CHAPTER

25

Biological activities of evening primrose oil

Haroon Elrasheid Tahir[1], *Gustav Komla Mahunu*[2], *Abdalbasit Adam Mariod*[3,4], *Zou Xiaobo*[1] *and Newlove A. Afoakwah*[5]

[1]School of Food and Biological Engineering, Jiangsu University, Zhenjiang, P.R. China [2]Department of Food Science & Technology, Faculty of Agriculture, Food and Consumer Sciences, University for Development Studies, Tamale, Ghana [3]Indigenous Knowledge and Heritage Center, Ghibaish College of Science & Technology, Ghibaish, Sudan [4]College of Sciences and Arts-Alkamil, University of Jeddah, Alkamil, Saudi Arabia [5]Department of Food Science & Technology, University for Development studies, Tamale, Ghana

25.1 Introduction

Evening primrose (*Oenothera* biennis L.), belongs to the family Onagraceae, is a wild plant which widely utilized as medicine and now it is one of the most frequently utilized herbal medicines in many countries (Montserrat-de la Paz et al., 2014; Munir et al., 2017). The evening primrose oil (EPO) has gained great attention due to the high concentrations of γ-linolenic acid (8%−14%) and linoleic acid (60%−80%), precursors of the series-1 prostaglandins (Mahboubi, 2019; Montserrat-de la Paz et al., 2014). Fig. 25.1 shows the flower, seed, and EPO products. Many studies have demonstrated the efficacy of EPO in the treatment of diseases such as atopic eczema (Bamford et al., 2013), breast problem (Balci et al., 2020), antineuropathic activity (Rock & DeMichele, 2003), rheumatoid arthritis (RA) (El-Sayed et al., 2014), antioxidant activity (Koo et al., 2010), anticancer (Montserrat-de la Paz et al., 2015), and other diseases (Mahboubi, 2019; Munir et al., 2017). These effects are mostly attributed to polyunsaturated fatty acids (PUFAs) of EPO. Besides these triacylglycerol fractions, other specific compounds (e.g., triterpenoid esters) existing in EPO might have a significant role in these positive effects (Knorr & Hamburger, 2004; Zaugg, Potterat, et al., 2006).

Multiple Biological Activities of Unconventional Seed Oils
DOI: https://doi.org/10.1016/B978-0-12-824135-6.00032-5

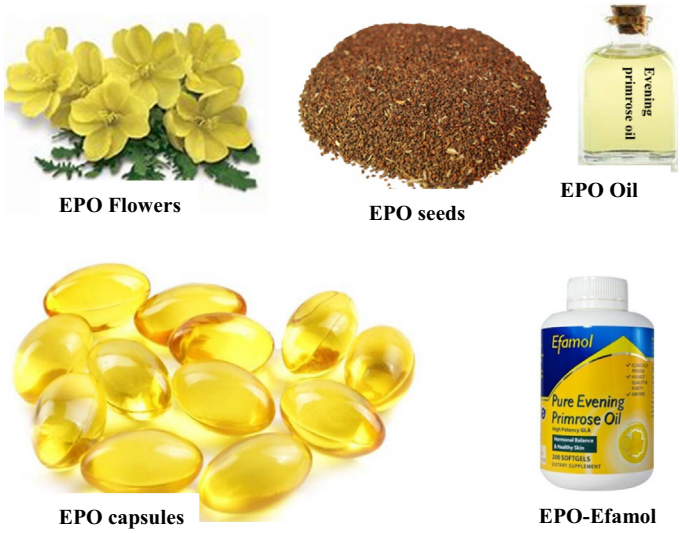

FIGURE 25.1 Evening primrose products.

25.2 Biological activities

25.2.1 Treatment of rheumatoid arthritis

Many trials have demonstrated that EPO can play a significant role in the treatment of inflammation and RA (Belch & Hill, 2000; Hauben, 1994; Horrobin, 1989). About 1% of the population of adults suffering from RA (Tyagi et al., 2020). RA is an autoimmune-mediated joint-based chronic inflammation ailment and more prevalent among women than in men (Abdulkhaleq et al., 2018). Up to now, the medicine of RA is still beyond our reach and inflammatory mediators are controlled by using artificial antiinflammatory compounds. Nowadays, the therapeutic protocols for inflammatory disease are steroidal (corticosteroids), nonsteroidal antiinflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs, biological drugs, and natural agents (Burmester & Pope, 2017; Tyagi et al., 2020). Recently, plant–extracted bioactive compounds have also been used for the treatment of RA disorder. Traditionally, EPO has been utilized for many biological activities and reported in the literature. The therapeutic effect of EPO is attributed to its various bioactive compounds such as linoleic acid, (gamma) linolenic acid, and vitamin E (Kleijnen, 1994).

A study was conducted on 40 patients with RA and upper gastrointestinal injuries as a result of nonsteroidal antiinflammatory drugs joined a prospective 6 months double-blind placebo-controlled study of dietary supplementation with γ-linoleic acid 540 mg/day (Brzeski et al., 1991). A treatment group (90 patients) received EPO (6 g/day) while the control group (21 patients) received olive oil 6 g/day (placebo). During this study, no participant stopped the nonsteroidal antiinflammatory medication; however, three participants in each group lower their dose. The findings indicated that only 23% of the treatment group could lower their NSAID dose and none could stop, similar to that observed in the control group. This contrary to the previous work (Belch et al., 1988) where the same treatment of EPO allowed 25% to stop and a further 38% to reduce their NSAID dosage after six months without

negative effects. Although that study continued for 12 months, most of the positive effects were achieved at 6 months. The participates in that trial have less severe RA and none was no one second-line therapy. This study showed that EPO could be only useful in mild RA while some earliest studies showed there no positive results of EPO (Darlington & Stone, 2001; Hansen et al., 1983). In the study of Brzeski et al. (1991), EPO showed a decrease in morning stiffness and articular index, although only the former obtained statistical significance. The authors do not recommend EPO for severe RA. Furthermore, the study has not demonstrated the potential of substituting EPO for NSAIDs in participants with NSAID-induced upper gastrointestinal side-effects.

In a clinical study on RA with γ-linoleic acid in the form of EPO, it was observed that the patients were enhanced without side effects (Leventhal et al., 1993). Cytokines aid from free radicals is accountable for the development and maintenance of RA. Some prostaglandins suppress cytokine formation. Thus, EPO, which provides γ-linoleic acid, the precursor of prostaglandin E1, ameliorates arthritic symptoms (Darlington & Stone, 2001). In a study, the consumption of fish oil alone or enriched with EPO showed higher incorporation of n-3 PUFA precursors for the antiinflammatory lipid mediators in plasma phospholipids (Veselinovic et al., 2017). This further prompt substantial enhancement in the clinical status of patients with RA disease. The authors suggested further trials with a large number of participants for a long period to approve the long-term effectivity of these supplementations.

Several small studies in animals have suggested benefits from EPO for rheumatoid treatment. In a study on animals ($n = 114$), arthritis was induced by subcutaneous injection of complete Freund's adjuvant (CFA) in the right hind paw of male albino rats. All treatments were administered orally from day 0 (EPO, 5 g/kg b.w.) or day 4 (celecoxib, 5 mg/kg; aspirin, 150 mg/kg) until day 27 after CFA treatment (El-Sayed et al., 2014). The results showed that EPO substantially depressed synovial hyperplasia and inflammatory cells invasion in joint tissues and the result was improved by combining with aspirin or celecoxib. This study showed that the combined use of EPO, which contains antiangiogenic, antiinflammatory, and antioxidant activities, is a promising approach to inhibit the development of RA.A systematic overview of 11 medical studies evaluated the use of oil rich in γ-linolenic acid (GLA) (including borage seed oil, blackcurrent seed oil, and EPO) revealed that it showed significantly lower pain as compared with placebo (Stonemetz, 2008). In a *meta*-analysis of seven clinical studies oils from borage, blackcurrant, and EPO containing GLA were used to treated RA. GLA dosages equal or bigger than 1400 mg/day presented benefits in the mitigation of rheumatic complaints while doses lower than 500 mg/day were ineffective (Cameron et al., 2009). In Cochrane updated systematic review of 22 studies investigated the use of herbal therapies in RA (Cameron et al., 2011). Results from seven studies specify the potential positive effect of GLA from EPO, borage seed oil, or blackcurrent seed oil, concerning reduce pain severity (Cameron et al., 2011).

25.2.2 Treatment of Mastalgia

Approximately 70% of women complain of breast pain at some stages of their life (Ader& Browne, 1997). Cyclic breast pain or Mastalgia is a common condition among

women of reproductive ages. It occurs due to changes in hormones during the menstrual cycle, whereas noncyclical breast pains are not related to the menstrual period (Gautam et al., 2016). The deficiency in GLA causes the breast tissues sensitive to sex hormones, which is accompanying by breast pain (Graham et al., 1994).

Parveen et al. (2007) compared the effect of Danazol and EPO on the management of cyclic breast pain. The findings showed that Danazol provides good pain management in mastalgia however with severe adverse effects, whereas OEP also presented better Mastalgia control but without severe adverse effects. Another study on the effect of EPO and vitamin E on the severity of cyclical breast pain was conducted by Fathizadeh et al. (2009). The findings indicated that EPO reduced the severity of pain and it was more beneficial and better than vitamin E. Other authors combined EPO and vitamin E for treating cyclical mastalgia (Pruthi et al., 2010). The results indicated that the daily doses of 1200 IU vitamin E, 3000 mg EPO or the combination of both treatments at the same dosage administered for 6 months might decrease the severity of periodical breast pain. Randomized clinical trial administered on 90 participants complaining of Mastalgia showed (Jaafarnejad et al., 2017). The results evidence the use of flaxseed powder, EPO, or vitamin E may decrease cyclical breast pain, and the former achieved statistical significance. Since flaxseed powder was more effective compared to the other two treatments. Therefore, the authors recommended using this herbal medicine which is characterized by the higher content of omega-3 essential fatty acids, contains phytoestrogens and antioxidants, due to its fewer adverse effects. In contrast to the study carried out by Farzaneh et al. (2016) who found the use of flaxseed powder, EPO, and vitamin E lead to a reduction in the severity of mastalgia; however, there were no significant differences among the three treatments. In a study, 120 participants were divided into four groups and treated with: (1) EPO and control oil, (2) fish oil and control, (3) fish and EPO, or (4) both control oils for six months (Blommers et al., 2002). Overall, EPO and fish oil had no better effect than the inexpensive wheat-germ oil and corn oil. Several research articles and reviews have demonstrated the potential use of EPO for the management of mastalgia with good response and minimal side effects (Balci et al., 2020; Cheung, 1999; Farzaneh et al., 2013; Mirzaiinajmabadi et al., 2017; Morvarid et al., 2020; Qureshi & Sultan, 2005) while some trials showed no significant effect (Goyal & Mansel, 2005; Sharma et al., 2012). Table 25.1 summarizes some clinical trials on EPO in the treatment of mastalgia.

25.2.3 Antiinflammatory activity

Patients with inflammatory diseases generally use complementary and alternative medicine, particularly herbal therapy. In a study, sterols were extracted from the EPO and accounted for about 49.40% from other fractions and nearly 1% from EPO. These results showed that the EPO is one of the richest sources of phytosterols as compared with other oils such as corn oils (0.95%), sunflower (0.73%), and olive oil (0.17%) (Montserrat-de la Paz et al., 2012; Richard et al., 2002). In a study, the ability of sterols extracted from EPO to impede the release of some proinflammatory mediators by cells involved in inflammation like macrophages was evaluated (Montserrat-de la Paz et al., 2012). The results showed that the extracted sterols may exert a substantial protective effect against the release of proinflammatory mediators. Multiple sclerosis is the most chronic inflammatory

TABLE 25.1 Some clinical studies on EPO in the treatment of mastalgia.

Trial/ailments	Intervention	Results	References
Prospective clinical trial	Participants ($n = 66$) received six EPO capsule (240 mg/d GLA) for 6 months	• Results showed EPO as the source of Gamolenic acid could be used for treatment for Oriental women with disturbing cyclical mastalgia. • An overall useful response rate was 97% after 6 months of intervention. • Adverse effects was12% but all were insignificant.	Cheung (1999)
Double-blind placebo-controlled parallel multicenter clinical trial	Participants ($n = 555$) were treated with 500 mg EPO (providing 40 mg GLA) plus 10 mg natural vitamin E. Placebo fatty acid capsule contained 500 mg hydrogenated coconut oil and 10 mg natural vitamin E. The active antioxidant vitamin and mineral capsule contained 3 mg beta-carotene, 100 mg vitamin C, 25 mg vitamin B6, 10 mg zinc, and 10 mg niacin, and 455 μg selenium. Placebo antioxidant vitamin and mineral capsule contained 255 mg of fractionated coconut oil.	No effectiveness of EPO in mastalgia	Goyal and Mansel (2005)
Randomized double-blind	Participants ($n = 50$) were treated with Piroxicam gel 0.5%, twice a day or 505 mg twice daily EPO, for 3 months.	• Piroxicam gel: excellent response (56%), substantial response (35%), poor response (8%) • EPO capsule: substantial response (64%), poor response (32%). • Only one participant reported adverse effects with OEP to include abdominal bloating, nausea, weight gain, headache, depression, giddiness, rash, and bad taste.	Qureshi and Sultan (2005)
Open nonrandomized comparative clinical study	The patients (15–35 years old) were treated with 500 mg EPO ($n = 50$ patients) or 100 mg oral danazol ($n = 50$ patients), twice daily, for 3 months. The effect of treatment was assessed at baseline 4 and 12 weeks after treatments.	• Results proved Danazol to be significantly effective (76%) in the treatment of mastalgia as compared to 68% effectiveness of EOP, which is relatively comparable. However, the higher adverse effect of Danazol (32%) hinders it is used for the treatment of mastalgia and encourages the usage of EPO due to its lower adverse effect (%). • Adverse effects of EPO were 20% while for Danazol was 24%.	Parveen et al. (2007)

(*Continued*)

TABLE 25.1 (Continued)

Trial/ailments	Intervention	Results	References
Randomized clinical study	Participants treated with 2.5 mg bromocriptine plus 3 mg EPO ($n = 36$) daily, LILT ($n = 40$), for three consecutive menstrual cycles.	Response to treatment 63.9% versus 82.5%	Saied et al. (2007)
Single-blind clinical study	Participants received 3 g EPO ($n = 31$) or 600 mg vitamin E ($n = 30$) daily, for one month	• The severity of cyclical breast pain in both groups reduced significantly before and after the treatment. • Reduction in pain severity 61.3% versus 26.7%	Fathizadeh et al. (2009)
Double-blind randomized placebo controlled trial	Patients were treated with 400 IU vitamin E ($n = 21$), 1000 mg EPO ($n = 21$), the combination of vitamin E (4001 U) and EPO (1000 mg) ($n = 21$), or placebo (two capsules) ($n = 22$) three times daily, for 6 months.	The results showed that EPO, vitamin E, and the combination of the dosage of vitamin E and EPO could be used to manage cyclical breast pain.	Pruthi et al. (2010)
Quasirandomized clinical trial	Participants received 30 g of powdered flaxseed ($n = 28$), 1000 mg capsules of EPO ($n = 28$), 400 IU Vitamin E ($n = 30$), daily, for 2 months.	flaxseed powder significantly decreased the breast pain during the two months of treatment, but despite reducing the duration of pain in the EPO group and Vitamin E, this reduction was not significant	Jaafarnejad et al. (2017)
Double-blind randomized placebo-controlled trial	Participants treated 2 g/day EPO ($n = 25$), 400 IU/day vitamin E ($n = 25$), EPO plus vitamin E ($n = 25$), placebo ($n = 25$) daily, for 6 month	Vitamin E and EPO presented similar therapeutic effect in the treatment of mastalgia	Alvandipour et al. (2011)
A randomized, double-blind factorial controlled trial	Participants treated with EPO 3 g/day ($n = 68$), centchroman 30 mg ($n = 67$) for 6 months	The results showed that the centchroman providing relief from mastalgia and nodularity with minimal side effects	Sharma et al. (2012)

disorder. Rezapour-Firouzi et al. (2013) evaluated the effect of EPO on multiple sclerosis patients. The results showed that EPO treatment has inhibited multiple sclerosis and numerous other inflammatory disorders. In another study, the long-chain fatty alcohols (LCFAs) of EPO demonstrated it is in vitro antiinflammatory effect (Montserrat-de la Paz et al., 2014). It is clear from the above-mentioned two studies both LCFAs and sterols are minor biological active compounds that might synergize the activity ascribed to the PUFAs of the EPO assisting to the overall antiinflammatory influence of this natural biologically active product. In a recent study, an attempt has been made to discover new anti-inflammatory therapy to recover remyelination and possibly prevent and reverse the development of the disease (Rezapour-Firouzi et al., 2020). The results demonstrate the potential therapeutic properties on the improve the structure of cell membranes and suppression of inflammation by EPO in experimental autoimmune encephalomyelitis.

In a double-blind, randomized trial, the activity of liver enzymes in multiple sclerosis participants treated with cosupplemented hemp seed, EPO, and hot-natured diet were assessed (Rezapour-Firouzi et al., 2014). The findings showed that the cosupplemented oil chemical components have positive effects on enhancing extended disability status score and activity of liver enzymes in relapsing-remitting multiple sclerosis patients. The active components of EPO have been shown to have antiinflammatory activities and effects. Another study was conducted to assess the effects of EPO and hemp seed oil on enhancing the membrane fatty acids composition of spleen and blood cells and immunologic factors in comparison to rapamycinin the experimental autoimmune encephalomyelitis model (Rezapour-Firouzi et al., 2020). The results showed EPO alone presents a targeted treatment for remyelinate whereas the combination of EPO and hemp seed oil suppresses any attempt for remyelination.

25.2.4 Antioxidant activity

Antioxidant activity is one of the functional properties that EPO can provide. Oils rich with biologically active agents are desirable by consumers, food processors, and pharmaceuticals. EPO is rich in sources of GLA (8%−10%) and linoleic acid (LA) (70%−74%) and it is assumed that this compound activity is the major contributing factor to the therapeutic assistance of this oil (Timoszuk et al., 2018). De La Cruz et al. (1999) were studied the influence of enrichment (15% wt./wt.) of a hyperlipemic diet (1.33% cholesterol) with EPO for six weeks in 10 rabbits. The results demonstrated that the EPO might be useful as an antioxidant defense factor, and possibly reducing lipid substances, in processes of hyperlipemia or atherosclerosis. However, further trials in humans are required to prove that EPO presents a similar action in less aggressive forms of hyperlipemia such as that examined in these experimental animals. In a study, the antioxidant effect of saponified EPO against isobutylmethylxanthine (IBMX)-induced melanogenesis in B16 melanoma cells was examined (Koo et al., 2010). In their study, saponified EPO successfully decreased melanogenesis in B16 melanoma cells and reduced pigmentation of UV exposed skin. It was concluded that saponified-EPO exhibits a pigment-whitening effect by preventing the expression of tyrosinase and associated enzymes; consequently, the authors believed that this action might be associated with the high concentrations of linoleic acid in EPO.

In experimental animal, it has been demonstrated that both EPO and fish oil, can affect papilloma development which can be attributed, at least in part, to their capability to inhibit benzo(a)pyrene binding to DNA and to increase the lipid peroxidation process (Ramesh & Das, 1998).

Another study on thoroughbred horses showed that EPO is useful and it enables horses to compensate with the maximal load without substantial disruption of the musculoskeletal. The study indicated that intake of EPO (150 mL/horse) significantly influenced aspartate aminotransferase and lactate dehydrogenase in the blood serum of the horses. However, this result needed further experiments to prove the usage of EPO as an effective agent for the improvement of the health condition of horses in load (Mikesova et al., 2014).

In the year 2011, the antioxidant activity of EPO in cases of subacute aflatoxin intoxication induced in mice was studied (Kanbur et al., 2011). It was found that EPO has a significant positive effect on aflatoxin-induced lipid peroxidation.

Hamburger et al. (2002) studied the compounds with radical scavenging, cyclooxygenase, and neutrophil elastase inhibitory activities in EPO. The results showed EPO rich in biologically active materials such as 3-*O*-trans-caffeoyl derivatives of betulinic, morolic, and oleanolic acid. These identified compounds evident antioxidant activity against the stable 2,2-diphenyl-1-picrylhydrazyl radical and were effective inhibitors of neutrophil elastase and cyclooxygenase-1 and -2 in vitro. The authors found that the commercial samples of EPO presented only traces of these biologically active materials. Thus, cold-pressed EPO is recommended to be used as a supplementary agent.

Khodeer et al. (2020) investigated the chemoprotective effects of EPO against the cytotoxicity of chemotherapeutics in the liver and pancreas of cyclophosphamide-intoxicated mice. It was noticed that EPO has strong antioxidant, antiinflammatory, and genoprotective properties against the toxic impacts of cyclophosphamide in mice hepatic and pancreatic tissues.

In human patients, it was observed that oral administration of the combination of EPO, vitamin C, vitamin E, and pycnogenol significantly prevented wrinkle development produced by chronic ultraviolet B irradiation (UVB) through significant inhibition of UVB-induced mitogen-activated protein activity along with improvement of collagen synthesis.

In a previous study, the efficacy of EPO against arsenic-induced oxidative stress in rats was investigated (Kaya & Eraslan, 2013). EPO did not show any side effect and even prevented oxidative stress when administered in association with arsenic. Hence, the authors suggested that the applied dosage (0.1 mL/rat/day) and study period (30 days) are determined accurately, EPO might be employed either to assist primary therapy or directly for prophylaxis or as a food additive in intoxication cases with arsenic or circumstances where such a risk arises.

25.2.5 Anticancer and antitumor activity

From the past years, the utilization of herbal medicines for the prevention and management of cancer has gained great attention. Nowadays, it has been found that GLA is cytotoxic to glioma cells, and it can improve gamma radiosensitivity (Antal et al., 2015). A previous study indicated that EPO (as a source of GLA) may be beneficial in nutritional methodologies of mammary gland tumor therapies (Muñoz et al., 1999). In 2015, it was reported for the first time that EPO phytosterols might be involved in phytosterol-activated liver X receptor (LXR) serving a cancer-protective role (Montserrat-de la Paz et al., 2015). In this study, the effect of phytosterols (namely, β-sitosterol and campesterol) isolated from EPO on proliferation, cell death, and the cell cycle of human colon adenocarcinoma (HT-29) cells was evaluated. The results demonstrated that the extracted phytosterols were effective antiproliferative mediators in a dose- and time-dependent manner, with an IC50 of 62.9 μg/mL after 48 h, lower than β-sitosterol and campesterol (79.0 and 71.6 μM respectively). Flow cytometry revealed that the extracted phytosterols have a stimulatory effect on apoptosis and necrosis, raising the number of cells in G0/G1 phase. The extracted phytosterols generated a significant upregulation in LXR gene expression that could be one of the basic mechanisms of the tumor reduction by EPO phytosterols.

25.2.6 Preventing and treatment of pain

Fibromyalgia is a chronic pain disease that is described by the existence of mechanical hyperalgesia and prevalent pain consistently felt in deep tissues (Montserrat-de la Paz et al., 2013). Besides pain, patients also commonly complain of other symptoms such as fatigue, sleep disorder, and illness like irritable bowel RA, and systemic lupus erythematosus (Wolfe et al., 1990). In a study conducted on experimental animals showed that dietary-EPO can change the nociceptive response and other symptoms related to fibromyalgia syndrome and also it can decrease the release of the inflammatory state (Montserrat-de la Paz et al., 2013).

25.2.7 Antiulcerogenic effects

Benefits of plant oil from their recorded medicinal uses as antiulcerogenic and gastroprotective properties (Azab et al., 2017). In 1997, the effect of EPO on a study on gastric ulceration and secretion induced by many ulcerogenic and necrotizing mediators in rats was evaluated. It was found that EPO has substantial antiulcer and cytoprotective effects on numerous experimentally prompted (aspirin or indomethacin) gastric lesions (Al-Shabanah, 1997).

25.2.8 Thrombolytic activity

Oils have numerous biological active agents that have antithrombotic activity (Deng et al., 2001; Mekhfi et al., 2012). Villalobos and coauthors found that the dietary supplementation with EPO the antithrombotic capability of the endothelium, decreased subendothelial thrombogenicity, and reduced the extent of vascular wall lesions resulting from the hyperlipemic diet (Villalobos et al., 1998).

25.2.9 Antibacterial activity

Lodhia et al. (2009) compared the antibacterial of EPO with palmarosa oil, lavender oil, and tuberose oil. Various levels of each oil ranging from 10% to 100% were examined. The results demonstrated that the lower concentrations of EPO have more effect on gram-negative conversely higher concentration presented more effect on gram-positive bacteria.

25.2.10 Antidiabetic activity

The global incidence of cases of diabetes mellitus has been increased rapidly (102.9%) (Liu et al., 2020). Many medicines are available for the management of diabetes mellitus; however; no perfect therapy has been reported yet. The herbal remedies are thought to provide better management of diabetes by enhancing the immunity of the body. A study of the antidiabetic activity of EPO was conducted by Takahashi et al. (1993). These results suggest that EPO treatment is beneficial in enhancing abnormal lipid and thromboxane (TX) A2 metabolism in diabetic patients.

Gestational diabetes occurs during pregnancy. It can affect pregnancy and the baby's health. After giving birth, gestational pregnancy returns to a normal level rapidly. In the

clinical study, the efficacy of 1000 mg EPO and 1000 IU vitamin D ($n = 30$) by comparison with placebo for six weeks on women with gestational diabetes was assessed on biochemical parameters at baseline and after treatment. Treatments with EPO and vitamin reduced in serum high sensitivity C-reactive protein level and malondialdehyde significantly, whereas the increase in plasma nitric oxide and total antioxidant activity level was detected in the combination of EPO and vitamin D as compared with the placebo group. Thus, women with gestational diabetes can use EPO as a source of natural antioxidant compounds (Jamilian & Afshar, 2017; Jamilian et al., 2016).

Recently, a study was carried out to evaluate the potential use of EPO as an antiinflammatory, antioxidant, and vasodilating effect in type 2 diabetic patients (Safaa Hussain et al., 2016). In this study, the first group ($n = 13$) treated with metformin (500 mg) tablets twice daily alone, and the second group ($n = 13$) treated with the combination of metformin (500 mg) and EPO (2 mg) capsule twice daily for three months treatment. The outcome of the study showed that early treatment with EPO with traditional hypoglycemic drugs could enhance therapeutic benefits and represent a good protocol to control the increase of diabetes complications. Another study on rats conducted to evaluate the effects of 14 days of oral administration with EPO (1.25 g/kg) and was compared to that of alpha-lipoic acid (ALPA) (100 mg/kg) and insulin (2 IU/day), administered individually or in a mixture (El-kossi et al., 2011). Compared with control diabetic rats, the combination of EPO and ALPA enhanced glycemic control, lipid abnormalities, and antioxidant activity; therefore recover the damaged functional properties of peripheral nerves greatly.

25.2.11 Treatment against kidney disorders

In 2009, the effects of EPO on calcium oxalate urinary stone risk factors in eight black and eight white healthy male (treated with 1000 mg EPO daily for 20 days while following a free diet) was investigated (Rodgers et al., 2009). It was reported that citraturia increased substantially in each group. Urinary oxalate revealed a trend to decline in the black group. Calciuria and the Tiselius risk index reduced significantly in each group. Carryover effects were detected.

25.2.12 Atopic eczema/dermatitis

Since 1980, great attention had been given to natural plant oil extract as a potential substitute to topical corticosteroids for the management of atopic dermatitis (Lovell et al., 1981; Wright & Burton, 1982). Although EPO was previously approved in the United Kingdom as medicine for atopic dermatitis, marketing approval was withdrawn in 2002 due to the lack of confirmation of effectiveness (Bayles & Usatine, 2009). In an earlier study, patients with atopic dermatitis were randomized to treated with EPO, EPO plus fish oil, or placebo for 16 weeks (Berth-Jones & Graham-Brown, 1993). No enhancement with active treatment was proved. In 1994, reports showed that EPO does not affect atopic dermatitis (Berth-Jones & Graham-Brown, 1994). In 2008, a randomized placebo-controlled study exhibited a significant difference in the outcome of treatment between the EPO group and the placebo group. No significant adverse effect was observed by any

patient/guardian at any stage of evaluation (Senapati et al., 2008).A *meta*-analysis indicated that EPO (efamol) positive effect on itch, pruritis, crusting, edema, and redness (erythema) that becomes apparent between 4 and 8 weeks after treatment is started. Nevertheless, the extent of this influence decreases in relation with the increasing rate of potent steroid use (Morse & Clough, 2006). There are numerous review articles on the effectiveness of EPO alone or along with other oils on atopic eczema (Bamford et al., 2013; Kerscher & Korting, 1992). A recent review concluded that treatment with EPO significantly improved atopic dermatitis as compared to the placebo and is presently suggested for management of atopic dermatitis (Schlichte et al., 2016). The previous review, published in 2012, had demonstrated no strong evidence of the effect of EPO in eczema, and they cannot be recommended for the public or for clinical practice at that time (Bath-Hextall et al., 2012). Overall, some studies showed that EPO is a nontoxic and effective treatment for atopic dermatitis, however, since there are some conflicting results further large trials are required.

25.2.13 Antineuropathic activity

It was reported that breast cancer survivors who have been treated with adjuvant chemotherapy might experience suffer from late effects of chemotherapy, namely, congestive heart failure, neuropathy, premature menopause, and osteoporosis. The study conducted by Rock and DeMichele (2003) showed that EPO is beneficial for patients suffering from chemotherapy-induced neuropathy. Patients who received EPO showed enhancements in nerve function assessments and symptoms.

25.2.14 Hypocholesterolemic activity

In a study, the hypocholesterolemic effects of Oenothera biennis Linn oil, EPO, bio-γ-linolenic acid oil, safflower oil, palm oil, and soybean in cholesterol-fed rats was evaluated (Fukushima et al., 1997). The findings demonstrated that EPO prevents the increase of serum total cholesterol and very-low-density lipoprotein, intermediate-density lipoprotein, and low density-cholesterol concentrations in the existence of surplus cholesterol in the diet after 13 weeks of treatment. Later systematic and *meta*-analysis of randomized clinical trials found that the oral administration of EPO at a dose of ≤ 4 g/day considerably decreases serum triglyceride concentration and substantially increases high-density lipoprotein concentration in hyperlipidemic subjects (Khorshidi et al., 2020). The authors suggested that large-scale and high-quality clinical studies are needed to demonstrate the efficiency of EPO on lipid profile levels. Also, further studies can apply a higher dosage of EPO and expand the study period.

25.2.15 Antiretroviral activity

Numerous patients who are treated with antiretroviral drugs also utilize alternative medicine involving dietary supplements such as EPO. A systematic review was carried out to explore the evidence for dietary supplement interactions with antiretrovirals

(Jalloh et al., 2017). This review showed that the EPO significantly increases the levels of antiretrovirals and patients should be examined for side effects whereas taking EPO with antiretrovirals. Furthermore, this review indicates the importance of monitoring all human immunodeficiency virus patients for dietary supplement receive to avoid treatment failure or side effects associated with an interaction.

25.3 Conclusion

This chapter has shown there is increasing scientific data for the utilization of dietary supplement of EPO as an integral part of the management of many diseases such as atopic eczema, cancer, antitumor activity, inflammatory, and prevention or treatment of pain. Although EPO has been utilized for centuries for much treatment of diseases, further studies regarding its effectiveness need to be strengthened. This does not mean that the effectiveness is insufficient, but it does mean that further studies are required to be completed.

References

Abdulkhaleq, L. A., Assi, M. A., Abdullah, R., Zamri-Saad, M., Taufiq-Yap, Y. H., & Hezmee, M. N. M. (2018). The crucial roles of inflammatory mediators in inflammation: A review. *Veterinary World*, *11*(5), 627–635.

Ader, D. N., & Browne, M. W. (1997). Prevalence and impact of cyclic mastalgia in a United States clinic-based sample. *American Journal of Obstetrics and Gynecology*, *177*(1), 126–132.

Al-Shabanah, O. A. (1997). Effect of evening primrose oil on gastric ulceration and secretion induced by various ulcerogenic and necrotizing agents in rats. *Food and Chemical Toxicology*, *35*(8), 769–775.

Alvandipour, M., Tayebi, P., Alizadeh Navaie, R., & Khodabakhshi, H. (2011). Comparison between effect of evening primrose oil and vitamin E in treatment of cyclic mastalgia. *Journal of Babol University Of Medical Sciences*, *13*(2), 7–11.

Antal, O., Péter, M., Hackler, L., Mán, I., Szebeni, G., Ayaydin, F., Hideghéty, K., Vigh, L., Kitajka, K., Balogh, G., & Puskás, L. G. (2015). Lipidomic analysis reveals a radiosensitizing role of gamma-linolenic acid in glioma cells. *Biochimica et Biophysica Acta (BBA)—Molecular and Cell Biology of Lipids*, *1851*(9), 1271–1282.

Azab, S. S., Abdel Jaleel, G. A., & Eldahshan, O. A. (2017). Anti-inflammatory and gastroprotective potential of leaf essential oil of Cinnamomum glanduliferum in ethanol-induced rat experimental gastritis. *Le Pharmacien Biologiste*, *55*(1), 1654–1661.

Balci, F. L., Uras, C., & Feldman, S. (2020). Clinical factors affecting the therapeutic efficacy of evening primrose oil on mastalgia. *Annals of Surgical Oncology*, *27*(12), 4844–4852.

Bamford, J. T., Ray, S., Musekiwa, A., van Gool, C., Humphreys, R., & Ernst, E. (2013). Oral evening primrose oil and borage oil for eczema. *Cochrane Database of Systematic Reviews (Online)*, *2013*(4)Cd004416.

Bath-Hextall, F. J., Jenkinson, C., Humphreys, R., & Williams, H. C. (2012). Dietary supplements for established atopic eczema. *Cochrane Database of Systematic Reviews (Online)* (2)Cd005205.

Bayles, B., & Usatine, R. (2009). Evening primrose oil. *American Family Physician*, *80*(12), 1405–1408.

Belch, J. J., Ansell, D., Madhok, R., O'Dowd, A., & Sturrock, R. D. (1988). Effects of altering dietary essential fatty acids on requirements for non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis: A double blind placebo controlled study. *Annals of the Rheumatic Diseases*, *47*(2), 96–104.

Belch, J. J., & Hill, A. (2000). Evening primrose oil and borage oil in rheumatologic conditions. *The American Journal of Clinical Nutrition*, *71*(1 Suppl.), 352s–356s.

Berth-Jones, J., & Graham-Brown, R. A. (1994). Evening primrose oil. Does not show promise in atopic dermatitis. *BMJ (Clinical Research ed.)*, *309*(6966), 1437.

Berth-Jones, J., & Graham-Brown, R. A. C. (1993). Placebo-controlled trial of essential fatty acid supplementation in atopic dermatitis. *The Lancet*, *341*(8860), 1557–1560.

Blommers, J., de Lange-de Klerk, E. S. M., Kuik, D. J., Bezemer, P. D., & Meijer, S. (2002). Evening primrose oil and fish oil for severe chronic astalgia: A randomized, double-blind, controlled trial. *American Journal of Obstetrics and Gynecology*, *187*(5), 1389–1394.

Brzeski, M., Madhok, R., & Capell, H. A. (1991). Evening primrose oil in patients with rheumatoid arthritis and side-effects of non-steroidal anti-inflammatory drugs. *Rheumatology*, *30*(5), 370–372.

Burmester, G. R., & Pope, J. E. (2017). Novel treatment strategies in rheumatoid arthritis. *The Lancet*, *389*(10086), 2338–2348.

Cameron, M., Gagnier, J. J., & Chrubasik, S. (2011). Herbal therapy for treating rheumatoid arthritis. *Cochrane Database of Systematic Reviews (Online)* (2)Cd002948.

Cameron, M., Gagnier, J. J., Little, C. V., Parsons, T. J., Blümle, A., & Chrubasik, S. (2009). Evidence of effectiveness of herbal medicinal products in the treatment of arthritis. *Phytotherapy Research*, *23*(12), 1647–1662.

Cheung, K. L. (1999). Management of cyclical mastalgia in oriental women: Pioneer experience of using gamolenic acid (EFAMAST®) in Asia. *Australian and New Zealand Journal of Surgery*, *69*(7), 492–494.

De La Cruz, J., Quintero, L., Galvez, J., Villalobos, M., & De La Cuesta, F. S. (1999). Antioxidant potential of evening primrose oil administration in hyperlipemic rabbits. *Life Sciences*, *65*(5), 543–555.

Darlington, L. G., & Stone, T. W. (2001). Antioxidants and fatty acids in the amelioration of rheumatoid arthritis and related disorders. *The British Journal of Nutrition*, *85*(3), 251–269.

Deng, Y.-C., Hua, H.-M., Li, J., & Lapinskas, P. (2001). Studies on the cultivation and uses of evening primrose (Oenothera spp.) in China. *Economic Botany*, *55*(1), 83–92.

El-kossi, A. E. A., Abdellah, M. M., Rashad, A. M., & Hamed, S. A. (2011). The effectiveness of evening primrose oil and alpha lipoic acid in recovery of nerve function in diabetic rats. *Journal of Clinical & Experimental Investigations*, *2*(3).

El-Sayed, R. M., Moustafa, Y. M., & El-Azab, M. F. (2014). Evening primrose oil and celecoxib inhibited pathological angiogenesis, inflammation, and oxidative stress in adjuvant-induced arthritis: Novel role of angiopoietin-1. *Inflammopharmacology*, *22*(5), 305–317.

Farzaneh, J., Elham, A. M., Seyyed, A. E., Azadeh, S., Maryam, H., & Mohammadzadeh Vatanchi, A. (2016). Comparative effect of Flaxseed and Evening primrose oil with vitamin E on severity of Cyclic Mastalgia in women. *The Iranian Journal of Obstetrics, Gynecology and Infertility*, *19*(22), 8–16.

Farzaneh, F., Fatehi, S., Sohrabi, M.-R., & Alizadeh, K. (2013). The effect of oral evening primrose oil on menopausal hot flashes: A randomized clinical trial. *Archives of Gynecology and Obstetrics*, *288*(5), 1075–1079.

Fathizadeh, N., Takfallah, L., Ehsanpour, S., Namnabati, M., & Askari, S. (2009). Effects of evening primrose oil and vitamin E on the severity of periodical breast pain. *Iranian Journal of Nursing and Midwifery Research*, *13*(3), 90.

Fukushima, M., Matsuda, T., Yamagishi, K., & Nakano, M. (1997). Comparative hypocholesterolemic effects of six dietary oils in cholesterol-fed rats after long-term feeding. *Lipids*, *32*(10), 1069–1074.

Gautam, S., Srivastava, A., Kataria, K., Dhar, A., Ranjan, P., & Kumar, J. (2016). New breast pain chart for objective record of mastalgia. *The Indian Journal of Surgery*, *78*(3), 245–248.

Goyal, A., & Mansel, R. E. (2005). A randomized multicenter study of gamolenic acid (Efamast) with and without antioxidant vitamins and minerals in the management of mastalgia. *The Breast Journal*, *11*(1), 41–47.

Graham, J., Franks, S., & Bonney, R. C. (1994). In vivo and in vitro effects of gamma-linolenic acid and eicosapentaenoic acid on prostaglandin production and arachidonic acid uptake by human endometrium. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*, *50*(6), 321–329.

Hamburger, M., Riese, U., Graf, H., & Melzig, M. (2002). Constituents in evening primrose oil with radical scavenging, cyclooxygenase, and neutrophil elastase inhibitory activities. *Journal of Agricultural*.

Hansen, T. M., Lerche, A., Kassis, V., Lorenzen, L., & Søndergaard, J. (1983). Treatment of rheumatoid arthritis with prostaglandin E1, precursors CIS-linoleic acid and γ-Linolenic acid. *Scandinavian Journal of Rheumatology*, *12*(2), 85–88.

Hauben, M. (1994). Comment: Evening Primrose oil in the treatment of rheumatoid arthritis-proper application of statistical analysis. *Annals of Pharmacotherapy*, *28*(7–8), 973.

Horrobin, D. F. (1989). Effects of evening primrose oil in rheumatoid arthritis. *Annals of the Rheumatic Diseases*, *48*(11), 965–966.

Jaafarnejad, F., Adibmoghaddam, E., Emami, S. A., & Saki, A. (2017). Compare the effect of flaxseed, evening primrose oil and Vitamin E on duration of periodic breast pain. *Journal of Education and Health Promotion*, *6*, 85.

Jalloh, M. A., Gregory, P. J., Hein, D., Risoldi Cochrane, Z., & Rodriguez, A. (2017). Dietary supplement interactions with antiretrovirals: A systematic review. *International Journal of STD & AIDS*, *28*(1), 4–15.

Jamilian, M., & Afshar, R. (2017). Effects of combined evening primrose oil and vitamin D intake on hs-CRP, oxidative stress and pregnancy outcomes in women with gestational diabetes. *Journal of Arak University of Medical Sciences*, *19*, 43–51.

Jamilian, M., Karamali, M., Taghizadeh, M., Sharifi, N., Jafari, Z., Memarzadeh, M. R., Mahlouji, M., & Asemi, Z. (2016). Vitamin D and evening primrose oil administration improve glycemia and lipid profiles in women with gestational diabetes. *Lipids*, *51*(3), 349–356.

Kanbur, M., Eraslan, G., Sarıca, Z., & Aslan, Ö. (2011). The effects of evening primrose oil on lipid peroxidation induced by subacute aflatoxin exposure in mice. *Food and Chemical Toxicology*.

Kaya, Z., & Eraslan, G. (2013). The effects of evening primrose oil on arsenic-induced oxidative stress in rats. *Toxicological & Environmental Chemistry*, *95*(8), 1416–1423.

Kerscher, M. J., & Korting, H. C. (1992). Treatment of atopic eczema with evening primrose oil: Rationale and clinical results. *Clinical Investigator*, *70*(2), 167–171.

Khodeer, D., Mehanna, E., & Abushouk, A. (2020). Protective effects of evening primrose oil against cyclophosphamide-induced biochemical, histopathological, and genotoxic alterations in mice. *Pathogens*.

Khorshidi, M., Zarezadeh, M., Moradi Moghaddam, O., Emami, M. R., Kord-Varkaneh, H., Mousavi, S. M., Alizadeh, S., Heshmati, J., Olang, B., & Aryaeian, N. (2020). Effect of evening primrose oil supplementation on lipid profile: A systematic review and *meta*-analysis of randomized clinical trials. *Phytotherapy Research*, *34*(10), 2628–2638.

Kleijnen, J. (1994). Evening primrose oil. *BMJ (Clinical Research ed.)*, *309*(6958), 824.

Knorr, R., & Hamburger, M. (2004). Quantitative analysis of anti-inflammatory and radical scavenging triterpenoid esters in evening primrose oil. *Journal of Agricultural and Food Chemistry*, *52*(11), 3319–3324.

Koo, J.-H., Lee, I., Yun, S.-K., Kim, H.-U., Park, B.-H., & Park, J.-W. (2010). Saponified evening primrose oil reduces melanogenesis in B16 melanoma cells and reduces UV-Induced skin pigmentation in humans. *Lipids*, *45*(5), 401–407.

Leventhal, L. J., Boyce, E. G., & Zurier, R. B. (1993). Treatment of rheumatoid arthritis with gammalinolenic acid. *Annals of Internal Medicine*, *119*(9), 867–873.

Liu, J., Ren, Z.-H., Qiang, H., Wu, J., Shen, M., Zhang, L., & Lyu, J. (2020). Trends in the incidence of diabetes mellitus: Results from the global burden of disease study 2017 and implications for diabetes mellitus prevention. *BMC Public Health*, *20*(1), 1415.

Lodhia, M., Bhatt, K., & Thaker, V. (2009). Antibacterial activity of essential oils from palmarosa, evening primrose, lavender and tuberose. *Indian Journal of Pharmaceutical Sciences*, *71*(2), 134.

Lovell, C. R., Burton, J. L., & Horrobin, D. F. (1981). Treatment of atopic eczema with evening primrose oil. *Lancet*, *1*(8214), 278.

Mahboubi, M. (2019). Evening primrose (Oenothera biennis) oil in management of female ailments. *Journal of Menopausal Medicine*, *25*(2), 74–82.

Mekhfi, H., Belmekki, F., Ziyyat, A., Legssyer, A., Bnouham, M., & Aziz, M. (2012). Antithrombotic activity of argan oil: An in vivo experimental study. *Nutrition (Burbank, Los Angeles County, Calif.)*, *28*(9), 937–941.

Mikesova, K., Hartlova, H., Zita, L., Chmelikova, E., Hulkova, M., & Rajmon, R. (2014). Effect of evening primrose oil on biochemical parameters of thoroughbred horses under maximal training conditions. *Czech Journal of Animal Science*, *59*(10), 488–493.

Mirzaiinajmabadi, K., Ghazanfarpour, M., & Sarayloo, K. (2017). Effects of the evening primrose oil on women's mastalgia: A systematic review of randomized controlled trials. *The Malaysian Journal of Nursing*

Montserrat-de la Paz, S., Fernández-Arche, M. A., Bermúdez, B., & García-Giménez, M. D. (2015). The sterols isolated from evening primrose oil inhibit human colon adenocarcinoma cell proliferation and induce cell cycle arrest through upregulation of LXR. *Journal of Functional Foods*, *12*, 64–69.

Montserrat-de la Paz, S., Fernández-Arche, Á., Ángel-Martín, M., & García-Giménez, M. D. (2012). The sterols isolated from Evening Primrose oil modulate the release of proinflammatory mediators. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology*, *19*(12), 1072–1076.

Montserrat-de la Paz, S., García-Giménez, M. D., Ángel-Martín, M., Marín-Aguilar, F., & Fernández-Arche, A. (2013). Dietary supplementation evening primrose oil improve symptoms of fibromyalgia syndrome. *Journal of Functional Foods*, *5*(3), 1279–1287.

Montserrat-de la Paz, S., García-Giménez, M. D., Ángel-Martín, M., Pérez-Camino, M. C., & Fernández Arche, A. (2014). Long-chain fatty alcohols from evening primrose oil inhibit the inflammatory response in murine peritoneal macrophages. *Journal of Ethnopharmacology*, *151*(1), 131–136.

Morse, N. L., & Clough, P. M. (2006). A meta-analysis of randomized, placebo-controlled clinical trials of Efamol evening primrose oil in atopic eczema. Where do we go from here in light of more recent discoveries? *Current Pharmaceutical Biotechnology*, *7*(6), 503–524.

Morvarid, I., Sedigheh, S., Khadivzadeh, T., Masoumeh, G., & Fatemeh, N. S. (2020). Comparative evaluation of evening primrose oil and vitamin E on the severity of cyclic mastalgia: A systematic review and meta-analysis. *The Iranian Journal of Obstetrics, Gynecology and Infertility*, *23*(3), 91–98.

Munir, R., Semmar, N., Farman, M., & Ahmad, N. S. (2017). An updated review on pharmacological activities and phytochemical constituents of evening primrose (genus Oenothera). *Asian Pacific Journal of Tropical Biomedicine*, *7*(11), 1046–1054.

Muñoz, S. E., Piegari, M., Guzmán, C. A., & Eynard, A. R. (1999). Differential effects of dietary Oenothera, Zizyphus mistol, and corn oils, and essential fatty acid deficiency on the progression of a murine mammary gland adenocarcinoma. *Nutrition (Burbank, Los Angeles County, Calif.)*, *15*(3), 208–212.

Parveen, S., Sarwar, G., Ali, M., & Channa, G. A. (2007). Danazol vs oil of evening primrose in the treatment of mastalgia. *Pakistan journal of surgery*, *23*(1), 10–13.

Pruthi, S., Wahner-Roedler, D. L., Torkelson, C. J., Cha, S. S., Thicke, L. S., Hazelton, J. H., & Bauer, B. A. (2010). Vitamin E and evening primrose oil for management of cyclical mastalgia: A randomized pilot study. *Alternative Medicine Review: A Journal of Clinical Therapeutic*, *15*(1), 59–67.

Qureshi, S., & Sultan, N. (2005). Topical nonsteroidal anti-inflammatory drugs vs oil of evening primrose in the treatment of mastalgia. *The Surgeon: Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland*, *3*(1), 7–10.

Ramesh, G., & Das, U. N. (1998). Effect of evening primrose and fish oils on two stage skin carcinogenesis in mice. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*, *59*(3), 155–161.

Rezapour-Firouzi, S., Arefhosseini, S. R., Ebrahimi-Mamaghani, M., Baradaran, B., Sadeghihokmabad, E., Torbati, M., Mostafaei, S., Chehreh, M., & Zamani, F. (2014). Activity of liver enzymes in multiple sclerosis patients with Hot-nature diet and co-supplemented hemp seed, evening primrose oils intervention. *Complementary Therapies in Medicine*, *22*(6), 986–993.

Rezapour-Firouzi, S., Arefhosseini, S. R., Mehdi, F., Mehrangiz, E.-M., Baradaran, B., Sadeghihokmabad, E., Mostafaei, S., Fazljou, S. M. B., Torbati, M.-A., Sanaie, S., & Zamani, F. (2013). Immunomodulatory and therapeutic effects of Hot-nature diet and co-supplemented hemp seed, evening primrose oils intervention in multiple sclerosis patients. *Complementary Therapies in Medicine*, *21*(5), 473–480.

Rezapour-Firouzi, S., Mohammadian, M., Sadeghzadeh, M., & Mazloomi, E. (2020). Effects of co-administration of rapamycin and evening primrose/hemp seed oil supplement on immunologic factors and cell membrane fatty acids in experimental autoimmune encephalomyelitis. *Gene*, *759*144987.

Richard, E., Ostlund, J., McGill, J. B., Zeng, C.-M., Covey, D. F., Stearns, J., Stenson, W. F., & Spilburg, C. A. (2002). Gastrointestinal absorption and plasma kinetics of soy Δ5-phytosterols and phytostanols in humans. *American Journal of Physiology-Endocrinology and Metabolism*, *282*(4), E911–E916.

Rock, E., & DeMichele, A. (2003). Nutritional approaches to late toxicities of adjuvant chemotherapy in breast cancer survivors. *The Journal of Nutrition*, *133*(11 Suppl. 1), 3785s–3793s.

Rodgers, A., Lewandowski, S., Allie-Hamdulay, S., Pinnock, D., Baretta, G., & Gambaro, G. (2009). Evening primrose oil supplementation increases citraturia and decreases other urinary risk factors for calcium oxalate urolithiasis. *The Journal of Urology*, *182*(6), 2957–2963.

Safaa Hussain, M., Abdulridha, M. K., & Khudhair, M. S. (2016). Anti-inflammatory, anti-oxidant, and vasodilating effect of evening primrose oil in type 2 diabetic patients. *International Journal. of Pharmaceutical Sciences Review and Research*, *39*, 173–178.

Saied, G. M., Kamel, R. M., & Dessouki, N. (2007). Low intensity laser therapy is comparable to bromocriptine-evening primrose oil for the treatment of cyclical mastalgia in Egyptian females. *Tanzania Health Research Bulletin*, *9*(3), 196–201.

Schlichte, M. J., Vandersall, A., & Katta, R. (2016). Diet and eczema: A review of dietary supplements for the treatment of atopic dermatitis. *Dermatology Practical & Conceptual*, *6*(3), 23–29.

Senapati, S., Banerjee, S., & Gangopadhyay, D. N. (2008). Evening primrose oil is effective in atopic dermatitis: A randomized placebo-controlled trial. *Indian Journal of Dermatology, Venereology and Leprology*, *74*(5), 447–452.

Sharma, N., Gupta, A., Jha, P. K., & Rajput, P. (2012). Mastalgia cured! Randomized trial comparing centchroman to evening primrose oil. *The Breast Journal*, *18*(5), 509–510.

Stonemetz, D. (2008). A review of the clinical efficacy of evening primrose. *Holistic Nursing Practice*, *22*(3), 171–174.

Takahashi, R., Inoue, J., Ito, H., & Hibino, H. (1993). Evening primrose oil and fish oil in non-insulin-dependent-diabetes. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*, *49*(2), 569–571.

Timoszuk, M., Bielawska, K., & Skrzydlewska, E. (2018). Evening primrose (Oenothera biennis) biological activity dependent on chemical composition. *Antioxidants (Basel, Switzerland)*, *7*(8), 108.

Tyagi, V., Singh, V. K., Sharma, P. K., & Singh, V. (2020). Essential oil-based nanostructures for inflammation and rheumatoid arthritis. *Journal of Drug Delivery Science and Technology*, *60*101983.

Veselinovic, M., Vasiljevic, D., Vucic, V., Arsic, A., Petrovic, S., Tomic-Lucic, A., Savic, M., Zivanovic, S., Stojic, V., & Jakovljevic, V. (2017). Clinical benefits of n-3 PUFA and ɤ-Linolenic acid in patients with rheumatoid arthritis. *Nutrients*, *9*(4).

Villalobos, M. A., De La Cruz, J. P., Martín-Romero, M., Carmona, J. A., Smith-Agreda, J. M., & de la Cuesta, S. F. (1998). Effect of dietary supplementation with evening primrose oil on vascular thrombogenesis in hyperlipemic rabbits. *Thrombosis and Haemostasis*, *80*(10), 696–701.

Wolfe, F., Smythe, H. A., Yunus, M. B., Bennett, R. M., Bombardier, C., Goldenberg, D. L., Tugwell, P., Campbell, S. M., Abeles, M., Clark, P., Fam, A. G., Farber, S. J., Fiechtner, J. J., Michael Franklin, C., Gatter, R. A., Hamaty, D., Lessard, J., Lichtbroun, A. S., Masi, A. T., … Sheon, R. P. (1990). The american college of rheumatology 1990 criteria for the classification of fibromyalgia. *Arthritis & Rheumatism*, *33*(2), 160–172.

Wright, S., & Burton, J. L. (1982). Oral evening-primrose-seed oil improves atopic eczema. *Lancet*, *2*(8308), 1120–1122.

Zaugg, J., Potterat, O., Plescher, A., Honermeier, B., & Hamburger, M. (2006). Quantitative analysis of anti-inflammatory and radical scavenging triterpenoid esters in evening primrose seeds. *Journal of Agricultural and Food Chemistry*, *54*(18), 6623–6628.