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Short communication

A preliminary randomized double blind clinical trial on the efficacy of aqueous extract of *Echium amoenum* in the treatment of mild to moderate major depression☆

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Abstract

Background: Based on a traditional belief, *Echium amoenum* (Boraginaceae) dried flowers are used in Iran as an anxiolytic remedy and also as a mood enhancer. In this study, efficacy of an aqueous extract of *E. amoenum* in patients with mild to moderate major depressive disorder (a score $\geq$18 on the Hamilton depression rating scale) was evaluated.
Methods: 35 patients were randomly assigned to receive daily either placebo or 375 mg of *E. amoenum* aqueous extract in a 6-week double blind, parallel-group trial. Patients were assessed in weeks 0, 1, 2, 4 and 6 by the Hamilton Rating Scale for Depression (HAM-D_{17}), the Hamilton Rating Scale for Anxiety (HAM-A_{14}), and a score sheet on adverse effects.
Results: In week 4, the extract showed a significant superiority over placebo in reducing depressive symptoms. The effect on anxiety was not significant. Headache, somnolence, vomiting, dry mouth, constipation and blurred vision are the most commonly reported side effects. However, with regards to these side effects, no significant difference between placebo and drug treated groups was observed.
Limitations: This study is performed with a small sample size, only with one dose and for 6 weeks.
Conclusion: *E. amoenum* aqueous extract may have some antidepressant activity.

Keywords: Clinical trial; *Echium amoenum*; Major depression

1. Introduction

Echium amoenum Fisch. et May., Boraginacea, is a wild annual herb, which is known in Iran as ox-tongue. This plant grows in northern mountains of Iran (Zargari, 1993). The tea, which is prepared with the flowers of ox-tongue, is one of the most commonly used herbal drinks in Iran. It is locally believed to have mood-stabilizing and anxiolytic effects. Furthermore, in Iranian traditional medicine this plant has also been used to treat anxiety and obsession and for mood enhancement (Moemen, 1967). Recently, anxiolytic effects of the aqueous extract of *E. amoenum* flowers have been shown in mice (Shafaghi et al., 2002). The extract was effective at intraperitoneal doses of 80–125 mg/kg (Shafaghi et al., 2002); with doses as high as 6 g/kg no toxicity was observed (unpublished data).

The extract contains flavonoids, saponins, unsaturated terpenoids and sterols (Shafaghi et al., 2002). On the other hand, the widely known traditional antidepressant medication, St. John's Wort, also contains flavonoids and is thought to exert its effect through flavonoids (Butterweck et al., 2004). Therefore, the presence of flavonoids in the *E. amoenum* extract was another convincing cause to carry on a clinical study on the possible antidepressant effect of the plant.

We examined the efficacy and safety of the aqueous extract of *E. amoenum* in treatment of mild to moderate major depressive disorder in Iranian patients.

Abbreviations: ANOVA, analysis of variance; DSM-IV, fourth edition of the Diagnostic and Statistical Manual of Mental disorder; HAM-A; Hamilton Rating Scale for Anxiety; HAM-D; Hamilton Rating Scale for Depression.

☆ Part of the results of this study has been published in Persian in Iran in "Journal of Medicinal Plants" (Saiiah Bargard et al., 2004).

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2. Methods

2.1. Participants and setting

Participants were patients who referred to the outpatient clinic of Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, with complaint of depressed mood. Participants were eligible for the study if they met DSM-IV criteria for mild to moderate major depressive disorder (American Psychiatric Association, 1994), had baseline score of 18 or higher on the Hamilton Rating Scale for Depression (HAM-D_{17}) (Hamilton, 1967), did not receive psychiatric medication during the 2 weeks prior to referring to the clinic, were between 18 and 60 years of age, and gave written informed consent for participation in the study. Subjects were disqualified if they had psychotic symptoms or suicidal idea, had concomitant other psychiatric or neurological disorder, had significant cardiac, renal or hepatic disease, had a history of sensitivity to medications with plant origin, were pregnant or breast-feeding, or were mentally retarded.

The study was conducted from October of 2003 through June of 2004, in the outpatient clinic of Roozbeh Psychiatric Hospital. Patients could withdraw their participation at any time and transfer to a conventional treatment. Those completing the trial were also guaranteed transfer to a conventional treatment. The study was conducted in accordance with the Declaration of Helsinki and Tokyo for humans and was approved by the ethical committee at Tehran University of Medical Sciences.

2.2. Preparation of medication

The fresh flowers of *E. amoenum* were collected from Chaloos (a city in north of Iran) mountains in May 2002. *E. amoenum* was authenticated by M. Kamalinejad and deposited in voucher no. 628 at the herbarium of Faculty of Pharmacy, Shaheed Beheshti University of Medical Sciences. Air-dried flowers of the plant (10 g) were boiled with 300 ml water for 15 min. The mixture was then filtered and the filtrate was concentrated with water bath at 37 °C. The flowers yielded 4.6 g w/w of extract (46%).

In order to preserve the double blind condition, *E. amoenum* extract and placebo were dispensed in capsules of identical appearance. *E. amoenum* capsules were filled with 125 mg of the extract and talcum powder while placebo capsules were only filled with talcum powder.

2.3. Procedures

After giving written informed consent, participants entered a parallel group, randomized, double blind, fixed-schedule, 6-week clinical trial. Patients were randomly assigned to treatment with the extract (375 mg/day) or placebo, using a computer-generated list of random numbers. All patients received one oral capsule 3 times daily. The dosage regimen was selected based on the traditional report about the efficacy of *E. amoenum* (Moemen, 1967). If the patients had insomnia, they were given oxazepam 5 mg, one oral tablet per night. No other psychotropic medication was prescribed. Participants did not receive any concomitant psychological treatment or psychosocial support. The patients were visited at weeks 0, 1, 2, 4, and 6 of treatment course. Efficacy was assessed using the Hamilton Rating Scale for Depression (HAM-D_{17}) (Hamilton, 1967) and Hamilton Rating Scale for Anxiety (HAM-A_{14}) (Hamilton, 1959). Treatment-induced adverse effects were assessed systematically at each visit by a score sheet designed for the present study. A second year resident of psychiatry (Mehdi Sayyah) who was trained in the usage of the scales performed all clinical research measurements.

2.4. Statistical analysis

Data was examined using intention-to-treat analyses. Missing data were replaced by a last-observation-carried-forward approach. Repeated measures analysis of variance (ANOVA) was used to assess the effects of treatment (two study group), time (weeks of visit), and interaction of treatment and time. Significance of difference in mean scores in each visit was assessed by un-paired Student's *t*-test. The frequency of treatment-induced adverse effects in the study groups was analyzed by Fisher's exact test. All statistical tests were two-sided, and were considered significant at $P<0.05$.

3. Results

3.1. Demographic characteristics

Thirty-five patients were enrolled in the study; 19 were assigned to the extract group and 16 to the placebo group. The characteristics of the two study groups are summarized in Table 1. The two groups were well matched and there were no statistically significant differences between the groups in demographic or recent episode characteristics.

3.2. Retention in treatment

Thirty-one patients completed the 6-week trial, while 4 patients discontinued treatment for consent withdrawal. The treatment retention did not differ between the two groups. Two patients dropped out from the trial in each study group.

Table 1
Demographic data of the patients

Characteristic	Extract ($n=19$)	Placebo ($n=16$)
Age (years, mean±S.D.)	29.5±10.1	34.7±13.6
Sex, *n* (%)		
Women	7 (36.8)	7 (43.8)
Men	12 (63.2)	9 (56.2)
Marital status, *n* (%)		
Married	13 (68.4)	9 (56.2)
Single	6 (31.6)	7 (43.8)
Duration of recent episode (months, mean±S.D.)	2.2±1.7	2.5±1.9