMIC SKIN SYMPTOMS: 2 capsules (500 mg) twice daily [45 mg GLA per capsule].

NOTE: EPO may be swallowed directly or may be taken with milk, another liquid, or with food. EPO taken with food may minimize any potential gastrointestinal side effects. Concurrent ingestion of the antioxidant vitamin E

will protect essential fatty acids (EFAs) from free radical damage and also prevent creation of counterproductive substances. Concurrent ingestion of a daily multiple vitamin may also provide nutritional cofactors (e.g., B6 and magnesium) required for EFA metabolism.

NOTE: EPO is a long-term therapy, so immediate results should not be expected. A patient may need to use EPO regularly for up to four months before a clinical response is observed. EPO appears to be safe for long-term use of at least one year.



CONTRAINDICATIONS

Some reports suggest that individuals diagnosed with schizophrenia and/or those already receiving epileptogenic drugs such as phenothiazines should consult a healthcare provider before using EPO. However, a recently published analysis of clinical trials involving polyunsaturated fatty acids in the treatment of schizophrenia indicates no clear positive effects of EPO supplementation on schizophrenic patients, but no adverse effects either.

PREGNANCY AND LACTATION: There are no known restrictions during pregnancy or lactation, and GLA, the essential fatty acid that EPO contains, is considered an important substance in human breast milk. According to the World Health Organization, 5% of pregnant women's total caloric intake should be from essential fatty acids.

ADVERSE EFFECTS

Adverse effects are rare at recommended dosages. Occasionally, headache, mild nausea, and abdominal bloating may occur. Overdose symptoms include loose stools and abdominal pain.

DRUG INTERACTIONS

There are no known drug interactions. Steroids and nonsteroidal anti-inflammatory drugs may potentially interfere with essential fatty acid metabolism.

Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of use. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.



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[Fam. *Onagraceae*]

OVERVIEW

Evening primrose is a plant native to North America. Traditionally, it was used externally to treat skin diseases and internally to treat breathing problems and arthritis (Manku *et al.*, 1982; Moerman, 1998; Willard, 1992). It was one of the first medicinal plants brought back to Europe by settlers in the 16th century (Willard, 1992). Evening primrose oil (EPO) has been the subject of hundreds of scientific studies, which led to it becoming one of the most widely used botanical medicines today (Brown, 1996). EPO is sold in over 30 countries as a dietary supplement, drug, or food (Chen, 1999). In 2000, evening primrose oil ranked 10th of all herbal dietary supplements in U.S. food, drug, and, mass-market retail outlets (Blumenthal, 2001). Clinical studies have focused on its use in treating problems associated with essential fatty acid (EFA) deficiency including atopic eczema, premenstrual syndrome, inflammation, and diabetic peripheral neuropathy. EPO is relatively high in essential fatty acids (EFAs), particularly gamma-linolenic acid (GLA, 7–10%) (Leung and Foster, 1996).



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DESCRIPTION

Evening primrose oil preparations consist of a clear, golden yellow, fixed oil extracted by cold expression, or solvent extraction, from the seeds of *Oenothera biennis* L. [Fam. *Onagraceae*] (Budavari *et al.*, 1996; Reynolds *et al.*, 1989), which first occur during the second year of plant growth. Evening primrose is a biennial herb, infertile for the first year (Schulz *et al.*, 1998).

PRIMARY USES

Dermatology

- Atopic dermatitis (Berth-Jones and Graham-Brown, 1993; Gehring *et al.*, 1999; Hederos and Berg, 1996; Schäfer and Kragballe, 1991)

Gynecology

- Mastalgia, cyclical (Wetzig, 1994; Gateley *et al.*, 1992; Cheung, 1999)
- Lactation (Cant *et al.*, 1991)

OTHER POTENTIAL USES

- Diabetic neuropathy (Keen *et al.*, 1993; Jamal and Carmichael, 1990)
- PMS symptoms (Khoo *et al.*, 1990; Ockerman *et al.*, 1986)
- Rheumatoid arthritis (Brzeski *et al.*, 1991)
- Nutritional deficiencies (essential fatty acids) (Brown, 1996)
- Dermatitis: seborrheic dermatitis (milk crust), and atopic dermatitis in infants (Schilcher, 1997)
- Infant formula fortification (Gibson and Rassias, 1990)
- Dry eyes associated with Sjögren's syndrome (Manthorpe *et al.*, 1990)
- Raynaud's disease (Brown, 1996; Chen, 1999)
- Uremic skin symptoms (Yoshimoto-Furuie *et al.*, 1999)

DOSAGE

Internal

ATOPIC DERMATITIS: 4–6 capsules (500 mg) twice daily (40 mg GLA per capsule) (Hederos and Berg, 1996; Schäfer and Kragballe, 1991; Schulz *et al.*, 1998).

CYCLICAL MASTALGIA: 6 capsules (500 mg) daily (40 mg GLA per capsule) for 4–6 months (Cheung, 1999; Gateley *et al.*, 1992b; McFayden *et al.*, 1992).

DIABETIC NEUROPATHY: 8–12 capsules (500 mg) daily (Bratman and Kroll, 1999).

LACTATION AID: 500 mg capsules, twice daily, morning and evening (Cant *et al.*, 1991).

RHEUMATOID ARTHRITIS: 10–20 capsules (500 mg) daily (Bratman and Kroll, 1999).

UREMIC SKIN SYMPTOMS: 2 capsules (500 mg) twice daily (45 mg GLA per capsule) (Yoshimoto-Furuie *et al.*, 1999).

NOTE: Evening primrose oil may be swallowed directly or may be taken with milk, another liquid, or with food (Newall *et al.*, 1996). Evening primrose oil taken with food may minimize any potential gastrointestinal side effects. Concurrent ingestion of the antioxidant vitamin E will protect essential fatty acids (EFAs) from free radical damage and also prevent creation of counterproductive substances (Reddy *et al.*, 1994). Concurrent ingestion of a daily multiple vitamin may also provide nutritional cofactors (e.g., zinc, B6, and magnesium) required for EFA metabolism (Brown, 1996).

External

ATOPIC DERMATITIS: Water-in-oil emulsion containing 20% evening primrose oil, twice daily is applied topically to affected area for at least four weeks (Gehring *et al.*, 1999).

DURATION OF ADMINISTRATION

Internal

Evening primrose oil is a long-term therapy, and immediate results should not be expected. A patient may need evening primrose oil regularly for up to four months before a clinical response is observed (Gateley *et al.*, 1992b; Newall *et al.*, 1996). Evening primrose oil appears to be safe for long-term use, at least up to one year (Keen *et al.*, 1993).

CHEMISTRY

Evening primrose seed contains ca. 14% fixed oil (EPO), which is composed of ca. 65–75% linoleic acid (LA), 7–10% gamma-linolenic acid (GLA), plus oleic, palmitic, and stearic acids and steroids campesterol and β -sitosterol (Leung and Foster, 1996; Newall *et al.*, 1996).

PHARMACOLOGICAL ACTIONS

Human

Improves EFA composition of plasma, erythrocyte, and platelet lipids, and α -tocopherol levels in non-diabetic persons and Type 1 diabetic patients (van Doormaal *et al.*, 1988); increases total fat and EFA content of mother's milk (Cant *et al.*, 1991); affects fatty acid composition of serum lipids and adipose tissue in men with low dihomogammalinolenic acid (DGLA) levels (Abraham *et al.*, 1990); helps maintain normal cellular structures and is a precursor of prostaglandins (Chen, 1999). GLA functions as the precursor of DGLA, which is the parent of the 1-series prostanoids, and as a precursor of arachidonic acid, the parent of the 2-series prostanoids (Pizzorno and Murray, 1999).

Animal

Reduces chronic inflammation (Kunkel *et al.*, 1981); inhibits mammary tumor growth (Karmali and Marsh, 1985); has a beneficial effect on plasma lipids and protects against diabetic nephropathy (Barcelli *et al.*, 1990); anti-asthmatic at high doses (Dorsch and Schmidt, 1995); prevents reduced nerve conduction velocity in streptozotocin-induced diabetes mellitus in rats (Dines *et al.*, 1995); inhibits thromboxane A₂ in diabetes (Dines *et al.*, 1996); antisecretory, anti-ulcerogenic, and cytoprotective in rats that exhibited gastric mucosal damage induced by varicose ulcerogenesis (al-Shabanah, 1997); inhibits binding of benzo(a)-pyrene to cancerous skin cell DNA in mice exposed to a two-stage carcinogenesis model (Ramesh and Das, 1998); inhibits tumor growth in mice with transplanted mammary gland adenocarcinoma (Munoz *et al.*, 1999); alters fatty acid composition of immune system cells; immunomodulatory (Peterson *et al.*, 1999).

In vitro

Cytostatic activity on malignant cell lines (Botha and Robinson, 1986; Leary *et al.*, 1982); suppresses cancer cell proliferation of human osteogenic sarcoma cells (Booyens *et al.*, 1984).

MECHANISM OF ACTION

EFAs are required for the normal structure of all cell membranes in the human body. They are not synthesized endogenously and thus must be obtained from dietary sources (Brown, 1996; Chen, 1999). Major EFAs are linolenic acid (LA) and alpha-linolenic

acid (ALA). Their metabolic products [long-chain polyunsaturated fatty acids including GLA, dihomogammalinolenic acid (DGLA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)] are functionally essential and involved in prostaglandin biosynthetic pathways (Newall *et al.*, 1996). LA is desaturated to GLA by the enzyme delta-6-desaturase (D6D). This conversion of LA to GLA by D6D is the rate-limiting step in the metabolic pathway for EFAs. Its activity is reduced/inhibited by increased demand caused by stress, aging, alcohol, smoking, diabetes, hypertension, and inflammatory diseases including arthritis, psoriasis, and others. In these circumstances, LA accumulates in the body, and an excess of LA may further limit the activity of the D6D enzyme (Giron *et al.*, 1989; Diboune, 1992). GLA is elongated to DGLA by the enzyme elongase and acts as a substrate for production of prostaglandins of series 1. It may also be desaturated to arachidonic acid.

Actions of Evening Primrose Oil (EPO)

- Supplies GLA: The bioactivity of evening primrose oil is due primarily to its GLA content. By supplying GLA, it bypasses the rate-limiting step in the metabolism of LA. After ingestion of evening primrose oil, GLA is rapidly absorbed and then converts directly to DGLA and other prostaglandin precursors (Chen, 1999; Pizzorno and Murray, 1999).
- Acts on the prostanoid pathway (Croft *et al.*, 1984).

Actions of Essential Fatty Acids (EFA)

- Elevate levels of DGLA in plasma, neutrophils, and epidermal phospholipids. DGLA is the precursor of the anti-inflammatory substances 15-hydroxy-eicosatrienoic acid and prostaglandin E₁ (Shafer and Kragballe, 1991).
- May reduce rheumatoid inflammation by metabolizing to the anti-inflammatory one-series prostaglandins and competitively inhibiting the synthesis of pro-inflammatory two-series prostaglandins and four-series leukotrienes (Joe and Hart, 1993).
- May inhibit papilloma formation *in vivo* by inhibiting the binding of benzo-(a)-pyrene to skin cell DNA and increasing the lipid peroxidation process (Ramesh and Das, 1998).
- Absorbed transdermally as well as internally (Houtsmuller and van der Berk, 1981).

CONTRAINDICATIONS

Previously not recommended for patients diagnosed with schizophrenia and/or those already receiving epileptogenic drugs such as phenothiazines, according to a data sheet produced by the leading marketer of evening primrose oil (Anon., 1994–95). However, a recently published analysis of clinical trials involving polyunsaturated fatty acids in the treatment of schizophrenia did not indicate a clear therapeutic or adverse effect of evening primrose oil supplements on schizophrenic patients (Joy, 2000).

PREGNANCY AND LACTATION: No known restrictions (Brown, 1996; McGuffin *et al.*, 1997). Non-teratogenic, based on animal studies (Anon., 1994–95; Horrobin, 1992). LA, GLA, and DGLA are important components of human breast milk, so it is reasonable to assume that evening primrose oil may be taken while nursing (Brown, 1996; Carter, 1988; Gibson and Rassias, 1990; Newall *et al.*, 1996). According to the World Health Organization, pregnant or lactating women should get 5% of their total daily caloric intake from EFAs (Chen, 1999).

ADVERSE EFFECTS

Adverse effects are rare at recommended dosages and are reported by less than 2% of people using evening primrose oil long-term (Brown, 1996; Chen, 1999). Occasional adverse effects include headache (Barber, 1988; Gateley *et al.*, 1992b; Hänsel *et al.*, 1993), mild nausea (Barber, 1988; Cheung, 1999; Gateley *et al.*, 1992b; Hänsel *et al.*, 1993), and abdominal bloating (Gateley *et al.*, 1992b). Overdose symptoms include loose stools and abdominal pain (Newall *et al.*, 1996).

DRUG INTERACTIONS

Early reports suggested that GLA might exacerbate temporal lobe epilepsy in schizophrenic patients being treated with epileptogenic drugs such as phenothiazines (Anon., 1994–95), though this possible effect has not been confirmed (Bratman and Kroll, 1999). Other reports have suggested that steroids and nonsteroidal anti-inflammatory drugs may interfere with GLA metabolism (Brenner, 1981), though this theoretical concern has not been proven (Brown, 1996). Steroids have been reported to inhibit the D6D enzyme, whereby the metabolism of LA to GLA is inhibited. For patients taking steroidal drugs, supplementation with a source of GLA such as evening primrose oil, borage oil (*Borago officinalis*), or black current oil (*Ribes nigrum*) may be beneficial (Marra and de Alaniz, 1990). In one clinical trial, 38 estrogen-dependent breast cancer patients showed a faster clinical response to tamoxifen after oral ingestion of GLA (as found in EPO) (Brinker, 2001).

AMERICAN HERBAL PRODUCTS ASSOCIATION (AHPA) SAFETY RATING

CLASS 1: Herbs that can be safely consumed when used appropriately (McGuffin *et al.*, 1997).

REGULATORY STATUS

CANADA: OTC schedule oral drug, requiring pre-market authorization and assignment of Drug Identification Number (DIN) (Health Canada, 2001).

FRANCE: Used in cosmetic products and toiletries (Bruneton, 1999).

GERMANY: Capsules containing 0.5 g evening primrose oil (corresponding to 40 mg GLA) are approved drugs for treatment and symptomatic relief of atopic eczema (Schulz *et al.*, 1998).

ITALY: No information available.

SWEDEN: Natural remedy for self-medication requiring marketing authorization by the Medical Products Agency (MPA) (Tunón, 1999; WHO, 1998). The only evening primrose-containing product listed in the “Authorised Natural Remedies” (Epogam®) was removed to the Deregistered Natural Remedies list in April of 2000 (MPA, 2001).

SWITZERLAND: Herbal medicine with positive classification (List D) by the *Interkantonale Kontrollstelle für Heilmittel* (IKS) and corresponding sales category D with sale limited to pharmacies and drugstores, without prescription (Morant and Ruppanner, 2001; Codex, 2000).

U.K.: Approved by the Department of Medicine for treatment of atopic eczema and mastalgia (Chen, 1999).

U.S.: Dietary supplement (USC, 1994).

CLINICAL REVIEW

Twenty-two studies are outlined in the following table “Clinical Studies on Evening Primrose,” with a total of 1,154 participants. All but six of these studies (Whitaker *et al.*, 1996; Oliwiecki and Burton, 1994; Berth-Jones and Graham-Brown, 1993; Oliwiecki *et al.*, 1993; Dove *et al.*, 1999; Jenkins *et al.*, 1996) demonstrated positive effects for indications including PMS, dermatological conditions, diabetic neuropathy, and arthritis. The table includes seven double-blind, placebo-controlled (DB, PC) studies investigating the use of evening primrose oil in dermatological conditions including uremic skin symptoms (Yoshimoto-Furuie *et al.*, 1999), chronic hand dermatitis (Whitaker *et al.*, 1996), atopic dermatitis (Berth-Jones and Graham-Brown, 1993; Gehring *et al.*, 1999; Hederos and Berg, 1996), chronic stable-plaque psoriasis (Oliwiecki and Burton, 1994), and psoriatic arthritis (PsA) (Veale *et al.*, 1994). Treatment of PMS symptoms was the subject of two DB, PC studies (Khoo *et al.*, 1990; Ockerman *et al.*, 1986). Other subjects of DB, PC studies in the table included treatment of cyclic mastalgia (Cheung, 1999), diabetic neuropathy (Keen *et al.*, 1993; Jamal and Carmichael, 1990), rheumatoid arthritis (Brzeski *et al.*, 1991), menopausal hot flash (Chenoy *et al.*, 1994), effect on fat composition and content of human milk (Cant *et al.*, 1991), and the effect of survival time of patients with primary liver cancer (van der Merwe *et al.*, 1990). A recent study on pregnant, low-risk, nulliparous women measured pregnancy length and activephase labor outcomes (Dove *et al.*, 1999). A meta-analysis of nine PC studies on atopic eczema correlated clinical improvement with a rise in plasma essential fatty acids (Morse *et al.*, 1989). Improvement in reported itching symptoms was highly significant ($p < 0.01$) compared to placebo. EPO showed a progressive effect as well as a dose/response relationship in the 311 atopic eczema patients evaluated in the nine trials. The protocol has been established for a systematic review of studies on EPO for the treatment of premenstrual syndrome (PMS), but it has not yet been concluded (Strid *et al.*, 2001).

BRANDED PRODUCTS

Efamast® 500 mg evening primrose oil: Scotia Pharmaceuticals Ltd. / Scotia House / Sterling / Scotland / FK9 4TZ / U.K. / <http://fox.nstn.ca/~scotlib/index.html>. 1 capsule contains 40 mg of GLA.

Efamol® 500 mg evening primrose oil: Scotia Pharmaceuticals Ltd. 75.0% linoleic acid (LA), 9.0% gamma-linolenic acid (GLA), 8.5% oleic acid (OE).

Efamol® Marine 500 mg: Scotia Pharmaceuticals Ltd. 430 mg evening primrose oil and 107 mg marine fish oil, providing 40 mg GLA, 20 mg EFA, 11 mg DHA, vitamin E.

Epogam® 500 mg EPO: Scotia Pharmaceuticals Ltd. 50 mg of GLA and 10 mg vitamin E per capsule.

Quest Vitamins: Quest Vitamins / 7080 River Road #129 / Richmond, BC / V6X 1X5 / Canada / Tel: (604) 273-0611 / Email: thartz@van.boehringer-ingenheim.com / www.questvitamins.com. Capsule containing 500 mg evening primrose oil.

Scotia Cream: Scotia Pharmaceuticals Ltd. Cream containing 0.1% beta-methasone valerate and 10% evening primrose oil.

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Clinical Studies on Evening Primrose (*Oenothera biennis* L.)

Breast Pain and PMS Symptoms

| Author/Year | Subject | Design | Duration | Dosage | Preparation | Results/Conclusion |
|-------------------------------|--|--|---|---|--|---|
| Cheung, 1999 | Cyclical mastalgia | P n=32 women with disturbing cyclical mastalgia, median dura- tion of pain 12 months, interfering with lifestyle (mean age 37 years) | 3 months if symptoms improved; if symptoms did not completely resolve, additional 3 months (6 months total) | Six, 500 mg capsules/day (240 mg GLA/day) | Efamast® capsules (500 mg EPO providing 40 mg GLA per capsule) | An overall, clinically useful response rate of 97% was observed at 6 months. One-third and one-half of women were pain-free at end of 3 and 6 months, respectively. Side effects greater than expected (12%) though mild and did not interfere with treatment. Authors conclude that EPO should be recommended as first-line specific treatment for women with disturbing cyclical mastalgia. |
| Gateley <i>et al.</i> , 1992b | Cyclical mastalgia | P n=85 women with cyclical mastalgia | 17 years (4-month treatment periods) | Two, 500 mg capsules 6x/day (240 mg GLA/day) | Efamast® capsules (500 mg EPO providing 40 mg GLA per capsule) | A clinically useful response was obtained in 51 of 85 patients (54%) at 4 months. An additional 12 of 29 patients (41%) who failed to obtain a useful response from EPO as a second line treatment. EPO was less effective than danazol but showed equivalent efficacy to bromocriptine. |
| Wetzig, 1994 | Cyclical and non-cyclical mastalgia with significant breast pain for more than 3 years | Cm n=170 (EPO group n=39) Australian women with cyclical or non-cyclical mastalgia (mean age 42 years) | 3 years | Two, 500 mg capsules 2–3x/day | EPO 500 mg capsules, (brand not stated) or Vitamin B6 50–100mg 2x/day or Danazol 100 mg 2x/day tapering to 100 mg daily after pain control (tamoxifen dose not specified if resistant to danazol and proges- terones) | 10 out of 39 (26%) had complete pain relief. 70% of women who did not respond to treatment had cyclical pain. Response rates of vitamin B6 and EPO were no better than placebo effect. 67% of women taking danazol had complete response. |
| Khoo <i>et al.</i> , 1990 | PMS symptoms | DB, PC, R, CO n=38 women with PMS | 6 months (crossover after 3 cycles) | Four, 500 mg capsules 2x/day (360 mg GLA/day) | Efamol® capsules (500 mg EPO providing 45 mg GLA) vs. placebo (500 mg liquid paraffin) | Substantial improvement in PMS symptoms for EPO and placebo suggesting a strong placebo effect. No significant differences in scoring of 10 PMS symptoms or menstrual symptoms between EPO and placebo. Authors conclude the improvement experienced by women with moderate PMS was solely placebo effect. |
| Ockerman <i>et al.</i> , 1986 | PMS symptoms | DB, PC n=36 women with severe PMS | 3 months | One, 500 mg capsule | Efamol® capsules (500 mg EPO providing 45 mg GLA) | Statistically significant difference (p<0.01) between EPO group and placebo for moderate to complete relief of symptoms. |

KEY: C – controlled, CC – case-control, CH – cohort, CI – confidence interval, Cm – comparison, CO – crossover, CS – cross-sectional, DB – double-blind, E – epidemiological, LC – longitudinal cohort, MA – meta-analysis, MC – multi-center, n – number of patients, O – open, OB – observational, OL – open label, OR – odds ratio, P – prospective, PB – patient-blind, PC – placebo-controlled, PG – parallel group, PS – pilot study, R – randomized, RC – reference-controlled, RCS – retrospective cross-sectional, RS – retrospective, S – surveillance, SB – single-blind, SC – single-center, U – uncontrolled, UP – unpublished, VC – vehicle-controlled.

Clinical Studies on Evening Primrose (*Oenothera biennis* L.) (cont.)

| Dermatological | | | | | | |
|---------------------------------------|---|---|---|---|--|---|
| Author/Year | Subject | Design | Duration | Dosage | Preparation | Results/Conclusion |
| Gehring <i>et al.</i> , 1999 | Atopic dermatitis | DB, VC, PC, R n=40 | 5 weeks (4-week treatment followed by 1 week no treatment) | Topical application to entire flexor side of forearm 2x/day | Amphiphilic oil-in-water emulsion containing 20% EPO vs. placebo (20% miglyol) and water-in-oil emulsion with 20% EPO vs. placebo (20% liquid paraffin) | Statistically significant stabilizing effect on barrier function was observed with EPO in water-in-oil emulsion ($p<0.05$) treatment vs. placebo, documented as a reduction in transepidermal water loss (TEWL). Peak effect not apparent until 5 weeks, including 1-week treatment-free period. Only water-in-oil emulsion proved to be an effective vehicle for EPO, demonstrating that choice in vehicle is an extremely important factor in the efficacy of topically applied EPO. |
| Yoshimoto-Furuie <i>et al.</i> , 1999 | Uremic skin symptoms (pruritus, erythema, dryness) | DB, PC, R n=16 male and female patients undergoing hemodialysis (ages 23–79 years) | 6 weeks plus 6-week observation | Two, 500 mg capsules 2x/day (180 mg GLA/day) | Efamol® capsules (500 mg EPO providing 360 mg linoleic acid, 50 mg oleic acid, 45 mg GLA) vs. placebo (500 mg linoleic acid) | EPO group had statistically significant overall improvement vs. linoleic acid group ($p<0.05$). EPO group had significant increase in mean lipid plasma concentration of DGLA at weeks 6 and 12 compared to baseline ($p<0.01$). EPO group also had significant increases in plasma GLA levels in cholesterol ester ($p<0.01$) and triglyceride ($p<0.05$) fractions at 6 and 12 weeks. |
| Whitaker <i>et al.</i> , 1996 | Chronic hand dermatitis (>1 year duration) | DB, PC, R n=39 | 8 weeks each, with an 8-week follow-up period | Twelve, 500mg capsules/day for 16 weeks (600 mg GLA/day) | Epogam® capsules (500 mg EPO providing 50 mg GLA) vs. placebo (500 mg sunflower oil) | No statistical difference between orally ingested EPO and placebo groups for any parameters tested. Therapeutic value of EPO for chronic hand dermatitis was not superior to placebo. |
| Hederos and Berg, 1996 | Children (ages 1–16 years) with atopic dermatitis who needed regular treatment with topical steroids (22 patients had asthma) | DB, PC, PG, R n=58 | 16 weeks | Four or six, 500 mg capsules 2x/day according to age (320–480 mg GLA/day) | Epogam® capsules (500 mg EPO providing 40 mg GLA w/10 mg vit. E) vs. placebo (500 mg sunflower oil with vitamin E) | EPO group had significantly increased plasma concentrations of EFAs ($p<0.001$). Both groups showed significant improvement from baseline symptoms ($p<0.001$ – $p<0.05$) without a significant difference between placebo and EPO. |
| Oliwiecki and Burton, 1994 | Chronic stable-plaque psoriasis | DB, PC, PG n=37 (ages 16–70 years) | 28 weeks (4 week placebo then treatment, or placebo for 24 weeks) | Six, 500 mg capsules 2x/day (480 mg GLA/day) | Efamol® Marine capsules (430 mg EPO and 107 mg fish oil, providing 40 mg GLA, 20 mg EPA, 11 mg DHA, and 10 mg vitamin E) vs. placebo (paraffin) | No significant difference between EPO and placebo groups in plaque thickness or transepidermal water loss. In the clinical assessment, no significant difference in LAS (linear analogue measurement) was seen in erythema or scaling and overall severity scores. Mean LAS score for overall severity was significantly higher in EPO group at week 8 ($p<0.05$). Authors conclude that EPO combined with fish oil produces no significant improvement in chronic stable plaque psoriasis. |
| Veale <i>et al.</i> , 1994 | Dermatological; psoriatic arthritis (PsA) | DB, PC, R n=38 | 1 year (9-month treatment followed by 3 month placebo) | Twelve, 500mg capsules/day (480 mg GLA/day) | Efamol® Marine capsules (430 mg EPO and 107 mg fish oil, providing 40 mg GLA, 20 mg EPA, 11 mg DHA and 10 mg vitamin E) vs. placebo (paraffin and vitamin E) | EPO and fish oil combination appears to alter prostaglandin metabolism in patients with PsA though this study failed to prove that it could substitute for NSAID therapy. All measures of skin disease activity were unaffected by treatment and did not allow reduction in NSAID requirement. Authors conclude that the study did demonstrate metabolic effects on prostanoid and leukotriene metabolism, suggesting that larger doses might produce a clinical response. |

KEY: C – controlled, CC – case-control, CH – cohort, CI – confidence interval, Cm – comparison, CO – crossover, CS – cross-sectional, DB – double-blind, E – epidemiological, LC – longitudinal cohort, MA – meta-analysis, MC – multi-center, n – number of patients, O – open, OB – observational, OL – open label, OR – odds ratio, P – prospective, PB – patient-blind, PC – placebo-controlled, PG – parallel group, PS – pilot study, R – randomized, RC – reference-controlled, RCS – retrospective cross-sectional, RS – retrospective, S – surveillance, SB – single-blind, SC – single-center, U – uncontrolled, UP – unpublished, VC – vehicle-controlled.

Clinical Studies on Evening Primrose (*Oenothera biennis* L.) (cont.)

Dermatological (cont.)

| Author/Year | Subject | Design | Duration | Dosage | Preparation | Results/Conclusion |
|------------------------------------|--------------------|--|----------|---|---|--|
| Berth-Jones and Graham-Brown, 1993 | Atopic dermatitis | DB, PC, R, PG n=102 adults and children with 3 treatment limbs | 16 weeks | Six, 500 mg capsules 2x/day (480 mg GLA/day) or six, 500 mg EPO & fish oil capsules 2x/day | Epogam® capsules (500 mg EPO, providing 321 mg LA, 40 mg GLA); Efamol® Marine capsules (430 mg EPO, 107 mg fish oil), vs. placebo (paraffin or olive oil) | No therapeutic effect was demonstrated for either EPO or EPO in combination with marine fish oil. No significant difference from placebo in mean improvement of any parameters used to monitor disease, severity including clinical severity scores (both Leicester score and Costa score systems used), percentage of skin affected, topical steroid requirement, and patient diaries. |
| Oliwiecki et al., 1993 | Epidermal thinning | Cm, R n=24 healthy volunteers with 2 treatment limbs | 3 weeks | Apply a thin layer of cream over an area of forearm 5 X 5 cm in diameter 2x/day | Scotia Cream A (0.1% beta-methasone valerate), Cream B (0.1% beta-methasone Valerate, 10% EPO), Cream C (10% arachis oil) | Concomitant administration of EPO and beta-methasone valerate did not prevent steroid-induced epidermal thinning, suggesting that steroid-induced epidermal thinning is not mediated by the inhibition of EFA release from cell membranes. EPO did not affect histological changes (e.g., absence of granular layer and flattening of rete ridges). |
| Schäfer and Kragballe, 1991 | Atopic dermatitis | R (3 dose levels) n=15 | 10 weeks | 4, 8, or 12 capsules/day (0.5g oil) | Quest Vitamins EPO capsules (500 mg EPO) | Supplementation at the highest dosage level, 6 g EPO/day, increased n-6 fatty acid level, especially DGLA by 15–60% in neutrophil and epidermal phospholipids (p<0.05). A beneficial shift in ratio between n-6 and monounsaturated fatty acids was also observed. Authors conclude that EPO at 6 g/day can effect moderate and favorable fatty acid changes in the epidermis of atopic dermatitis patients. |

Other

| Author/Year | Subject | Design | Duration | Dosage | Preparation | Results/Conclusion |
|------------------------|--|--|--|--|---|---|
| Dove and Johnson, 1999 | Pregnancy labor | R, PC, RS n=108 | 7 years, entering at different times (1991–98) | 500 mg 3x/day for 1 week at week 37 of gestation, followed by 500 mg/day until labor | Brand not stated | No significant differences between EPO and placebo on age, Apgar score, days of gestation (p>.05). There was slight significant difference in birth weight (p = .043), with infants in EPO group averaging 156 g larger than those in control group. Women in EPO group had labor averaging 3 hours longer than for the placebo, and an increase in active-phase labor abnormalities including protracted active phase, prolonged rupture of membranes, increased oxytocin, and arrest of descent, some of which may be attributed to larger infant weight. |
| Jenkins et al., 1996 | Liver damage due to chronic hepatitis B | PC, R n=20 patients with chronic hepatitis B | 1 year | Four, 500 mg capsules 2x/day before meals | Efamol® capsules (500 mg EPO plus 10 mg vitamin E) vs. placebo (liquid paraffin) | EPO treatment showed no improvement over placebo in biochemical or histological indices of liver damage, or in rate of loss of circulating surface or e-antigen. |
| Chenoy et al., 1994 | Menopausal hot flash (at least 3x daily) | DB, PC, R n=35 menopausal women (mean age EPO group 53.7 years; mean age placebo group 54.2 years) | 6-month treatment periods | Four, 500 mg capsules 2x/day | Efamol® capsules (500 mg EPO with 10 mg natural vitamin E) vs. placebo (500 mg liquid paraffin) | The only significant improvement in EPO group was reduction in maximum number of nighttime flushes (p<0.05). Authors concluded that EPO provides no benefit over placebo in treatment of menopausal hot flashes. |
| Keen et al., 1993 | Diabetic neuropathy | DB, PC, R, PG, MC n=111 | 1 year | 500 mg capsule 12/day (480 mg GLA/day) | EF4- capsules (500 mg EPO providing 40 mg GLA) | EPO was significantly superior to placebo in relieving 13 of 16 parameters. Both neurological and conduction values improved significantly vs. placebo group. Researchers concluded that EPO may prevent deterioration and reverse the condition in patients with mild diabetic polyneuropathy. |

KEY: C – controlled, CC – case-control, CH – cohort, CI – confidence interval, Cm – comparison, CO – crossover, CS – cross-sectional, DB – double-blind, E – epidemiological, LC – longitudinal cohort, MA – meta-analysis, MC – multi-center, n – number of patients, O – open, OB – observational, OL – open label, OR – odds ratio, P – prospective, PB – patient-blind, PC – placebo-controlled, PG – parallel group, PS – pilot study, R – randomized, RC – reference-controlled, RCS – retrospective cross-sectional, RS – retrospective, S – surveillance, SB – single-blind, SC – single-center, U – uncontrolled, UP – unpublished, VC – vehicle-controlled.

Clinical Studies on Evening Primrose (*Oenothera biennis* L.) (cont.)

Other (cont.)

| Author/Year | Subject | Design | Duration | Dosage | Preparation | Results/Conclusion |
|----------------------------|--|--|---|--|--|---|
| Brzeski et al., 1991 | Rheumatoid arthritis and upper gastrointestinal lesions due to non-steroidal anti-inflammatory drugs | DB, PC, P, R n=30 (mean age EPO group 60 years; mean age placebo group 61 years) | 6 months | 500 mg capsule 12/day (540 mg GLA/day) | Efamol® capsules (500 mg EPO plus 10 mg vitamin E) vs. placebo (olive oil) | EPO produced statistically significant reduction in morning stiffness but only small reduction in articular index. Only 23% (3/13) of EPO group could reduce NSAID dose and none could stop, similar to olive oil group. Of EPO group, 77% (10/13) showed a significant rise in plasma DGLA. Authors conclude that EPO cannot be substituted for non-steroidal anti-inflammatory drugs (NSAIDs) in patients with NSAID-induced upper gastrointestinal side effects. |
| Cant et al., 1991 | Effect on milk composition in nursing mothers | DB, PC, R n=36 breast-feeding women | 8 months | Four, 500 mg capsules 2x/day (2,800 mg LA/day, 320 mg GLA/day) | Efamol® capsules (500 mg EPO) vs. placebo (liquid paraffin) | Total fat and EFA content in milk declined 17-23% in placebo group and increased an unspecified percentage in EPO group. This study demonstrates that supplementing the maternal diet with EPO changes milk fatty acid composition and may provide other beneficial effects by increasing fat content and energy content of breast milk while also increasing ratio of polyunsaturated to saturated fats. |
| Jamal and Carmichael, 1990 | Diabetic neuropathy | DB, PC, R n=22 patients with distal diabetic polyneuropathy | 6 months | Two, 500 mg capsules 4x/day (360 mg GLA/day) | EPO (500-mg capsules providing 45 mg GLA) (brand not stated) | In comparison to placebo, patients in EPO group showed statistically significant increase in both median ($p<0.01$) and peroneal nerve conduction ($p<0.05$), as well as an improvement in neuropathy symptom scores ($p=0.001$) such as abnormal sensations of heat, cold, numbness, pain, weakness, and paresthesias. |
| van der Merwe et al., 1990 | Liver cancer | DB, PC, R n=62 patients with primary liver cancer | 2 years, volunteers entering at different points during this period | 500 mg capsule 36/day (1,440 mg GLA/day) | Efamol® capsules (500 mg EPO providing 40 mg GLA) vs. placebo (500 mg olive oil) | Mean survival time for EPO group was 58 vs. 42 days in placebo group. Effect of EPO on survival in primary liver cancer was not significantly better than placebo. In objective and subjective measurements, EPO scored better than placebo, but was not significant. EPO had a statistically significant beneficial effect on gamma-glutamyl transferase values, as a measure of liver function ($p=0.0192$). |

KEY: C – controlled, CC – case-control, CH – cohort, CI – confidence interval, Cm – comparison, CO – crossover, CS – cross-sectional, DB – double-blind, E – epidemiological, LC – longitudinal cohort, MA – meta-analysis, MC – multi-center, n – number of patients, O – open, OB – observational, OL – open label, OR – odds ratio, P – prospective, PB – patient-blind, PC – placebo-controlled, PG – parallel group, PS – pilot study, R – randomized, RC – reference-controlled, RCS – retrospective cross-sectional, RS – retrospective, S – surveillance, SB – single-blind, SC – single-center, U – uncontrolled, UP – unpublished, VC – vehicle-controlled.