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Review article

The Efficacy of Evening Primrose in Rheumatoid Arthritis: a Systematic Review

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Abstract

Considering the different side effects of the long-time conventional anti-rheumatic drugs prescribed for the treatment of rheumatoid arthritis, numerous studies have focused on herbal medicines to reduce inflammation in autoimmune diseases. Although the beneficial properties of evening primrose on rheumatoid arthritis have been determined, the results of the studies have not been systematically reported. The present review has investigated the effects of evening primrose on rheumatoid arthritis systematically. We searched the following electronic databases until March 2023: PubMed, the Cochrane Library, the China National Knowledge Infrastructure, Scopus, ProQuest, Google Scholar electronic databases, allied and complementary medicine database (AMED), and scientific information database (SID) databases for relevant studies. We excluded non-English articles and those not meeting our criteria. We chose all of the correlated original clinical, animal, and in vitro studies. Each article was assessed critically for the possible risk of bias. Thirteen articles were analyzed. Animal and in vitro research confirmed the desired effects of evening primrose on clinical, inflammatory, oxidative, and immunologic factors in rheumatoid arthritis. Also, the results of clinical studies showed the change and improvement of inflammatory and oxidative biomarkers in rheumatoid arthritis. Evening primrose could control rheumatoid arthritis in multiple ways such as decreasing inflammation, inhibiting oxidative stress, and modulating the immune system. This article provides convincing evidence to support the efficacy of evening primrose in rheumatoid arthritis and explains the significance of future clinical trials. Further large-scale high-quality randomized controlled trials (RCTs) assessing the efficacy of evening primrose on rheumatoid arthritis as a primary outcome variable are recommended.

Keywords: evening primrose; *Oenothera biennis*; Onagraceae; rat; rheumatoid arthritis

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Introduction

Rheumatoid arthritis is a chronic inflammatory autoimmune disorder that affects the joints and causes cartilage and bone damage as well as systemic problems such as pulmonary, cardiovascular, and psychological complications. The clinical appearances of symmetrical joint involvement consist of arthralgia, redness, swelling, and limiting the range of movement. The global prevalence of this disease varies between 0.5 and 1.0% of the world population [1,2]. Rheumatoid arthritis significantly reduces the quality of life and functional capacity along

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with increased morbidity and mortality and inflicts significant costs on health and social care systems [3].

B and T Lymphocytes, and inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), IL-6, IL-1, and IL-17 have main roles in developing rheumatoid arthritis symptoms [4].

Various pharmaceutical therapies have been marketed for rheumatoid arthritis treatment such as nonbiologic and biologic disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and immunosuppressants [5]. Although these conventional remedies commonly reduce the symptoms, adverse effects lead to more research tendency in complementary and alternative medicine [6]. Recently, herbal medicines have achieved a lot of attention and have been used to treat several diseases all over the world. There is helpful evidence on how some of these medicinal plants can be effective in the remedy of rheumatoid arthritis symptoms [7].

Evening primrose, *Oenothera biennis* L. is a species of the Onagraceae family and has been grown as a useful herbal supplement. The whole plant was used by native Americans and European settlers for pain relief maladies such as stomachaches, bruising, and dyspnea [8]. Evening primrose oil is obtained by solvent extraction or the cold-pressing method from the seeds of the *Oenothera biennis*. Linoleic acid (LA) (60%–80%) and gamma-linolenic acid (GLA) (8%–14%) are two types of omega-6 fatty acids in evening primrose oil [9]. Studies have presented that evening primrose oil can be helpful for the treatment of several disorders caused by GLA defects [10].

Evening primrose oil is anti-inflammatory, and was found to prevent multiple sclerosis and some other inflammatory diseases [11]. Furthermore, it was also found to have an anti-inflammatory function in the treatment of Crohn's disease, ulcerative colitis and inflammatory bowel disease (IBD) [12]. The potential protective mechanisms of evening primrose in rheumatoid arthritis are shown in Figure 1.

The purpose of this research was to provide a systematic review of the available studies about the effects of *Oenothera biennis* on rheumatoid arthritis in cellular models, animal and clinical studies and introduce the possible mechanisms that lead to such effects.

Methods

The current systematic literature search was conducted according to the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The protocol of the study is available on the Prospective Register of Systematic Reviews (PROSPERO) database (http://www.crd.york.ac.uk/PROSPERO, registration number: CRD42020222044).

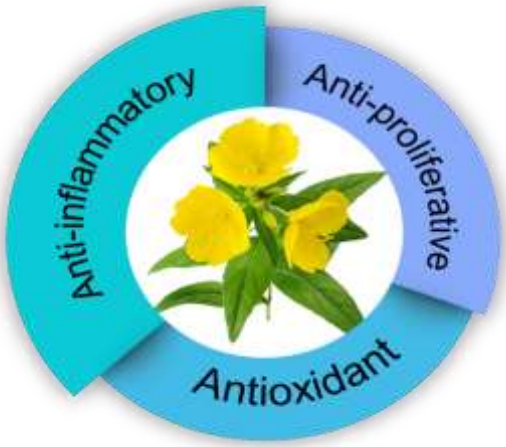

Figure 1. The potential protective mechanisms of evening primrose in rheumatoid arthritis

Search strategy and article selection

We searched the following databases from January 1980 until March 2023: PubMed, the Cochrane Library, the China National Knowledge Infrastructure, Scopus, ProQuest, Google Scholar e-resources, and the allied and complementary medicine database (AMED) as well as the scientific information database (SID). The search strategy was based mainly on medical subject headings (MESH) terms, which were ("evening primroses" or "evening primrose" or "primroses, evening" or "primrose, evening" or "*Oenothera biennis* L. " or "*biennis, Oenothera*" or "night willow herb" or "evening star" or "golden candlestick" or " coffee plant" or "fever-plant" or "cure-all") and ("arthritis, rheumatoid" or "rheumatoid arthritis" or ra or rheumatoid or arthritis).

Eligible studies included only original research articles based on randomized clinical trials (RCTs), controlled clinical trials (CCT), prospective cohort studies, nested case-control, and case-cohort studies. We excluded review articles, case reports, abstracts from symposiums and congresses, and articles discussing the effects

of evening primrose oil mixed with other plants. The data were extracted independently by three reviewers, and then the titles and abstracts of each article were evaluated to remove duplicates. Searches were conducted using identical search terms in a blinded manner. Any doubts were resolved in a meeting to review the queried articles against the inclusion and exclusion criteria after identifying eligible articles. The following criteria were considered to select articles: (i) the study was an RCT involving evening primrose oil; (ii) the route of administration was oral; (iii) the dosage and duration of the evening primrose oil administration was described; (iv) comparison was made with placebo or a treatment of established efficacy; (v) the study involved human patients with rheumatoid arthritis; (vi) the study involved rheumatoid arthritis animal model or related in vitro study; and (vii) the study was published in English. Publications until the end of March 2023 were eligible for inclusion in the review. Studies that did not meet any of the inclusion criteria were excluded (Figure 2).

Results and Discussion

Study characteristics

We found 62 related articles. After deleting duplicates, 52 papers remained that were screened by reviewing both titles and abstracts. Of these, 31 papers were excluded after the revision. Eventually, out of 21 potentially relevant publications, 8 studies were removed for the following reasons: evening primrose had been mixed with additional botanicals (total of 4 instances), there was one unpublished conference presentation, and three articles lacked accessible full texts. Finally, 13 papers were entered in the systematic review (Figure 2). The entered studies were classified into clinical (n = 9), animal (n = 3) and in vitro (n = 1) studies. Characteristics of the investigations are demonstrated in Tables 1, 2.

Human studies

In 2021, our team conducted a clinical trial involving patients with rheumatoid arthritis who were administered evening primrose oil and nettle leaf extract orally for a duration of 12 weeks. The results of the study indicated a notable decrease in the patients' disease activity score 28 (DAS 28) and pain severity, as well as the levels of IL-17 and C- reactive protein (CRP) in their serum when compared to the control group ($p \leq 0.05$). However, other indicators of rheumatoid arthritis severity, such as visual analogue scale (VAS), anti-cyclic-citrullinated peptide antibody (anti-CCP), and erythrocyte sedimentation rate (ESR), did not show any significant differences [13].

The effect of evening primrose oil consumption on rheumatoid arthritis patients was evaluated in nine studies only (Table 1).

In a study by Veselinovic et al., 2017 [15] on 60 female rheumatoid arthritis patients, evening primrose oil supplementation for 12 weeks caused a significant decrease in DAS 28 score, painful joints, VAS score and ESR compared with the control group ($p < 0.001$). Supplementation with evening primrose oil resulted in significantly improved clinical variables, the severity of pain and the number of swollen and/or tender joints. These results demonstrate the anti-inflammatory properties of GLA and DGLA in evening primrose oil.

In another research by Veselinovic et al., [16] on 60 rheumatoid arthritis patients, evening primrose oil supplementation (2600 mg/day) for 12 weeks caused the alleviation of oxidative stress and inflammation by increasing antioxidant enzyme activities.

Furthermore, in a study by Jantti et al. [19] on 18 rheumatoid arthritis patients, evening primrose oil supplementation (20 mL/day) for 12 weeks led to increased linoleic acid concentrations, y-linolenic acid concentrations, and dihomo-y-linolenic acid concentrations ($p < 0.01$). In other research by the same authors [20] on 18 rheumatoid arthritis patients, evening primrose oil supplementation (20 mL/day) for 12 weeks led to no significant changes in ESR, blood hemoglobin or platelet count, serum CRP and immunoglobulin levels, number of swollen or tender joints, pain, and duration of morning stiffness or grip strength of hands. However, plasma PGE2 decreased in the majority of patients. There was an increase in the serum level of TXB-2 (thromboxane B2) in most patients treated with evening primrose oil.

In a study by Brazeski et al. [18] on 30 patients with rheumatoid arthritis, evening primrose oil supplementation (6 g/day) for 24 weeks caused a significant decrease in morning stiffness, but pain scores did not change. Moreover, the marked fall in articular index did not reach significance

($p<0.05$). There was no change in well-being or health assessment questionnaire (HAQ) scores in either group. As expected, there were no changes in laboratory parameters of inflammation.

In a research by Tomic-Smiljanic et al. [14] on 60 rheumatoid arthritis patients, evening primrose oil supplementation (2600 mg /day) for 12 weeks led to lower levels of EPA (eicosapentaenoic acid), DHA (Docosahexaenoic Acid), and n-3 PUFA (n-3 polyunsaturated fatty acids) as antiplatelet aggregation markers were higher, and the n-6/n-3 ratio ($p<0.05$). There was no statistically significant difference in values of other laboratory parameters of platelet function (ESR, CRP) and HAQ, the number of swollen and tender joints between groups.

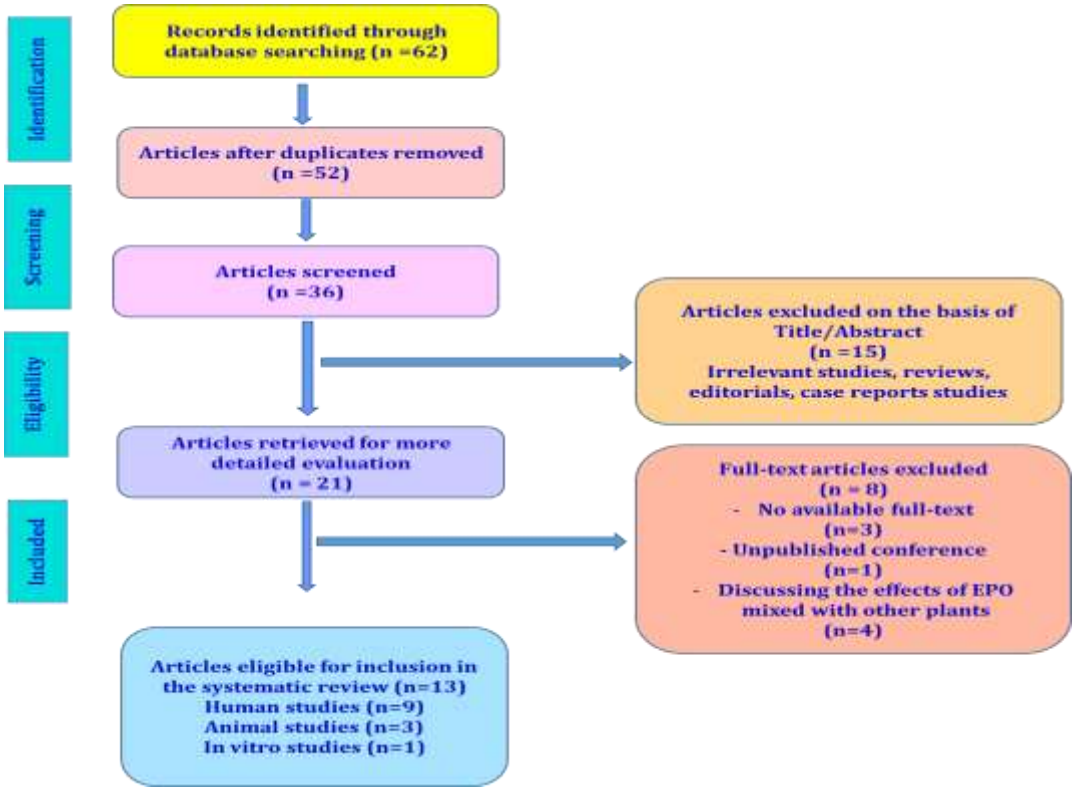

Figure 2. PRISMA flowchart of study screening and inclusion; EPO: evening primrose oil

Table 1. Characteristics of human studies regarding the effect of evening primrose in rheumatoid arthritis

Country	Intervention	Route of administration	Duration of study	Ref.
Iran	Evening primrose oil and nettle leaf extract 90 (group 1:16, group 2:15, group 3:18)	Oral	12 Weeks	[13]
Serbia	Evening primrose oil and fish oil 60 (N = 20 per group)	Oral	12 weeks	[14]
Serbia	Evening primrose oil and fish oil 60 Female patients (40, 20)	Oral	12 Weeks	[15]
Serbia	Evening primrose oil and fish oil 60 (N = 20 per group)	Oral	12 Weeks	[16]
Egypt	Fish oil, evening primrose oil and *Nigella sativa*, in conjunction with vitamin E; 112 (N = 28 per group)	Oral	8 Weeks	[17]
England	Evening primrose oil and olive oil 30 Patients after withdrawal (17 group one,13 group two)	Oral	24 Weeks	[18]
Finland	Evening primrose oil and olive oil 18 Patients (9, 9) 1 men and 9 women in each group	Oral	12 Weeks	[19]
Finland	Evening Primrose oil and olive oil 18 Patients (9, 9) 1 men and 9 women in each group	Oral	12 Weeks	[20]
UK	Evening primrose oil and fish oil 49 (group 1=16, group 2=15, group 3=18)	Oral	48 Weeks	[21]

In a research by Al-Okbi et al. [17] on 112 rheumatoid arthritis patients, evening primrose oil supplementation (2 g/day) for 8 weeks led to a significant reduction of superoxide dismutase (SOD), ESR, plasma copper, PGE2, and a significant increase of plasma zinc, plasma vitamin C and vitamin E ($p<0.001$). Moreover, plasma uric acid levels decreased compared to the control group.

In a study by Belch et al. [21] on 49 patients with rheumatoid arthritis, evening primrose oil supplementation (containing 540 mg GLA/day) for 48 weeks led to reduced or stopped using NSAIDs to control their symptoms after 12 months ($p<0.05$). The clinical and laboratory measurements were not significantly different compared to the control group. Although there were no significant changes in objective measures of disease activity, 94% of the evening primrose oil group.

Animal studies

According to the inclusion criteria, two animal investigations were entered in the current systematic review and supported the effect of evening primrose oil on rheumatoid arthritis (Table 2).

A study conducted by Basant et al. [22] involved 48 male adult rats with arthritis that were treated with evening primrose oil (5 mg/g) for a period of 10 to 21 days. The results of the study showed a substantial decrease in inflammation biomarkers and mitotic figures, as well as lymphoblast activation. Additionally, the white blood cell and platelet counts of the rats improved.

El-Sayed et al. [23] reported that evening primrose oil (5 g/kg/day) caused a considerable reduction in ankle circumference compared to aspirin or celecoxib in chronic adjuvant induced polyarthritis rats. The combination of Evening Primrose oil with celecoxib revealed the maximum reduction in ankle circumference among all treatment groups. A single treatment with evening primrose oilsignificantly ($p<0.05$) reduced plasma ANG-1 to reach normal levels. The combination of evening primrose oil with aspirin or celecoxib was superior to corresponding individual treatments in reducing plasma ANG-1 levels. The treatment either alone or combined with aspirin or celecoxib significantly ($p<0.05$) reduced ANG-1 on day 27 to reach normal levels.

Individual treatment with aspirin, celecoxib, or evening primrose oil showed a significant ($p<0.05$) reduction in TNF-α levels compared to arthritic control on days 9, 18 and 27. The combination of evening primrose oil with aspirin or celecoxib showed a further reduction in plasma TNF-α levels compared to individual treatment. The treatment either alone or in combination showed a further significant ($p<0.05$) reduction in the total histopathological scores. The combination of evening primrose oil with aspirin or celecoxib produced a significant reduction in malondialdehyde (MDH) levels. Daily treatment with aspirin or celecoxib in combination with evening primrose oil successfully normalized malondialdehyde levels on day 27.

Table 2. Characteristics of animal and in vivo / in vitro studies regarding the effect of evening primrose in rheumatoid arthritis

Animal Model	Country	Intervention	Route of administration	Duration of study	Ref.
Adjuvant-induced arthritic rat models	Egypt	Extra virgin olive oil (EVOO) and evening primrose oil 48 Male adult Wistar rats (n=6 per group)	Oral	10 and 21 Days	[22]
Chronic adjuvant induced polyarthritis rat	Egypt	Evening primrose and aspirin and celecoxib 114 Adult male albino rats (108 arthritis model (n=18 per group) + 6 normal rats)	Oral	27 Days	[23]
LPS stimulated female Swiss mice peritoneal macrophage	Spain	Long chain fatty alcohols (LCFAs) were isolated from the non-triacylglycerol fraction of the Evening Primrose oil $1*10^6$ Macrophages/well	Cell Culture	24 Hours	[24]
Chronic adjuvant induced polyarthritis rat	Japan, USA	Evening primrose oil not mentioned	Oral	2 Weeks before adjuvant challenge	[25]

Treatment with evening primrose oil and celecoxib led to normalization of superoxide dismutase activity (increase versus untreated group) on day 27. Glutathione levels decreased after treatment with evening primrose oil alone (on day 27) or in combination with aspirin (on day 27) or celecoxib (on days 18 and 27).
Another study by L. Kunkel et al. [25] in adjuvant-induced polyarthritis rats also indicated that evening primrose oil (0.75 mL/day) for 2 weeks led to more than 60% reductions in chemotaxis of neutrophils isolated from the evening primrose oil-treated rats. The polyarthritis response was both delayed and suppressed in rats whose diets were supplemented with evening primrose oil two weeks before the adjuvant challenge.

In vitro studies

Findings from an in vitro study by Montserrat-de la Paz [24] supported the strong anti-inflammatory and antioxidant effects of evening primrose oil. these results show that the treatment of female Swiss mice peritoneal macrophages with the non-triacylglycerol fraction of the evening primrose oil (25, 50 or 100 μg/mL) for 24 hours can decrease significantly, and dose-dependently nitric oxide production induced by lipopolysaccharide (LPS) ($p \leq 0.001$) and the inhibitory effect seems to be the result of reduced expression of the inducible nitric oxide synthetase (iNOS) enzyme gene rather than a direct inhibitory effect on enzyme activity.
The release of phospholipase A2 (PLA2) and thromboxane B2 (TXB2) as direct or indirect modulator of pro-inflammatory mediators was notably suppressed by a mixture of long chain fatty alcohols (LCFAs) ($P \leq 0.001$), even though LCFAs had no impact on the production of PGE2. Nonetheless, according to the western blot analysis, LCFAs decreased the gene expression of the cyclooxygenase-2 enzyme across all tested doses. Similarly, the production of inflammatory cytokines IL-1β and TNF-α from LPS-stimulated murine macrophages was significantly diminished ($p \leq 0.001$).
The release of PLA2 and TXB2 also was significantly inhibited by LCFAs ($p \leq 0.001$) although LCFAs did not affect to PGE2 generation; however, the western blot assay showed that LCFAs reduced cyclooxygenase-2 enzyme gene expression at all doses assayed. In the same way, the creation of inflammatory cytokines IL-1β and TNF-α from LPS-stimulated murine macrophage was also significantly reduced ($p \leq 0.001$).

Methodological quality and risk of bias

Articles with potential risk of bias were evaluated using various tools. Clinical studies were assessed using the Cochrane Collaboration's tool [26], in vitro studies using the checklist for reporting (CRIS) guideline [27], and animal studies using the SYRCLE's risk of bias tool [28]. The SYRCLE's risk of bias tool is based on the Cochrane Rob tool and has been adapted for aspects of bias that have a particular function in animal intervention. Both of the tools have six domains, and each domain was evaluated as having a low, unclear, or high risk of bias.
This is the first systematic review of the effects of evening primrose on rheumatoid arthritis that assessed the available in vitro, animal, and clinical studies. The only available in vitro study in this field had noted the strong anti-inflammatory and antioxidant effects of evening primrose oil [24]. Furthermore, two available animal studies revealed that the oil can have helpful effects on clinical, inflammatory, immunological, and oxidative parameters in rheumatoid arthritis of animal models [22,23,25]. Clinical studies have shown the desirable effects of evening primrose oil on clinical, immunological and oxidative parameters of rheumatoid arthritis [14,15,17-21,29]. All available studies in this article, have investigated the effect of evening primrose oil on rheumatoid arthritis whereas a notable limitation of these studies is the lack of attention to standardization or quantification of bioactive compounds in the evening primrose oil preparations. Therefore, further studies should investigate the effect of the bioactive compounds of evening primrose oil in more detail.
Rheumatoid arthritis is a chronic autoimmune disease characterized by predominant synovial proliferation, bone destruction, and degradation of articular cartilage [30]. Th17 cells which mainly generate IL-17, IL-21, and IL-22 have been shown to have a crucial role in tissue damage in joints affected by rheumatoid arthritis [31]. Some other cytokines including TNF-α, IL-1, and IL-6 induce chronic inflammation during rheumatoid arthritis [32-34]. CRP is another

potential marker of rheumatoid arthritis that directly contributes to bone degradation and RA progression [35].

For evening primrose oil efficiency in the clinical improvements of rheumatoid arthritis, several potential mechanisms can be proposed. Evening primrose oil is very high in linoleic acid (LA) and γ-linolenic acid (GLA), but low in palmitic acid, oleic acid, and stearic acid. LA and GLA are precursors of anti-inflammatory eicosanoids and help in the treatment of rheumatoid arthritis. LA is converted into GLA and following that can be transformed into dihomo- γ -linolenic acid (DGLA) and subsequently into series-1 prostaglandins (PGs), which belong to eicosanoids known for their possible anti-inflammatory and immune-regulating properties [36]. GLA also suppresses inflammation agents such as TNF-α, IL-1β, and IL-6 [37]. Nonetheless, a small fraction of evening primrose oil, palmitic acid and stearic acid, have been shown to influence TNF-α production and contribute to pro-inflammatory conditions [38]. However, given that their proportion is lower than that of LA and GLA, any potential side effects they may induce are likely mitigated by the anti-inflammatory effects of LA and GLA. The body also can convert LA to arachidonic acid as a polyunsaturated fatty acid within the cellular membranes of most cells. When there is irritation or injury, arachidonic acid is liberated and undergoes oxygenation through enzymatic processes [39]. Eicosapentaenoic (EPA) and docosahexaenoic acids (DHA) are important modulators of a host's inflammatory immune responses because they interfere with the enzymatic conversion of arachidonic acid to pro-inflammatory prostaglandins and leukotrienes.

Oxidative stress is another factor that has been implicated in the pathogenesis of rheumatoid arthritis. Free radicals can be produced by neutrophils at the site of inflammation and diffuses into the blood. Increased lipid peroxidation and disruptions in antioxidant levels suggest that individuals with RA are at greater risk of oxidative damage caused by free radicals [40]. It has been investigated that evening primrose seeds potentially have high antioxidant activity. Paulina Pająk et al investigated the antioxidant activity of evening primrose seeds in different assays and reported as follows: DPPH [234.13 mg trolox/g dry mass], ABTS [210.54 mg trolox/g dry mass], and FRAP [669.768 mmol Fe^{2+}/100g dry mass]. This high antioxidant activity is due to the presence of some phenolic compounds like caffeine and ferulic acid [41].

Conclusion

In this article, we tried to discuss the efficacy of evening primrose in rheumatoid arthritis management and its several mechanisms of function. The antioxidant, anti-inflammatory and anti-proliferative properties of evening primrose make this plant susceptible to clinical improvements of rheumatoid arthritis.

Acknowledgement

None.

Author contributions

Bahareh Abd-Nikfarjam, Mehri Hajiaghayi and Amir Hossein Dolati-Somarin contributed in conception and design of the work, data collection, drafting the manuscript, analysis and interpretation of the data; Bahareh Abd-Nikfarjam, Amir Hossein Dolati-Somarin, Mehri Hajiaghayi, Fatemeh Gholizadeh were involved in critical revision of the manuscript; Fatemeh Gholizadeh contributed in methodological quality and risk of bias assessment.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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Abbreviations

RA: rheumatoid arthritis; EPO: evening primrose oil; DMARD: disease-modifying antirheumatic drugs; NSAID: nonsteroidal anti-inflammatory drugs; DAS28: disease activity score 28; VAS: visual analogue scale; TAC: total anti-oxidant capacity; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide antibodies; CRP: C reactive protein; ESR: erythrocyte sedimentation rate; CAMs: complementary and alternative medicines; LA: linoleic acid; GLA: γ-linolenic acid; DGLA: dihomo-γ-linolenic acid; DPPH: 1,1-diphenyl-2-picrylhydrazyl; ABTS: 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid; FRAP: ferric-reducing antioxidant power