Gamma linolenic acid (GLA)  

**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 dehourrache, 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-trienoi 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 mucoceles (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:**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Evidence Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic neuropathy</td>
<td><strong>B</strong></td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
<td><strong>C</strong></td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td><strong>C</strong></td>
</tr>
<tr>
<td>Attention deficit hyperactivity disorder</td>
<td><strong>C</strong></td>
</tr>
<tr>
<td>Blood pressure control</td>
<td><strong>C</strong></td>
</tr>
<tr>
<td>Cancer treatment (adjunct)</td>
<td><strong>C</strong></td>
</tr>
<tr>
<td>Immune enhancement</td>
<td><strong>C</strong></td>
</tr>
</tbody>
</table>
Mastalgia

Menopausal hot flashes

Migraine

Osteoporosis

Pre-eclampsia

Premenstrual syndrome

Pruritis

Rheumatoid arthritis

Sjogren's syndrome

Ulcerative colitis

C

C

C

C

C

C

C

C

C

C

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)-hydorxy-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**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Study Design</th>
<th>Author, Year</th>
<th>N</th>
<th>Statistically Significant?</th>
<th>Quality of Study</th>
<th>Magnitude of Benefit</th>
<th>ARR</th>
<th>NNT</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic neuropathy</td>
<td>Randomized clinical trial</td>
<td>Keen, 1993</td>
<td>111</td>
<td>Yes</td>
<td>5</td>
<td>High</td>
<td>NA</td>
<td>NA</td>
<td>480mg daily for over 1 year.</td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td>Randomized clinical trial</td>
<td>Jamal, 1986</td>
<td>22</td>
<td>Yes</td>
<td>4</td>
<td>Medium</td>
<td>NA</td>
<td>NA</td>
<td>360mg daily for 6 months.</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome (ARDS)</td>
<td>Randomized clinical trial</td>
<td>Pacht, 2003</td>
<td>43</td>
<td>Yes</td>
<td>5</td>
<td>Medium</td>
<td>NA</td>
<td>NA</td>
<td>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.</td>
</tr>
<tr>
<td>Acute respiratory</td>
<td>Randomized clinical trial</td>
<td>Gadek, 1999</td>
<td>98</td>
<td>Yes</td>
<td>4</td>
<td>Medium</td>
<td>NA</td>
<td>NA</td>
<td>EPA+GLA or an isonitrogenous,</td>
</tr>
<tr>
<td>Condition</td>
<td>Study Type</td>
<td>Author</td>
<td>N</td>
<td>Controlled</td>
<td>Status</td>
<td>Meta-Analysis</td>
<td>Number of Trials</td>
<td>Additional Details</td>
<td></td>
</tr>
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<td>-----------------------------------</td>
<td>-----------------------------</td>
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<td>------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Acute respiratory distress syndrome (ARDS)</td>
<td>Randomized clinical trial</td>
<td>Nelson, 2003</td>
<td>98</td>
<td>No</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>Isocaloric standard diet at a minimum caloric delivery of 75% of basal energy expenditure x 1.3 for at least 4-7 days.</td>
<td></td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>Meta-analysis</td>
<td>Van Gool, 2004</td>
<td>&gt;745</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>19 trials; 11 used to calculate overall severity; trials limited by methodology.</td>
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</tr>
<tr>
<td>Atopic dermatitis</td>
<td>Randomized clinical trial</td>
<td>van Gool, 2003</td>
<td>118</td>
<td>No</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>100mg daily GLA for 6 months.</td>
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<tr>
<td>Atopic dermatitis</td>
<td>Randomized clinical trial</td>
<td>Takwale, 2003</td>
<td>140</td>
<td>No</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>920mg daily for adults, 460 mg daily for children.</td>
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<tr>
<td>Atopic dermatitis</td>
<td>Randomized single-blind clinical trial</td>
<td>Callaway, 2005</td>
<td>20</td>
<td>No</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>Hempspeed oil; amount based on dietary incorporation.</td>
<td></td>
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<tr>
<td>Atopic dermatitis</td>
<td>Case series</td>
<td>Fiocchi, 1994</td>
<td>P</td>
<td>Yes</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>5g daily for 28 days in infants.</td>
<td></td>
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<tr>
<td>Attention deficit hyperactivity disorder</td>
<td>Double crossover, randomized - sequence, placebo controlled trial</td>
<td>Arnold, 1989</td>
<td>18</td>
<td>No</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>In children, a combination of DHA, EPA, AA and GLA for 4 months was investigated.</td>
<td></td>
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<tr>
<td>Attention deficit hyperactivity disorder</td>
<td>Randomized clinical trial</td>
<td>Stevens, 2003</td>
<td>50</td>
<td>Yes</td>
<td></td>
<td>P</td>
<td>Small</td>
<td>360mg daily vs. D-amphetimine vs. placebo.</td>
<td></td>
</tr>
<tr>
<td>Blood pressure control</td>
<td>Randomized clinical trial</td>
<td>Deferne, 1996</td>
<td>27</td>
<td>Yes</td>
<td></td>
<td>P</td>
<td>P</td>
<td>Amt GLA as blackcurrant seed oil.</td>
<td></td>
</tr>
<tr>
<td>Blood pressure control</td>
<td>Randomized clinical trial</td>
<td>Mills, 1989</td>
<td>30</td>
<td>Yes</td>
<td></td>
<td>P</td>
<td>P</td>
<td>Amt GLA as borage oil.</td>
<td></td>
</tr>
<tr>
<td>Blood pressure control</td>
<td>Randomized clinical trial</td>
<td>Leng, 1998</td>
<td>120</td>
<td>Yes</td>
<td></td>
<td>P</td>
<td>Medium</td>
<td>280mg GLA plus 45mg EPA.</td>
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<tr>
<td>Blood pressure control</td>
<td>Randomized clinical trial</td>
<td>Deferne, 1992</td>
<td>18</td>
<td>Yes</td>
<td></td>
<td>P</td>
<td>P</td>
<td>4g oil rich in GLA, EPA and DHA</td>
<td></td>
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<tr>
<td>Cancer treatment (adjunct)</td>
<td>Randomized clinical trial</td>
<td>McIlmurray, 1987</td>
<td>54</td>
<td>No</td>
<td></td>
<td>4</td>
<td>NA</td>
<td>500mg GLA and 10mg Vitamin E daily for 44 months; colorectal.</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Design</td>
<td>Study Name</td>
<td>Year</td>
<td>Country</td>
<td>N</td>
<td>Status</td>
<td>Patients</td>
<td>Dose Description</td>
<td></td>
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<tr>
<td>-------------------------------</td>
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<td>----------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Cancer treatment (adjunct)</td>
<td>Randomized clinical trial</td>
<td>van der Merwe, 1987</td>
<td>62</td>
<td>No</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>1.44g daily for up to 7 months; hepatic cancer patients.</td>
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<tr>
<td>Cancer treatment (adjunct)</td>
<td>Equivalence trial</td>
<td>Kenny, 2000</td>
<td>38 + 47 comparison patients</td>
<td>No</td>
<td>0</td>
<td>NA</td>
<td>2.8 g GLA daily in addition to tamoxifen 20mg daily; breast cancer patients.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune enhancement</td>
<td>Randomized clinical trial</td>
<td>Wu, 1999</td>
<td>40</td>
<td>Yes</td>
<td>3</td>
<td>Small</td>
<td>NA</td>
<td>675mg GLA as blackcurrant seed oil.</td>
<td></td>
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<tr>
<td>Immune enhancement</td>
<td>Randomized clinical trial</td>
<td>Miles, 2004</td>
<td>74</td>
<td>Yes</td>
<td>0</td>
<td>Small</td>
<td>NA</td>
<td>2g GLA as compared with EPA, stearidonic acid or blends; Small changes in natural killer cell count and plasma IgE only.</td>
<td></td>
</tr>
<tr>
<td>Mastalgia</td>
<td>Randomized clinical trial</td>
<td>Goyal, 2005</td>
<td>555</td>
<td>No</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>4g evening primrose oil (320mg GLA) daily.</td>
<td></td>
</tr>
<tr>
<td>Mastalgia</td>
<td>Case series</td>
<td>Cheung, 1999</td>
<td>66</td>
<td>NA</td>
<td>0</td>
<td>Medium</td>
<td>NA</td>
<td>Gamolenic acid provided in evening primrose oil.</td>
<td></td>
</tr>
<tr>
<td>Menopausal hot flashes</td>
<td>Randomized clinical trial</td>
<td>Chenoy, 1994</td>
<td>56</td>
<td>No</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>GLA as 4g evening primrose oil</td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>Open label</td>
<td>Wagner, 1997</td>
<td>168</td>
<td>Yes</td>
<td>NA</td>
<td>Large</td>
<td>NA</td>
<td>1800mg GLA and alpha-linolenic acid</td>
<td></td>
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<tr>
<td>Osteoporosis</td>
<td>Randomized clinical trial</td>
<td>Kruger, 1998</td>
<td>65</td>
<td>No</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>GLA+EPA and calcium 600mg daily for 18 months and 36 months.</td>
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<tr>
<td>Pre-eclampsia</td>
<td>Randomized clinical trial</td>
<td>D'Almeida, 1992</td>
<td>P</td>
<td>Yes</td>
<td>P</td>
<td>P</td>
<td>NA</td>
<td>GLA as evening primrose oil plus fish oil</td>
<td></td>
</tr>
<tr>
<td>Premenstrual syndrome</td>
<td>Randomized clinical trial</td>
<td>Puolakka, 1985</td>
<td>30</td>
<td>Yes</td>
<td>P</td>
<td>Small</td>
<td>NA</td>
<td>Efamol.</td>
<td></td>
</tr>
<tr>
<td>Pruritis</td>
<td>Randomized clinical trial</td>
<td>Yoshimoto-Furuie, 1999</td>
<td>16</td>
<td>No</td>
<td>P</td>
<td>NA</td>
<td>NA</td>
<td>GLA as 2g evening primrose oil.</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Randomized clinical trial</td>
<td>Belch, 1988</td>
<td>49</td>
<td>Yes</td>
<td>P</td>
<td>P</td>
<td>NA</td>
<td>540mg GLA (as EPO) or 450mg GLA (as EPO) plus fish oil versus placebo.</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Randomized clinical trial</td>
<td>Brzeski, 1991</td>
<td>40</td>
<td>No</td>
<td>P</td>
<td>P</td>
<td>NA</td>
<td>540mg GLA per day for 6 months versus olive oil.</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Randomized clinical trial</td>
<td>Leventhal, 1993</td>
<td>37</td>
<td>Yes</td>
<td>4</td>
<td>Medium</td>
<td>NA</td>
<td>1.4g daily.</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Randomized clinical trial</td>
<td>Leventhal, 1993</td>
<td>P</td>
<td>Yes</td>
<td>P</td>
<td>P</td>
<td>NA</td>
<td>GLA as blackcurrant seed oil.</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Randomized clinical trial</td>
<td>Zurier, 1996</td>
<td>56</td>
<td>Yes</td>
<td>4</td>
<td>Medium</td>
<td>NA</td>
<td>2.8g daily of GLA for 6 - 12 months.</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Randomized clinical trial</td>
<td>Remans, 2004</td>
<td>66</td>
<td>No</td>
<td>P</td>
<td>NA</td>
<td>NA</td>
<td>EPA, DHA and GLA for 4 months showed no improvements.</td>
<td></td>
</tr>
</tbody>
</table>
### 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

AUTHOR INFORMATION

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Blinded Peer-Review: Natural Standard Editorial Board.

REFERENCES


