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A review study of therapeutic effects of Iranian borage (*Echium amoenum Fisch*)

Sepide Miraj[1] and Sara Kiani[2*]

[1]*MD, Resident of Obstetrics and Gynecology, Cellular and Molecular Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran*
[2]*Research Assistant, Cellular and Molecular Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran*

ABSTRACT

Echium amoenum belong to Boraginaceae family is a biennial or perennial herb indigenous to the narrow zone of northern part of Iran and Caucasus.the aim of this study was to overview the therapeutic effects of Iranian borage (Echium amoenum Fisch).This review article was carried out by searching studies in PubMed, Medline, Web of Science, and Iran Medex databases .The initial search strategy identified about 98 references. In this study, 43 studies was accepted for further screening and met all our inclusion criteria (in English, full text, therapeutic effects of borage and dated mainly from the year 1991 *to 2016).The search terms were "borage, echiumamonium", "therapeutic properties" ,pharmacological effects. It is commonly used for its rheumatoid arthritis, atopic dermatitis, diabetic neuropathy, and menopause-related symptoms*

Key words:" borage", "echiumamonium", "therapeutic properties", pharmacological effects.

INTRODUCTION

Iranian borage[Echium amoenum] belong to Boraginaceae family[1] that is a biennial or perennial herb[2] native to the northern part of Iran and Caucasus[3]. It grows at an altitude ranging from 60 to 2200 m. It is one of the important medicinal herbs in traditional Iranian medicine. E. ammonium have been advocated for variety of effects such as demulcent, anti-inflammatory[4], antioxidant[5, 6] and analgesic, especially for common cold, anxiolytic and sedative [3, 7, 8] and anticonvulsant effects[9] . The leaves are edible and the plant is grown in gardens for that purpose in some parts of Europe. The plant is also commercially cultivated for borage seed oil extracted from its seeds. Its flowers and leaves, as well as the oil from its seeds are used as medicine. Borage flower and leaves are used for fever, cough, and depression. Borage seed oil is used for skin disorders including eczema, seborrhea dermatitis, and neurodermatitis. It is also used for rheumatoid arthritis [RA], stress, premenstrual syndrome [PMS], diabetes, attention deficit-hyperactivity disorder [ADHD], acute respiratory distress syndrome [ARDS], alcoholism, obsessive compulsive disorder, pain and swelling [inflammation], and for preventing heart disease and stroke[10-12].Borage is also used for a hormone problem called adrenal insufficiency, for "blood purification," to increase urine flow, to prevent inflammation of the lungs, as a sedative, and to promote sweating. Borage is also used to increase breast milk production and to treat bronchitis and colds. Borage is applied to the skin for infantile seborrheic dermatitis and is also used in a dressing to soften the skin. Traditionally, *Borago officinalis* has been usedin hyperactive gastrointestinal, respiratory and cardiovascular disorders[10], Naturopathic practitioners use borage for regulation of metabolism and the hormonal system[13], and consider it to

be a good remedy for PMS and menopause symptoms such as the hot flash. The flowers can be prepared in infusion. One case of status epilepticus has been reported that was associated with borage oil ingestion.

Mechanism of action
Borage seed oil contains a fatty acid called gamma-linolenic acid (GLA). GLA seems to have anti-inflammatory effects. Borage flower might have an antioxidant effect.

Chemical compound
The seeds contain 26-38% of borage seed oil, of which 17-28% is gamma-linolenic acid (GLA), the richest known source(8). The oil also contains the fatty acids palmitic acid (10-11%), stearic acid (3.5-4.5%), oleic acid (16-20%), linoleic acid (35-38%), eicosenoic acid (3.5-5.5%), erucic acid(1.5-3.5%), and nervonic acid (1.5%)(14). The oil is often marketed as "starflower oil" or "borage oil" for use as a GLA supplement, although healthy adults will typically produce ample GLA from dietary linoleic acid[15].

The leaves contain small amounts of the liver-toxic Pyrrolizidine alkaloids [PA] intermedine, lycopsamine, amabiline and supinine and the non-toxic saturated PA thesinine. PAs are also present in borage seed oil, but may be removed by processing. The German Federal Institute for Risk Assessment has advised that honey from borage contains PAs, transferred to the honey through pollen collected at borage plants[14], and advise that commercial honey production could select for raw honey with limited PA content to prevent contamination.

Method
This review article was carried out by searching studies in PubMed, Medline, Web of Science, and IranMedex databases .The initial search strategy identified about 98 references. In this study, 43studies was accepted for further screening and met all our inclusion criteria [in English, full text, therapeutic effects of *borage*and dated mainly from the year 1991 to 2015].The search terms were “borage, echiumamonium”, “therapeutic properties”, pharmacological effects.

Antimutagenic and cytotoxic effects
In an animal study, the protective effect of *Echium amoenum* total anthocyanin extract [ETAE] on partial/transient cerebral ischemia in the rats was evaluated. Results showed that motor function significantly decreased in ischemia/reperfusion [I/R] group as compared to the sham group besides, The anthocyanin rich fraction from *E. amoenum* was found to have protective effects against some brain damages postischemic reperfusion. Nonetheless, the exact mechanisms of the effect of this plant is unknown in the prevention of cerebral ischemia in human.[16]

The genotoxic and antigenotoxic effects of this plant was investigated and it concluded that chloroform extracts were more effective than the methanol extracts of *E. amoenum* [17].

In an in vitro and in vivo study, toxicity, genotoxicity, antigenotoxicity, cytotoxicity of borage seed oil was examined and compared with those of GLA. It showed that Low doses of borage seed oil increased the health span of D. melanogaster while GLA significantly decreased the life span of D. melanogaster. Its antimutagenic and cytotoxic effects of this plant was showed in this study and this herb is able to exerts cytotoxic activity towards promyelocytic HL60 cells.[18]

Antioxidant effects
The protective and antioxidant effects of anthocyanin-rich *E. amoenum* extract were evaluated on human vascular endothelial cells [HUVECs] under oxidative stress. These results suggest antioxidant and protective effect of anthocyanin-rich extract of the petals of *E. amoenum* against H_2O_2-induced oxidative stress in HUVECs. However, further investigations are needed for understanding the detailed mechanisms of cytoprotective effects of this traditional herbal medicine[19].

The nutritional composition and antioxidant activity [in aqueose and solvent extracts] of two medicinal plants of Iranian origin Borage [*Echium amoenum*] and Valerian [Valerian officinalis] used as tea were determined. It showed that borage and valerian exhibited antioxidant activity in all extracts. The antioxidant activity could be attributed to their polyphenol and tannin and flavonoids contents.[8]

Anti-inflammatory, immunomodulatory and antioxidant effects
The protective effect of petals of *E. amoenum* extract [EAE] on a murine model of pancreatitis was examined and it showed that EAE reduce the severity of cerulein-induced acute pancreatitis with an anti-inflammatory, immunomodulatory and antioxidant effects[20].

Anti-Anxiety effect
The efficacy and tolerability of the aqueous extract of *Echium amoenum* in combination with SSRIs in patients with General Anxiety Disorder was assessed. The results showed that *E. amoenum* is effective on anxiety disorder, especially in higher dosage, without any serious side effects [21].

Anxiolytic effect
In an animal study, The anxiolytic effect of the flower of Echium. Amoenum was assessed in a study to determine whether tolerance develops to anxiolytic action of *E. amoenum* in mice. results suggest that one week treatment with extract of the *E. amoenum* does not produce tolerance to its anxiolytic action. Longer period of treatment using implant procedure is probably necessary to cause molecular changes in order to induce tolerance[22].

Immunomodulatory properties
In an animal study,aqueous and alcoholic extracts of Iranian borage for treatment of L. major infection in BALB/c mice was evaluated and it was found that both extracts had immunomodulatory properties and increased the level of IFN-γ and lowered the parasite burden in the proximal lymph nodes and prevented the necrosis of the footpad as compared with the untreated infected mice. [23].

Antiviral activity
An aqueous extract of dried borage (*Echium amoenum*) flowers was tested in vitro for its antiviral activity. results showed that this plant is useful for treatment of infectious diseases and antifebrile activity(24).

Antiobsessive and compulsive effects
The efficacy and safety of an aqueous extract of *E. amoenum* in treatment of obsessive-compulsive disorder was investigated. The results suggest that *E. amoenum* aqueous extract has some anti-obsessiveand compulsive effects.(11).

Antioxidant Activity
the antioxidant properties of the decoction of the flowers of *Echium amoenum* Fisch& C.A. Mey in humans was examined and it showed that this antioxidative stress potential of *E. amoenum* may be due to its bioactive antioxidant components, especially rosmarinic acid and flavonoids. (25).

Anti-depression
Efficacy of an aqueous extract of *E. amoenum* in patients with mild to moderate major depressive disorder was evaluated and it showed that aqueous extract of this plant possess some antidepressant activity(26).

Analgesic effect
The analgesic effect of the methanolic extract of the petals of this plant on male albino mice was evaluated by formalin and hot-plate test. The results suggested that *Echium amoenum* extract possess analgesic effect ;however, further studies are needed to confirm this result(26).

Antibacterial effect
The aqueous extract of borage dried flowers in vitro for its antibacterial activity was tested. The extract showed concentration-dependent antibacterial activity against Staphylococcus aureus 8327. This activity was heat resistant, but the activity of freeze-dried extract gradually diminished during a 90-day period. The traditional use of Iranian borage flowers for infectious diseases and for controlling fever appears to be justified(4).

Anxiolytic effects
The ethanolic extract of *Echium amoenum* flowers at the dose of 50 mg/kg increased the percentage of time-spent and the percentage of arm entries in the open arms of the elevated plus-maze (EPM) and decreased the percentage of time-spent in the closed arms of EPM. Moreover, it prolonged the ketamine-induced latency to sleep but had no significant effects on total sleeping time induced by ketamine. Also, the locomotor activity was affected but not to

the same extent as observed for diazepam. These results suggested that the extract of *E. amoenum* seems to possess anxiolytic effect with lower sedative activity than that of diazepam[3].

Anti-skin disease

The effects of oral evening primrose oil or borage oil for treating the symptoms of atopic eczema was assesse and it showed that use of Oral borage oil and evening primrose oil have no effect on eczema; improvement was similar. Oral BO and EPO are not effective treatments for eczema. Mild adverse effects was observed. Long term use of this herb lead to inflammation, thrombosis, and immunosuppression, bleeding [27].

In a review study, effect of borage oil for the treatment of atopic dermatitis were highly examined.it was shown 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. Borage oil is well tolerated in the short term but no long-term tolerability data are available[28].

In a human study, effects of undershirts coated with borage oil rich in gamma-linolenic acid on atopic dermatitis were evaluated. Those children who had worn undershirts coated with borage oil for 2 weeks showed improvements in their erythema and itch, which were statistically significant. Transepidermal water loss from the back was decreased. The undershirts coated with borage oil were found to be statistically effective, and had no side-effects on children with mild atopic dermatitis[29].Ingestion of selected nutrients modulates dermal properties.it was demonstrated skin properties can be modulated by an intervention with dietary lipids[30].

A mixture of borage oil, catechins, vitamin E and probiotics, all known for their reported effects on epidermal function, in a fermented dairy product, for the first time was investigated. It suggested that this oil has more enhanced bioavailability effect on skin barrier function occurred than reported previously for the individual ingredients. Nevertheless, body mass index significantly influenced various outcome measurements [31].

the systemic efficacy of borage oil and gromwell was compared in epidermal hyperproliferation induced in guinea pigs by a hydrogenated coconut oil diet for 8 weeks and it was demonstrated that gromwell is more effective in reversing epidermal hyperproliferation with a remarkable increase in ceramides[32].

In another study, the effect of Dietary supplementation with GLA-rich seed oil of borage was tested in impaired activity of delta 6-desaturase. The consumption of borage oil induced a statistically significant improvement of cutaneous barrier function in the elderly people, as reflected in a mean decrease of 10.8% in the transepidermal water loss. Thirty-four percent of the people noted itch before borage oil consumption and 0% afterwards. Dry skin was claimed to be reduced from 42 to 14%, but no significant alteration of skin hydration was measured. Besides, the consumption of borage oil by elderly people lead to alteration of FA metabolism and improved skin function[33].

The efficacy of dietary sources of gamma-linolenic acid, borage oil and evening primrose oil are compared in treating skin disorders and it was demonstrated that the antiproliferative efficacy of GLA in the epidermis is preferably exerted from sn-2 stereospecificity of GLA in BO[34].

The effect of a higher percentage GLA-containing borage oil in adults with stable atopic eczema of moderate severity was tested. It showed that Although several clinical symptoms improved compared with placebo, it shows no overall efficacy of GLA-containing borage oil in atopic eczema, with steroid use being the primary response parameter, although it suggests that a subgroup of patients may benefit from this well-tolerated treatment[35].

the efficacy and tolerability of borage oil, which contains a high concentration of gamma linolenic acid, in children and adults with atopic eczema was examined and it showed that there was No significant differences two between treatment groups .besides, it was found that treatments were well tolerated. Gamma linolenic acid is not beneficial in atopic dermatitis[36].

The effect of borage oil against palm seed oil as placebo in a total of 12 patients was investigated and it showed that five out of seven patients treated with borage oil showed a favourable effect with regard to the skin changes assessed by the ADASI-score. In contrast, only one out of the five patients treated with placebo showed a significant improvement in skin changes. In view of the positive effect of borage oil in patients with atopic dermatitis, a trial

therapy for a certain period seems justified. Our study demonstrates both the value of our ADASI-scoring system as well as the advantages that time series or trend analysis methods might have for the evaluation of therapeutic effects in chronic skin diseases such as atopic dermatitis(37).

The effect of different proportions of borage oil on the in vitro transcutaneous delivery of tamoxifen were examined and it was suggested vehicular complexation between tamoxifen and polyunsaturated constituents of borage oil and that such complexes permeated the skin intact. The 1H NMR data supported the hypothesis that such complexation was a consequence of preferential pi-pi orbital interactions between the phenyl groups of tamoxifen and the multiple double bonds of GLA. The mechanism for the permeation of intact complexes across skin remains to be elucidated(38).

Anti-cancer

The the effects of ethanol and 1,8-cineole on the transcutaneous delivery of tamoxifen and gamma-linolenic acid (GLA) as a two-pronged anti-breast cancer therapy was evaluated and it demonstrate the ability of 1,8-cineole and ethanol to enhance the in-vitro permeation of tamoxifen and GLA across the skin and support the plausibility of simultaneously delivering tamoxifen and GLA transcutaneously as a two-pronged anti-breast cancer system.

Anti-inflammatory effect

In an animal study, local modulatory effect of borage oil in the epidermis was evaluated and it found that dietary oils influence the distribution of PUFA in epidermal phospholipids and the epidermal levels of PUFA-derived hydroxy fatty acids. Besides, it showed that the altered profiles of epidermal 15-lipoxygenase products generated from particular dietary oils may be responsible, at least in part, for reported ameliorative effects of oils on chronic inflammatory skin disorders(39).

Neonatal Brain growth

Previous research in rats and mice has suggested that gamma-linolenic acid (GLA) derived from borage oil (BO: 23% GLA) may be an appropriate source for increasing levels of long-chain n-6 FA in the developing brain. Recently, transgenic technology has made available a highly enriched GLA seed oil from the canola plant (HGCO: 36% GLA). The first objective of this study was to compare the effects of diets containing equal levels of GLA (23%) from either BO or HGCO on reproduction, pup development, and pup brain FA composition in mice. The second objective was to compare the effects of the HGCO diluted to 23% GLA (GLA-23) with those of undiluted HGCO containing 36% GLA (GLA-36). The diets were fed to the dams prior to conception and throughout pregnancy and lactation, as well as to the pups after weaning. The behavioral development of the pups was measured 12 d after birth, and anxiety in the adult male offspring was assessed using the plus maze. The findings show that despite equivalent levels of GLA, GLA-23 differed from BO in that it reduced pup body weight and was associated with a slight increase in neonatal pup attrition. However, there were no significant effects on pup behavioral development or on performance in the plus maze. An increase in dietary GLA resulted in an increase in brain 20:4n-6 and 22:4n-6, with a corresponding decrease in 22:6n-3. Again, despite their similar levels of GLA, these effects tended to be larger in GLA-23 than in BO. In comparison with GLA-23, GLA-36 had larger effects on growth and brain FA composition but no differences with respect to effects on reproduction and behavioral development. These findings suggest that the HGCO can be used as an alternative source of GLA(40).

Cardiovascular diseases

the effects of Borage oil on cardiac remodeling after myocardial infarction (MI)was investigated and it illustrated that Borage oil attenuates progression of cardiac remodeling after myocardial infarction and congestive heart failure(41).

Anti-liver disease

the hepatoprotective effect of borage oil containing predominantly gamma-linolenic acid in rats with alcoholic steatohepatitis was evaluated and it showed that Borage oil normalized CYP450 content compared with the ethanol-treated group. CYPI450 2E1 isoform is a main source of free oxygen radicals in the liver of ethanol-treated rats and we propose that the antioxidant effect of borage oil is realized via the normalization of CYP450 content and activities of CYP450-related microsomal oxidases, as borage oil can improve the lipid surrounding of CYP450. In our opinion, the hepatoprotection by borage oil in alcoholic steatosis is connected with its antioxidant properties(42).

Serum activity of exoglycosidases
The aim of this study was to determine the activity of the lysosomal exoglycosidases: alpha-mannosidase [MAN], alpha-fucosidase [FUC], and beta-glucuronidase [GLUCUR] in serum of alcohol-dependent men supplemented and not supplemented with borage oil enriched with vitamin E. Serum was collected from eight social drinkers and 16 alcohol-dependent men after a drinking period. The activity of exoglycosidases and the concentration of protein in serum were determined. The increase in specific activity of MAN and GLUCUR was significant in serum of alcohol-dependent men both not supplemented and supplemented with borage oil enriched with vitamin E, in comparison with the specific activity in serum of social drinkers. In serum of alcohol-dependent men treated with borage oil enriched with vitamin E, specific activity of MAN and GLUCUR fluctuated in comparison with alcohol-dependent men not supplemented. Specific activity of FUC in serum of alcohol-dependent men both not supplemented and supplemented with borage oil enriched with vitamin E showed a tendency to increase, in comparison with social drinkers. Specific activity of FUC had a tendency to decrease in serum of alcohol-dependent men supplemented with borage oil enriched with vitamin E, in comparison with alcohol-dependent men not supplemented. Thus, supplementation of alcohol-dependent men after a long-lasting drinking period with borage oil and vitamin E did not change the rate of catabolism of the oligosaccharide chains of glycoconjugates, as evaluated by serum activity of exoglycosidases[43].

Anti-respiratory problem
In a study, it was investigated whether dietary GLA would suppress biosynthesis of PMN-LTB4 isolated from asthma patients and attenuate asthma and it was demonstrated dietary fatty acid modulation of endogenous inflammatory mediators without side effects and thus warrant further explorations into the roles of GLA at higher doses, leukotrienes and asthma [44].

Preterm infants
To test the efficacy and safety of long-chain polyunsaturated fatty acid [LCPUFA] supplementation with gamma-linolenic acid, a precursor of arachidonic acid, and docosahexaenoic acid in preterm infants. This trial, using the strategy of providing gamma-linolenic acid as a source of arachidonic acid, showed efficacy for growth and for neurodevelopment in boys, with no adverse effects. These data have important implications for LCPUFA-supplementation strategy in preterm infants[45].

There was no significant influence of GLA or fish oil addition to the diet. GLA had only a very limited effect on AA status which was too small to obtain satisfactory concentrations [concentrations similar to breast-fed babies] under the circumstances tested. The effect of GLA on AA is independent of the EPA and DHA content in the diet within the dose ranges studied[46].

Anti-tumor effect
Recent double blind studies have shown some benefit of borage oil in treatment of rheumatoid arthritis. Tumor necrosis factor-alpha has been shown to be a central mediator of inflammatory and joint destructive processes in rheumatoid arthritis. In this paper, evidence from published research is reviewed that indicates gamma linolenic acid component of borage oil increases prostaglandin E levels that increase cAMP levels that in turn suppress tumor necrosis factor-alpha synthesis. If this biochemical path of borage oil is correct then concomitant non-steroidal anti-inflammatory drug use would tend to undermine borage oil effects, and borage oil would be contraindicated in pregnancy given the teratogenic and labor inducing effects of prostaglandin E agonists[47].

Anti-rheumatologic effects
In a review study, the efficacy of borage in rheumatoid arthritis was overviewed and The results of most of these studies suggest some clinical benefit to these treatments[48].

Anti-hypertensive effect
the effects of dietary borage oil on fatty acid composition in the plasma, liver and vascular tissue in WKY and SHR was investigated and it was illustrated that dietary borage oil produces significant changes in the metabolism of GLA which may contribute to its blood pressure lowering effect in WKY and SHR[49].

Potential side effects

the effect of borage extracts on DNA of hepG2 cells using the comet assay was assessed. Although *E. amoenum* and N. jatamansi are highly used in medicine, these herbs have genotoxic effects in determined concentrations and they should be used cautiously(50).

Dietary supplementation of a high-gamma-linolenic acid canola oil (HGCO) containing approximately 36% (w/w) of gamma-linolenic acid (GLA, 18:3n-6) from the seeds of a genetically transformed canola strain, was assessed for its long-term biological effects and it showed that its long term use should be done cautiously(51).

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