



Review

Borage oil in the treatment of atopic dermatitis

Rachel H. Foster B.Pharm.^a, Gil Hardy Ph.D., F.R.S.C.^{a,b}, Raid G. Alany Ph.D., M.P.S., Reg. Pharm. N.Z., F.N.Z.C.P.^{a,b,*}

^a School of Pharmacy, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, New Zealand

^b Drug Delivery Research Unit (DDRU), School of Pharmacy, The University of Auckland, Auckland, New Zealand

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ABSTRACT

Nutritional supplementation with omega-6 essential fatty acids (ω -6 EFAs) is of potential interest in the treatment of atopic dermatitis. EFAs play a vital role in skin structure and physiology. EFA deficiency replicates the symptoms of atopic dermatitis, and patients with atopic dermatitis have been reported to have imbalances in EFA levels. Although direct proof is lacking, it has been hypothesized that patients with atopic dermatitis have impaired activity of the delta-6 desaturase enzyme, affecting metabolism of linoleic acid to gamma-linolenic acid (GLA). However, to date, studies of EFA supplementation in atopic dermatitis, most commonly using evening primrose oil, have produced conflicting results. Borage oil is of interest because it contains two to three times more GLA than evening primrose oil. This review identified 12 clinical trials of oral or topical borage oil for treatment of atopic dermatitis and one preventive trial. All studies were controlled and most were randomized and double-blind, but many were small and had other methodological limitations. The results of studies of borage oil for the treatment of atopic dermatitis were highly variable, with the effect reported to be significant in five studies, insignificant in five studies, and mixed in two studies. Borage oil given to at-risk neonates did not prevent development of atopic dermatitis. However, the majority of studies showed at least a small degree of efficacy or were not able to exclude the possibility that the oil produces a small benefit. Overall, the data suggest that nutritional supplementation with borage oil is unlikely to have a major clinical effect but may be useful in some individual patients with less severe atopic dermatitis who are seeking an alternative treatment. Which patients are likely to respond cannot yet be identified. Borage oil is well tolerated in the short term but no long-term tolerability data are available.

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Introduction

Atopic dermatitis (atopic eczema) is a chronic-relapsing inflammatory skin condition that can be distressing and, when severe, can be functionally and socially disabling [1]. It affects up to 15–20% of children in developed countries, and the incidence is increasing [2,3]. The condition improves or resolves with age in most patients. However, many patients will require intermittent treatment for exacerbations through to early adulthood or beyond with agents such as topical corticosteroids that have significant adverse effects (Table 1) [2–4].

The pathogenesis of atopic dermatitis is multifactorial and involves a complex interaction between environmental, immunological, and genetic factors [1,5]. It is associated with

hyperreactivity to environmental triggers. T-cell-mediated processes and various cytokines and chemokines play an essential role. Most, but not all, cases are IgE-mediated. Atopic dermatitis often co-occurs with other atopic conditions such as asthma and hayfever. The condition has been linked to various regulatory genes, and it is strongly linked to a family history of atopy. The pathophysiology of atopic dermatitis includes skin barrier defects causing increased transepidermal water loss (TEWL) and increased permeability to irritants and allergens. There is increased susceptibility to infection, and colonization of the skin with *Staphylococcus aureus* contributes to inflammation of the skin.

It has been proposed that atopic dermatitis is associated with an abnormality in essential fatty acid (EFA) metabolism, in particular, affecting production of gamma-linolenic acid (GLA), and possibly also impaired incorporation of EFAs into membrane phospholipids [6–8]. In the body, EFAs and their products, particularly those of the omega-6 (ω -6) series, are important for skin structure and physiology. EFAs play a crucial role in cell

* Corresponding author. Tel.: +64 9 373 7599, ext: 86967; fax: +64 9 367 7192.

E-mail address: r.alany@auckland.ac.nz (R. G. Alany).

Table 1
Overview of treatments for atopic dermatitis (AD)*

Treatment	Role	Limitations
Emollients	Standard of care for both preventive and maintenance therapy	Often underused. Need to be applied liberally at least 3–4 times daily
Topical corticosteroids	Corticosteroid-sparing Standard of care for acute exacerbations Provide symptomatic relief	Recommended only for short-term or intermittent use Adverse cutaneous effects limit long-term use (e.g., striae, skin atrophy, telangiectasia) Specialist monitoring required for infants <2 years and with use of more potent steroids Concerns regarding systemic effects (e.g., HPA suppression, reduction of bone density, growth retardation in children) [†]
Topical calcineurin inhibitors	Second-line use only in patients who have failed to respond adequately to, or cannot be treated with, topical corticosteroids Reduce severity of symptoms Tacrolimus: moderate-to-severe AD Pimecrolimus: mild-to-moderate AD	Can be used only in patients aged ≥2 years Recommended only for short-term or intermittent use Fewer adverse cutaneous effects but can cause a transient burning sensation at site of application Concerns regarding malignancy with long-term continuous use [†]
Antihistamines	Sedating antihistamines may be useful when symptoms disrupt sleep	Nonsedating antihistamines have little effect on symptoms
Oral antibiotics	Treatment of secondary skin infections	In the absence of infection, reduction of skin bacterial colonization with use of antibiotics has little benefit in AD Resistance concerns with excessive use
Oral immunomodulators	Oral corticosteroids and cyclosporin Effective in refractory and severe AD	Rebound flaring/relapse when treatment discontinued Long-term use limited by serious adverse effects

GLA, gamma-linolenic acid; HPA, hypothalamic-pituitary-adrenal axis

* Based on guidelines from the American Academy of Dermatology [4] and the Primary Care Dermatology Society and British Association of Dermatologists [3].

[†] Data regarding the risk of these effects with topical application are inconclusive and such events are rare, but caution is warranted with extensive or long-term use.

membrane fluidity and flexibility and affect activity of membrane-associated proteins such as receptors and enzymes. Notably, EFAs are key components in the membrane systems that maintain the structural integrity of the skin and epidermal function as a permeability barrier. Furthermore, EFAs are metabolized to highly active eicosanoid products, such as prostaglandins and leukotrienes, that modulate inflammatory, immunologic, and proliferative responses including those of the skin cells [6,8–10].

In states of EFA deficiency, skin changes similar to those of atopic dermatitis are replicated [6,8]. The skin becomes inflamed with dry, scaly, red, and weeping lesions. There is an increased rate of proliferation of epidermal cells, metabolic activity, and formation of sterol esters and abnormal keratinocytes. The skin's normal function as a barrier to water loss becomes markedly impaired [6,8]. There is increased colonization with *S. aureus* [11]. This atopic dermatitis-like skin disorder is reversed by treatment with ω -6 EFAs [9].

There remains controversy over the exact importance of EFA disturbances as a pathophysiological factor in atopic dermatitis, and current data fall short of direct proof. Nevertheless, the finding that EFA abnormalities can be detected prior to the development of atopic dermatitis does support a causative role [12]. EFA abnormalities could contribute to atopic dermatitis in two ways: first, through a direct effect on the skin structure and function, and, second, by affecting maturation and sensitization of the immune system affecting the skin [6]. The abnormalities in EFA metabolism could potentially reduce levels of the prostaglandin PGE₁, resulting in reduced levels of cyclic AMP, and thereby affecting parts of the immune system causing selective hyperactivity.

Such data have stimulated interest in whether EFA-containing oils, particularly oils such as evening primrose oil that are rich in the ω -6 EFAs, are of value in the treatment of atopic dermatitis. More recently, borage oil (also known as starflower oil) has become of interest because of its high GLA content, which is two to three times higher than that of evening primrose oil [13,14].

While there have been a number of reviews on the use of evening primrose oil in atopic dermatitis, there have been very few, if any, comprehensive reviews focused solely on borage oil. One meta-analysis [15] considered all types of EFA supplementation including borage oil but was published several years ago and does not include more recent important data. The aim of this article is to outline the rationale behind the interest in the potential use of borage oil in atopic dermatitis and to review the clinical data on its use in this indication. This review focuses only on data relating to borage oil specifically. Studies testing GLA alone or other GLA-containing oils may not be applicable to borage oil because activity of different GLA-containing oils is potentially affected not only by the GLA content but also by the position of the GLA on the triglyceride and the balance between ω -6, ω -3, ω -9, and other fatty acids present in the oil [9,13,14].

Rationale for borage oil supplementation in atopic dermatitis

Borage oil contains high levels of the ω -6 series EFAs that are particularly important in skin structure and function, among other functions [8]. Borage oil does not contain significant amounts of the ω -3 series EFAs; while the ω -3 EFAs have some role in maintaining skin health, they are more important for neuronal development and are of particular importance in the retina, brain, and cardiovascular systems [16].

Within the body, the ω -6 series of EFAs derives from linoleic acid, which is converted to GLA and subsequently other important EFAs such as dihomo-gamma-linolenic acid (DGLA) and arachidonic acid, as shown in Figure 1. (Within the body, EFAs are present as unesterified fatty acids or as components of cholesterol esters, triacylglycerols, and phospholipids. For simplicity, such distinctions will not be made in this article except where specifically necessary.) For both ω -6 and ω -3 EFAs, metabolism involves alternating steps of desaturation and elongation. Binding to the desaturase enzymes is competitive and thus increasing the levels of ω -6 EFAs can affect metabolism of the ω -3 EFAs and vice versa.

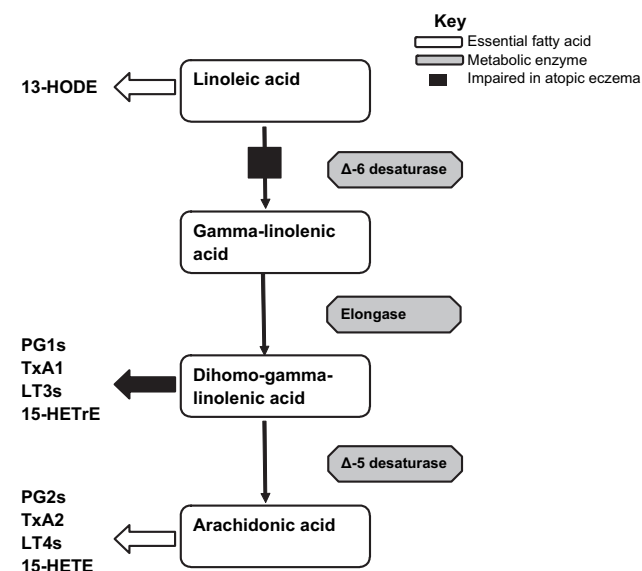


Fig. 1. Pathways of omega-6 essential fatty acid metabolism of interest in the treatment of atopic eczema. The black box indicates the metabolic step believed to be impaired in atopic eczema. This potentially affects production of all metabolites beyond this point. Supplementation with gamma-linolenic acid in borage oil is believed to shift metabolism of dihomo-gamma-linolenic acid toward anti-inflammatory products such as PGE₁ and 15-HETRe (shown by the black block arrow) rather than toward arachidonic acid and production of pro-inflammatory mediators such as LTB₄ [6,8–10]. 13-HODE, 13-hydroxyoctadecadienoic acid; 15-HETE, 15-hydroxyeicosatetraenoic acid; 15-HETRe, 15-hydroxyeicosatrienoic acid; LT, leukotriene; PG, prostaglandin; Tx, thromboxane.

Borage oil normally contains approximately 35–40% linoleic acid and 22–24% GLA, although some individual products contain more or less, as is shown in Table 2. Borage oil also contains saturated and monosaturated fatty acids and ω -9 series fatty acids. (ω -9 fatty acids are not true EFAs because they can be synthesized within the body.) The GLA content of borage oil is higher than most other similar oils, with the possible exception of fungal oils (GLA 15–25%) and some, but not all, preparations of blackcurrant oil (GLA 12–20%) [9,13,14,17]. The composition of borage oil differs significantly from that of evening primrose oil, which normally contains around 70–80% linoleic acid and 8–12% GLA. Conventionally, evening primrose oil has been perceived as one of the most reliable natural sources of GLA, and it is the most widely studied of the ω -6 EFA oils in atopic dermatitis [19,20]. It is not yet fully established whether the higher GLA content of borage oil directly translates in terms of relative *in vivo* potency and biological activity compared with evening primrose oil. [9,13,14].

Although borage oil is edible, it is not widely used as a culinary oil.

Role of linoleic acid

The linoleic acid in borage oil may contribute to its therapeutic actions in atopic dermatitis. Linoleic acid has a direct role in maintaining the integrity of the water permeability barrier of the skin [8,10,21,22].

Topical application of borage oil normalized impaired barrier function of the skin, as measured by TEWL, in infants and children with seborrheic or atopic dermatitis [23,24]. In healthy elderly people, borage oil capsules provide 360 or 720 mg/d. GLA significantly improved cutaneous barrier function with a mean decrease of 11% in TEWL [25].

Table 2

Comparison of typical fatty acid compositions of borage oil and evening primrose oil [9,13,14,17,18]. *

Common name [†]	Lipid name [†]	Borage	Evening primrose
Saturated fatty acids total		12–17	6–14
Palmitic	16:0	9–12	5–10
Stearic	18:0	3–5	1–4
Monounsaturated fatty acids total		5	—
Gadoleic	20:1	5	—
Omega-3 series polyunsaturated fatty acids total		0–5	0–1
Omega-6 series polyunsaturated fatty acids total		50–68	72–94
Linoleic	18:2 (n-6)	34–42	65–80
Gamma-linolenic	18:3 (n-6)	16–26	7–14
Eicosadienoic	20:2 (n-6)	—	—
Dihomo-gamma-linolenic	20:3 (n-6)	—	—
Arachidonic	20:4 (n-6)	—	—
Omega-9 series monounsaturated fatty acids total		15–19	6–12
Oleic	18:1 (n-9)	15–19	6–12
Omega-9 series polyunsaturated fatty acids total		5–6	—
Erucic	22:1 (n-9)	3–4	—
Nervonic	24:1 (n-9)	2	—

—, negligible (generally <0.5%) or zero levels; however, in some cases these fatty acids may be present but were not reported in the analysis the data were taken from.

* Ranges also include data from numerous individual commercially available products that provided an analysis of the fatty acid composition of their product.

[†] Nomenclature is derived from: (i) GP Moss. IUPAC-IUB Commission on Biochemical Nomenclature. Nomenclature of Lipids. Appendix A: Names of and symbols for higher fatty acids [online]. Available at: <http://www.chem.qmul.ac.uk/iupac/lipid>. Accessed June 20, 2007. (ii) Nutrition Data—Fatty Acids [online]. Available at: <http://www.nutritiondata.com/topics/fatty-acids>. Accessed June 20, 2007. The full systematic name for each fatty acid can be found at these sites.

The major metabolite of linoleic acid in the skin is 13-hydroxyoctadecadienoic acid (13-HODE), which has antiproliferative actions [10]. When compared with safflower oil in animal models, borage oil produced either similar or lower levels of 13-HODE in the skin (Table 3) [26,27]. Safflower oil would be expected to produce significant levels of 13-HODE because it is high in linoleic acid.

Role of subsequent EFAs

While linoleic acid has some role in skin function, it is the EFAs and eicosanoid products later in the ω -6 metabolic pathway, e.g., GLA, DGLA, and arachidonic acid and their products, that are proposed to be more important in atopic dermatitis and the possible therapeutic effects of borage oil [6,8,10].

The vital first stage in the metabolic pathway of the ω -6 EFAs is desaturation by the enzyme delta-6-desaturase, which converts linoleic acid to GLA. This is a rate-limiting step that is relatively inefficient in humans and is suggested to be impaired in patients with atopic dermatitis [8,9]. Such an impairment would affect production of not only GLA but also all subsequent EFAs and their products [6–8].

Supporting the hypothesis of dysfunction of the delta-6-desaturase enzyme, studies have shown atopic dermatitis to be associated with increased levels of linoleic acid and decreased levels of the subsequent ω -6 EFAs such as GLA, DGLA, and/or arachidonic acid. Such EFA imbalances have been shown in the

Table 3
Mechanistic effects of oral supplementation with borage oil (Bo)^a

Study group (reference)	Regimen	Tissue	Mean EFA levels at the end of treatment (% of total fatty acids)						Other effects of Bo vs control
			GLA		DGLA		AA		
			Bo	Control	Bo	Control	Bo	Control	
Human studies									
Healthy adult volunteers (n=12) [28]	Bo (GLA 480mg/day) x 6 wks ^b	PMN ph-L	–	–	1.96 [*]	1.45	9.77	9.33	LTB4 generation inhibited by 46% [*]
	Bo (GLA 1500mg/day) x 6 wks ^b	PMN ph-c	–	–	0.64 [*]	0.28	0.97 [*]	0.59	LTB4 generation inhibited by 65% [*]
		PMN ph-e	–	–	0.90 [*]	0.44	0.74	0.67	
Children aged ≤4 years with AD (n=20) [29]	Bo 60 oral drops (GLA 16.5%) x 12 wks ^d	EM lipids	0.76	0.71	1.67	1.81	3.53	3.91	
Neonates at risk of AD (n=121) [18]	Bo 446mg (GLA 103mg/day) x 6 mo	Plasma ph-L	0.11 ^{††, c}	0.075 ^c	3.1 ^{††, c}	2.6 ^c	7.3 ^{**, c}	6.3 ^c	
Animal studies									
Guinea pigs [27]	Bo (GLA 25%) as 4% w/w of diet x 8wk	Epidermal ph-L	0.66 ^{††}	–	2.07 ^{††}	0.5	10.62 [†]	7.94	13-HODE decreased by 55%. ^{**, c} PGE1 increased to 2 ng/mg protein. ^{**, c,e} 15-HETrE increased 3-fold. ^{††, c} PGF _{2α} , PGE ₂ and PGD ₂ increased by 74, [*] 56 ^{**} and 83%. [*] NS change in 12-HETE and 15-HETE
Guinea pigs [26]	Bo-EE (GLA 39.5%) as 5% of diet+1% safflower oil x 8 wks	Epidermal ph-c	NR	NR	1.27 [*]	0.26	3.77 [*]	2.45	NS change in 13-HODE.
		Epidermal ph-e	NR	NR	2.85 [*]	0.90	14.26	11.30	15-HETrE increased 4-fold. [*]
		Epidermal ph-s	NR	NR	2.50 [*]	0.71	1.92	1.91	12-HETE increased 36% [*]
		Epidermal ph-i	NR	NR	2.70 [*]	0.64	7.30	6.16	15-HETE increased 12% [*]
									Leukotriene inhibition potential ^f 68% higher than control

AA, arachidonic acid; AD, atopic dermatitis; Bo-EE, ethyl ester concentrate of borage oil; DGLA, dihomogamma-linolenic acid; EM, erythrocyte membrane; GLA, gamma-linolenic acid; LT, leukotriene; NR, not reported; NS, not significant; PG, prostaglandin; ph-c, phosphatidylcholine; ph-e, phosphatidylethanolamine; ph-i, phosphatidylinositol; ph-L, phospholipids; ph-s, phosphatidylserine; PMN, polymorphonuclear neutrophil; wk, weeks; w/w, weight by weight; 13-HODE, 13-hydroxyoctadecadienoic acid; 15-HETE, 15-hydroxyeicosatetraenoic acid; 12-HETE, 12-hydroxyeicosatetraenoic acid; 15-HETrE, 15-hydroxyeicosatrienoic acid; –, trace or undetectable levels

^a Only borage oil and control arms from each study are included; some studies also tested other types of oils. Control was olive oil [28,29] sunflower oil [18], or safflower oil [27]. In Miller et al. [26], all arms received 1% safflower oil, and the control group additionally received 5% hydrogenated coconut oil.

^b Low-dose and high-dose Bo were tested in separate study phases, separated by 6 months.

^c Values estimated from a graph.

^d Dosage not reported.

^e PGE₁ levels undetectable in control group.

^f The leukotriene inhibition potential was calculated by factoring in both the epidermal level and the potency in inhibiting LTB4 generation of all 15-lipoxygenase products derived from the essential fatty acids contained in each oil.

^{*} $P < 0.05$ versus control

^{**} $P < 0.01$ versus control

[†] $P < 0.005$ versus control

^{††} $P < 0.001$ versus control.

umbilical cord blood of neonates preceding development of atopic dermatitis [12], in the breast milk of mothers of babies who subsequently develop atopic dermatitis [30,31], and in adipose tissue and the phospholipids of serum, plasma, and red blood and mononuclear cells of children and adults with established atopic dermatitis [6,7,32–37]. However, not all data have clearly shown such a relationship [6,38].

If the proposed hypothesis of abnormal EFA metabolism in atopic dermatitis is correct, it is of potential therapeutic significance that borage oil supplies a high level of GLA directly. The GLA content is also important because linoleic acid is not converted into GLA to any significant extent in the skin itself because the required desaturase enzyme is not present in adequate amounts. Only a small amount (5–10% or possibly even less) of the linoleic acid in borage oil would be expected to be converted to GLA. Borage oil does not contain DGLA or arachidonic acid. However, GLA is readily converted to DGLA in the body by the elongase enzyme [9,10,39]. The supply of GLA by oral borage oil increases levels of DGLA in phospholipids, including the lipids of the skin (Table 3) [18,26–29,40,41]. Levels of GLA itself can be relatively low because of its rapid metabolism. The reported effect of borage oil on arachidonic acid levels is more variable (Table 3).

These ω -6 EFAs have effects on skin both as components of membrane structures and through biochemical effects such as modulating cytokine release and activity [9]. The eicosanoids produced from the ω -6 EFAs modulate normal skin physiological processes, and they can have anti-inflammatory or pro-inflammatory effects depending on concentrations and which agents predominate [6,9,10]. Supplementation with ω -6 EFAs is believed to alter eicosanoid metabolism to shift the balance toward production of anti-inflammatory prostaglandins (PG) and leukotrienes (LT) [6,8,10].

GLA supplementation increases levels of DGLA in the skin, which leads to increased production of the anti-inflammatory products PGE₁ and 15-hydroxyeicosatrienoic acid (15-HETrE; also known as 15-OH-DGLA) that are metabolites of DGLA [6, 8–10]. Increased epidermal production of one or both of these anti-inflammatory mediators has been demonstrated in animals supplemented with borage oil or ethyl esters of borage oil (Table 3) [26,27,42]. Increased production of PGE₁ is particularly important because this prostaglandin has diverse desirable actions. As well as being an anti-inflammatory agent, PGE₁ modulates immune responses and inhibits phospholipase A₂, which is involved in the release of arachidonic acid during inflammation [9].

Arachidonic acid has important biological functions in the skin and is an essential constituent of membranes. However, some of the arachidonic acid-derived eicosanoids, especially LTB₄, have pro-inflammatory activity when present in high concentrations and are at least partially responsible for the pain, redness, and swelling of acute inflammation [9,10,43]. The balance between DGLA and its products and arachidonic and its products may be one of the key factors in determining whether GLA supplementation produces pro-inflammatory or anti-inflammatory actions. Importantly, the activity of the enzyme delta-5-desaturase required for conversion of DGLA into arachidonic acid is rate-limited and effectively absent in the skin [10]. Thus, while oral borage oil supplementation does increase arachidonic acid levels in phospholipids, the increases are usually moderate compared to the proportional increases in levels of DGLA (Table 3). As well as being converted to anti-inflammatory products, DGLA seems to have a role in maintaining arachidonic acid in membranes, where it has desirable actions.

Furthermore, the presence of high levels of DGLA prevents the conversion of arachidonic acid to potentially harmful metabolites [9].

The most pro-inflammatory product of arachidonic acid is LTB₄. In healthy adult volunteers, dietary supplementation with borage oil 480 or 1500 mg/d elevated DGLA levels in polymorphonuclear neutrophil (PMN) phospholipids, and this paralleled a decrease of 46–65% in the capacity of calcium ionophore-activated PMN to generate LTB₄ (Table 3) [28]. The ability of borage oil to suppress generation of LTB₄ from PMNs is believed to be primarily mediated by the hydroxy derivative of DGLA, 15-HETrE [26]. Epidermal levels of 15-HETrE were increased three- to four-fold after oral supplementation with borage oil (or ethyl ester concentrates of borage oil) in guinea pigs [26,27]. Borage oil has also been reported to modify PMN activation responses in guinea pigs [44].

Epidermal levels of the arachidonic acid-derived series 2 prostaglandins, including PGE₂, PGF_{2 α} , and PGD₂, were also increased by oral borage oil supplementation in guinea pigs (Table 3) [27]. While PGE₂ is considered to be primarily pro-inflammatory, this may be concentration-dependent. PGD₂, and possibly PGF_{2 α} , has anti-inflammatory activity [45]. Oral borage oil was also found to increase, or not significantly change, levels of the arachidonic acid derivative 15-hydroxyeicosatetraenoic acid, which is also anti-inflammatory [10,26,27].

One clinical study that failed to find a greater improvement of atopic dermatitis with borage oil than with olive oil placebo reported that erythrocyte membrane arachidonic acid levels were increased versus baseline with both borage oil and the olive oil control (Table 3; statistical significance not reported) [29]. Of note, with olive oil treatment there was an increase in levels of the ω -3 EFA eicosapentaenoic acid (EPA). In contrast, borage oil appeared to divert metabolism away from the ω -3 pathway and slightly reduced EPA levels. EPA is a precursor to LTB₅, which has lower inflammatory potential than LTB₄. Furthermore, where there are greater levels of EPA, there is less production of LTB₄ and PGE₂ from arachidonic acid. The authors of the latter study concluded that the therapeutic efficacy of borage oil was limited by the inflammatory actions of arachidonic acid-derived eicosanoids, which were not countered by greater EPA production as was seen with olive oil [29]. In contrast, authors from another study concluded that although borage oil slightly increased arachidonic acid levels in infants, there appeared to be sufficient production of the anti-inflammatory products of DGLA (i.e., PGE₁ and 15-HETrE) to inhibit formation of pro-inflammatory arachidonic acid-derived metabolites [18].

Interestingly, GLA also has an antibacterial effect. In particular, it has bactericidal activity against *S. aureus* colonized on skin, which is a common problem in atopic dermatitis [46].

Efficacy of borage oil in atopic dermatitis

A literature search not limited by date or language identified 11 clinical trials of oral borage oil [17,29,40,41,47–53] and one clinical trial of topical borage oil [54] for treatment of atopic dermatitis. Additionally, a study of preventive use of borage oil supplementation in neonates at risk of developing atopic dermatitis was included [18]. All studies that assessed clinical outcomes with use of borage oil for either treatment or prevention of atopic dermatitis were included. The total number of patients in all studies was 812.

All the trials of borage oil were controlled, and most were double-blind and randomized. However, most of the studies were likely underpowered given that power calculations

indicated that a sample size of at least 120 patients was needed to provide an accurate result, a criterion that was met in only three studies [18,40,50]. Many studies enrolled heterogeneous patient populations without clearly defined inclusion and exclusion criteria. A wide variety of outcome measures were used in the trials, but this reflects the current lack of consensus about how to best measure disease severity in atopic dermatitis. All studies were conducted in Europe.

Overview

Of the 12 studies of oral or topical borage oil for treatment of atopic dermatitis, a significant effect was reported in five studies [17,41,47,51,52], while another five studies found borage oil to be ineffective (Table 4) [29,48–50,54]. In the remaining two studies, a response to borage oil was seen in only some patients [40,53].

Although it is difficult to draw firm conclusions about the efficacy of borage oil on the basis of the available data, it is reasonable to suggest that borage oil potentially has some beneficial effect but is unlikely to have a profound clinical effect. Importantly, the majority of studies found at least some beneficial effect or could not exclude the possibility that the treatment had a small effect that was not detected. The reliability of the data from studies that found borage oil to have a significant effect is unclear because the studies were small and had other methodological limitations [17,41,47,51,52]. Results may also have been confounded by the large placebo effect reported in a number of studies [29,40,48,49,53].

An important study that was not included in the previous meta-analysis of GLA supplementation including borage oil [15] was the large study by Takwale et al. that was reported in 2003 [50]. This study was well designed and adequately powered ($n = 151$; 140 evaluable) and used a high dose of oral borage oil (4000 (GLA 920) mg/d for adults; 2000 (460) mg/d for children) for 12 weeks. Borage oil was not found to be effective. There was a large placebo effect, and the mean six area, six sign atopic dermatitis score fell from 30 to 27 in the borage oil group and from 28 to 23 in the placebo group. However, the authors concluded that their data could not exclude the possibility that borage oil has a small beneficial effect.

In the other large trial by Henz et al. [40], there was no significant difference between the borage oil and placebo groups over 24 weeks of treatment in the primary efficacy endpoint, which was the total amount of corticosteroid used up to the time a response was achieved (defined as a 50% reduction in the Costa Score). Borage oil did improve erythema, vesiculation, crusting, lichenification, and insomnia, but not pruritus, which is often the most distressing symptom from the patient's perspective. Importantly, this study identified a subgroup of patients (with adequate systemic absorption and metabolism of GLA and good compliance) in whom borage oil had a significant effect (see Response according to patient characteristics). The results of this study are somewhat difficult to interpret because they varied greatly between the four treatment centers involved in the study, which may have been related to different patterns of rescue corticosteroid use. Nevertheless, this study is important because of its size. Also it was one of the few to clearly define a relatively homogeneous group of patients; only patients with moderate stable atopic dermatitis who were aged ≥ 14 y were included. One hundred patients were treated with oral borage oil 1500 mg twice daily (GLA $\approx$ 690 mg/d) or placebo (bland miglyol oil) for 24 wk.

Only one study compared borage oil to another potential treatment for atopic dermatitis. Oral borage oil and evening

primrose oil were compared at equivalent GLA dosages in a very small study (10 patients per group) [52]. However, the results are brought into question because there was no placebo arm. The response rates of 90–100% that were reported for the two treatments appear to be unrealistic when compared to results from other trials and may indicate that it was uncontrolled for placebo effect.

The data with regards to whether borage oil is corticosteroid-sparing are contradictory [17,29,40,50]. This issue is complicated because corticosteroids may interfere with the effects of GLA supplementation [19]. Thus, a number of studies did not allow corticosteroids to be used during the study treatment period.

There are only limited data regarding whether topical application of borage oil is effective. In 100 adults and children with atopic dermatitis affecting the extremities, 10% borage oil in urea-containing emollient cream applied twice daily to the arm or leg on one side of the body was no more effective than the same urea-containing but GLA-free emollient cream applied to the contralateral side [54]. However, both sides of the body would be expected to improve if topically applied borage oil has beneficial systemic effects and/or improves skin distant from the site of application, as has been previously reported [23,55]. In a small placebo-controlled Japanese study, erythema and itch in children with atopic dermatitis were improved by coating undershirts with borage oil [24].

Response according to patient characteristics

Although data were not thoroughly analyzed in relation to this, there is some evidence to suggest that some individuals will gain benefit from borage oil treatment, whereas other individuals will not gain any benefit [40,53]. This might explain the inconsistent and often relatively small magnitude of benefit reported for borage oil when averaged over the entire patient population.

It would be helpful to be able to identify which individuals will respond. Borrek et al. [53] reported that 10 of 24 patients treated with borage oil for 10–14 wk in a crossover trial responded to borage oil, but they were not able to identify any characteristics to define a “responder type.” Two studies suggest that some benefit from borage oil may be achieved when the individual is compliant and when there is good uptake and appropriate metabolism of GLA [18,40]. Van Gool et al. [18] found that in the first 3 mo of treatment with borage oil in neonates, there was a strong negative correlation between the infant's increase in GLA plasma phospholipid concentrations and severity of symptoms. Similarly, Henz et al. [40] reported that borage oil had a significant effect when patients who met any of the following criteria were excluded:

- negligible increase of DGLA levels in erythrocytes
- poorly compliant
- used excessive amounts of corticosteroid cream
- undertook treatment for < 11 wk and did not have a response in that time
- had a decrease in Costa score to < 18 within 2 wk; it is unlikely that such patients truly had stable moderate disease as required by the study's inclusion criteria.

Around one-third of patients treated with borage oil did not have the expected increase in erythrocyte DGLA levels in this latter study [40]. While this could indicate noncompliance, it also suggests that in some patients the GLA in borage oil is not appropriately absorbed or is not converted into DGLA.

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Table 4 (continued)

Study	Regimen	No. patients	Patient population	Results	
				Main findings (scale)	Rating [†]
Van Gool et al. 2003 [18]	Bo* (GLA) mg/d 446 (103)* × 6 mo	121	Neonates aged 7–14 d born to atopic mothers and at high risk for AD	Bo did not prevent development of AD. Trend (NS) toward reduction in severity of symptoms with Bo vs PL (SCORAD)	■

ADASI, Atopic Dermatitis Area and Severity Index; bid, twice daily; Bo, borage oil; bw, bodyweight; co, crossover; CS, corticosteroid; EPo, evening primrose oil; GLA, gamma-linolenic acid; liq, oral liquid; mo, months; mod, moderate; no, number; NR, not reported; NS, not statistically significant; ped, pediatric dosage given to the children in the study; PL, placebo; pt, patient; QOL, quality of life; SASSAD, six area, six sign, atopic dermatitis score; SCORAD, Scoring Atopic Dermatitis index; wk, weeks; y, years

* Oral capsules unless otherwise stated.

† Efficacy rating scale: ■■■, most or all efficacy parameters significantly improved; ■■■, some efficacy parameters significantly improved but interpretation of results limited by mixed findings and/or poor study design; ■■■, improvement observed but not statistically significant; □, no improvement.

‡ GLA content not stated. Bo stated to be Glandol, which is advertised to contain 120 mg GLA per 500 mg Bo capsule.

§ Estimation based on description of GLA content being 17.6%/70.

¶ GLA content not stated. Based on a minimum 23% of GLA content in Bo, as stated in the paper.

|| Primary endpoint: cumulative amount of CS cream used until response (50% reduction in Costa score).

** The intervention was a daily supplement powder containing fish gelatin 135 mg, maltodextrin 397 mg, silicic acid 21 mg, and either Bo 446 mg or sunflower oil 446 mg (PL control) with vitamin C and E. Neonates were also formula-fed from age 2 wk with standard formula not containing GLA or other long-chain polyunsaturated fatty acids.

†† GLA 480 mg/d × 4 wk and then 360 mg/d (age ≥ 4 y) or 240 mg/d (age ≤ 3 y).

‡‡ Foreign language; papers were not fully translated so not all details are available.

§§ Only 32 of the 50 patients were evaluable.

¶¶ For each patient, one side was treated with urea-based emollient cream containing Bo and the other side was treated with the same emollient cream without Bo.

Studies including young children [29,49,50,53] do not support the suggestion that treatment with borage oil at an earlier age before immunological hypersensitivity becomes fully established would be more successful [6]. Borage oil was not more effective in children than in adults in the large Takwale et al. trial [50]. Importantly, supplementation with borage oil from 2 wk of age did not prevent development of atopic dermatitis in neonates at high risk (see Preventive use) [18].

It is unclear whether the effect of borage oil differs depending on whether or not there is an allergic IgE-mediated basis to the patient's atopic dermatitis. Borage oil had a significant effect in the one study that included only patients with atopic dermatitis of presumed allergic basis, but this study was small and had other methodological limitations [17]. The effect of borage oil on IgE levels was inconsistent, with decreases [40], increases [18], and no significant changes [41,48,49] reported.

From the EFA cascade, it seems likely that EFA supplementation targets the inflammatory aspects of atopic dermatitis and would therefore be expected to be most effective in patients with active inflammation [15]. However, borage oil did not provide a significant benefit in the studies involving only patients with active lesions or symptomatic disease [48,53].

The efficacy of borage oil according to severity of disease has not been clearly reported and many patient populations were heterogeneous. However, it seems unlikely that the oil is effective in patients with severe disease. Borage oil was not significantly effective in five of the six studies in outpatients or studies that specified that patients with severe disease were included [29,47,48,50,53,54]. Patients with atopic dermatitis presenting to an outpatient clinic may represent a more severe or poorly responsive population than those treated in primary care.

Response according to duration of treatment and dosage

The effects of GLA supplementation take up to 8 wk to become fully evident [19]. Immediate responses would not be expected because adequate time is required for the normal fatty acid balance in skin cells to be restored. The effects of borage oil have been mainly studied over 12–24 wk of treatment. Little is known about its efficacy or tolerability beyond this timeframe. The only data on long-term efficacy come from five patients who continued long-term open treatment (duration not stated) after completing double-blind treatment in one study [17]. Beneficial effects were reported to be maintained but no specific data were provided.

The dosage of oral borage oil capsules used in the studies of treatment of atopic dermatitis varied from 2000 to 4000 mg/d (400–1000 mg GLA) in adults and young people and 1000 to 2000 mg/d (240–480 mg GLA) in children. No study provided a rationale for the dose used. The GLA content of the borage oil was normally 20–25%, although two studies [29,48] used a borage oil with only around 16% GLA. Efficacy did not appear to be related to dose, and no significant effect of borage oil was found in the large study of high-dose borage oil (920 mg/d GLA) [50].

Preventive use

Atopic dermatitis develops early in infancy and EFA abnormalities in the umbilical cord blood of neonates preceding development of atopic dermatitis have been reported [12]. To investigate borage oil as a preventive measure, 121 neonates at high risk of atopic dermatitis who were born to mothers with a history of atopy were formula fed and randomized to receive

a daily supplement powder containing either borage oil 446 mg (GLA 103 mg) or sunflower oil 446 mg (placebo control) for the first 6 months of life (details provided in Table 4) [18].

Supplementation with borage oil did not prevent the development of atopic dermatitis, which was diagnosed at 1 y of age in 38% of borage oil recipients and 48% of placebo recipients [18]. However, there was a trend toward the severity of symptoms being reduced in the borage oil group. This led the authors to conclude that GLA supplementation influenced the inflammatory but not the IgE-mediated components of atopic dermatitis.

Tolerability

The short-term tolerability of borage oil is good. Studies reported that either no adverse effects occurred or that adverse effects occurred with similar frequency with borage oil and placebo oil (liquid paraffin, olive oil, miglyol, or sunflower oil) [17,18,29,40,47,50]. Clinical laboratory parameters were not adversely affected by borage oil administration.

There are no data on the long-term tolerability of borage oil. Excessive intake of polyunsaturated fatty acids is not recommended; intake from all sources should not exceed >10% of total dietary energy intake [56].

Discussion

The mainstay of treatment of atopic dermatitis is the use of emollients and avoiding aggravating factors, but acute exacerbations can require treatment with topical corticosteroids or possibly other immunomodulators [2–4]. As outlined in Table 1, existing treatment options have various limitations, including significant adverse effects.

There is a proposed pathophysiological basis to support the concept of ω -6 EFA supplementation in the treatment of atopic dermatitis. EFAs play a vital role in skin structure and physiology; EFA deficiency replicates the symptoms of atopic dermatitis, and EFA imbalances have been reported in the blood of patients with atopic dermatitis [6–8]. However, to date, studies of EFA supplementation in atopic dermatitis have produced conflicting results, and the data for evening primrose oil have been surrounded by controversy [2,15,19,20,57]. The evening primrose oil product Epogam was initially licensed for use in atopic dermatitis in a number of countries. The product license for Epogam was withdrawn in the UK in 2002 after a review by the UK Medicines Control Agency and Committee on Safety of Medicines concluded that there was insufficient evidence that these products reached the necessary standard of efficacy for them to be licensed as medicines [19,57].

It was proposed that borage oil could be more effective than evening primrose oil because of its much higher GLA content. However, as with evening primrose oil, this review shows that borage oil does not meet rigorous standards for evidence-based efficacy, even when given in high doses. Nevertheless, the majority of studies of borage oil in atopic dermatitis have shown at least a small degree of efficacy, have found a benefit in a subgroup of patients, or have not been able to exclude the possibility that the oil produces a small benefit. This is consistent with findings from a well-performed meta-analysis of EFA supplementation in atopic dermatitis [15]. Combining results for evening primrose, borage oil, and blackcurrant oil, the overall treatment effect for GLA supplementation (0.15 [range –0.25 to 1.43]) was described as small and probably not clinically important, i.e., equivalent to a 1.5 reduction in Costa score values or about a 5% reduction in severity. For the four trials of borage

oil for which an effect size could be calculated in the meta-analysis, the effect size ranged from –0.25 to 0.53. Although a large clinical benefit could be excluded, the authors stated that they could not exclude the possibility that a small beneficial effect is achieved [15]. Similarly, the large, well-designed study by Takwale et al. [50] did not find borage oil to be significantly effective, but these authors also commented that they could not exclude a small benefit, at most in the region of a two-point improvement in six area, six sign atopic dermatitis score.

It is not clear why results with borage oil have been so variable. The available clinical studies have not identified any clear patterns in response according to age, presence of active lesions, or IgE levels. Efficacy of borage oil does appear to require adequate intestinal uptake of GLA, appropriate metabolism, and incorporation of the EFAs into phospholipids [18,40]. It seems probable that borage oil will be more effective in mild-to-moderate atopic dermatitis rather than more severe cases. Other potential factors affecting response have not been investigated.

Role of borage oil in the treatment of atopic dermatitis

Current guidelines for atopic dermatitis do not support the use of borage oil or other EFA supplementation because efficacy has not been clearly demonstrated [4]. Importantly, borage oil has not been compared to any of the established treatments for atopic dermatitis. Any role of borage oil would be as a maintenance treatment, along with continued emollient use, to control the dermatitis and prevent flare-ups in mild-to-moderate disease. Borage oil is not expected to be of any significant value in the treatment of acute exacerbations or severe disease, where use of topical corticosteroids or other immunomodulators is recommended.

Borage oil is not a proven or widely recognized treatment for atopic dermatitis. However, when a patient specifically expresses interest in a more natural treatment approach rather than use of the established conventional treatments for atopic dermatitis, an 8- to 12-wk trial of nutritional supplementation with borage oil can be suggested along with continued use of emollients, provided disease is not severe. The patient should be given a realistic expectation of the relatively small benefit that can be expected with borage oil. Patients who perceive that borage oil is beneficial may wish to continue the supplement but should be aware that it is not yet known whether efficacy is maintained or whether there are any health risks over the long term. Dosages used should not exceed those tested in clinical trials (1–2 g/d for children and 2–4 g/d for adults). If any worsening of disease is seen, treatment with borage oil should be discontinued.

The greatest advantage of borage oil is its apparent good tolerability, which may appeal to people who are concerned about the adverse effects of corticosteroids. Topical corticosteroids cause cutaneous and potentially, in rare circumstances, serious systemic adverse effects [2,4]. As many as three-quarters of patients, or parents of young patients, with atopic dermatitis express concerns about the adverse effects of topical corticosteroids [58]. One of the most important questions that remain to be answered is whether borage oil is corticosteroid-sparing (see *Directions for further research*).

Directions for further research

Although it has been proposed that disturbance in EFA metabolism is an important factor in the pathogenesis of atopic dermatitis [6,8], this concept is not universally accepted and remains controversial [57,59,60]. This review is not intended to

contribute to this debate, but rather to provide a balanced summary of the available data on borage oil in atopic dermatitis to establish its clinical utility. Nevertheless, the question remains as to why GLA supplementation with either borage oil or evening primrose oil is not highly effective if disturbance in EFA metabolism does play a key role in atopic dermatitis. The most likely answer is that atopic dermatitis is multifactorial. Factors other than deficiency of GLA may also affect the balance of prostaglandin production, and other pathophysiological factors may be more important than such imbalances. Unfortunately, the validity of some of the foundation research in this area has been potentially compromised by commercial interests [59,60]. Any further research into the use of GLA supplementation will be of limited value until direct proof of the role of GLA deficiency in atopic dermatitis can be established.

Nevertheless, in the context of the existing clinical data on borage oil, there are some important issues that have not yet been adequately explored. Perhaps the most important of these is whether borage oil is corticosteroid-sparing. Current data are inconsistent [17,29,40,50] and further clarification is needed. Furthermore, how borage oil will interact with topical corticosteroids needs to be better understood [19]. Corticosteroids interfere with metabolism of DGLA to arachidonic acid and prevent arachidonic acid being released from membranes and producing pro-inflammatory eicosanoids. However, corticosteroids also block the release of DGLA, impeding production of its anti-inflammatory metabolites PGE₁ and 15-HETE. This may counteract the effects of borage oil because the ability to increase PGE₁ and 15-HETE levels is thought to be key to the actions of borage oil in atopic dermatitis [26,27].

Current data raise the possibility that some patients will respond to borage oil while others will not. Further research is required to establish if this is the case, and what the possible reasons are for this variability in response. One of the key questions to address is how patients who are most likely to respond to borage oil can be identified.

It would also be of interest to determine whether combining borage oil with an ω -3 oil would be more effective than borage oil alone in atopic dermatitis. Borage oil supplies only ω -6 EFAs. However, ω -3 EFAs also have some role in skin health, and the ω -3 EFA-derived eicosanoids are involved in inflammatory responses [10,16,43,61]. The ω -3 series EFAs such as EPA and docosahexaenoic acid are found primarily in fish and fish oils, but also some plant oils (mainly as alpha-linolenic acid). The ω -3 and the ω -6 EFAs compete for metabolism by the same rate-limiting desaturation enzymes, and combining them further shifts the balance away from production of arachidonic acid-derived pro-inflammatory eicosanoids toward less inflammatory products [10,43].

Conclusions

The current review identified 11 clinical trials of oral borage oil and one trial of topical borage oil for the treatment of atopic dermatitis, and a further trial of borage oil for prevention of atopic dermatitis in at-risk neonates. Although controlled and usually double-blind and randomized, many of the studies had significant methodological limitations particularly in regards to small patient numbers and heterogeneous and poorly defined patient populations. Possibly in part as a consequence of this, results of the clinical trials of borage oil were highly variable.

Borage oil was reported to be effective for the treatment of atopic dermatitis in five studies, while another five studies found it to be ineffective. In the remaining two studies, a response to

borage oil was seen in only some patients. Borage oil was not effective in preventing development of atopic dermatitis in a neonatal study. However, the majority of studies showed at least a small degree of efficacy or were not able to exclude the possibility that the oil produces a small benefit.

Thus, while borage oil is unlikely to have a highly significant clinical effect, it is possible that it will be therapeutically useful in some individual patients with less severe atopic dermatitis. Where patients, or parents of young patients, express a desire to try a more natural treatment approach, a 2- to 3-mo trial of borage oil can be suggested and the response monitored. If future research can establish which patients are more likely to respond to borage oil, its clinical utility may be increased.

We are still left with the fundamental question of what role EFA metabolism plays in atopic dermatitis, and why attempts at GLA supplementation have not been as successful as would be expected if proposed EFA-mediated pathophysiological mechanisms are central to atopic dermatitis.

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