



Antidepressant Effect of *Asperugo procumbens* L. in Comparison with Fluoxetine: a Randomized Double Blind Clinical Trial

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Abstract

Background and objectives: *Asperugo procumbens* is used as antianxiety and depression in Iranian traditional medicine; however no clinical trial has been performed about these properties. The aim of this study was to evaluate the antidepressant efficacy and safety of hydroalcoholic extract of *A. procumbens*. **Methods:** In this double blind study, 30 outpatients with mild to moderate depressive disorder (according to DMS-IV-TR criteria who had a score of 18-25 on the Hamilton Depression Rating Scale (HDRS) were randomly divided in two group, 1) received 10 mg fluoxetine capsule, 2) received 1.2 g dried extract of *A. procumbens* capsule (6 mg flavonoid,) orally per day. Patients were followed up for 6 weeks; the recovery process was assessed by the HDRS in weeks 0, 2, 4 and 6. **Results:** A significant decrease in HDRS was observed in both groups after the fourth week. After the sixth week, fluoxetine had a greater anti-depressant activity than *A. procumbens* (p value =0.03). There were no significant differences in terms of adverse effects in both groups. **Conclusions:** The hydroalcoholic extract of *A. procumbens* can be considered as an effective and safe remedy for mild to moderate depressive disorder.

Keywords: *Asperugo procumbens*; badranjbuyeh; depression; fluoxetine

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Introduction

Depression (DR) is an increasing public health problem with deteriorating conditions that affects all aspects of individual's life and behavior [1,2]. Social phobia, reduction in daily individual performance, anhedonia, emotional and psychological stress are the common symptoms of DR [1]. Prevalence of the DR is about 10-25% in females and 5-12% in males [3]. According to the WHO reports, more than 350 million persons suffer from DR all over the world. Approximately two thirds of DR patients'

experience suicidal thoughts 10- 15% of them being dead from suicide before the age of 40 [3,4]. Unfortunately, many of these patients being unaware of their disease do not receive any medications. Several synthetic antidepressant drugs are available in pharmaceutical markets; however, their effectiveness are not satisfactory along with undesirable side effects such as dry mouth, hypotension, fatigue, sexual dysfunction and drowsiness as well as drug interactions as the major restrictions for the clinical utility [5].

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In addition, the success rate of treatment is low in which at least 40% of the patients do not response to the antidepressant drugs [6]; therefore, finding safe medications with appropriate therapeutic effects is necessary. People from different regions of the world have been used medicinal herbs to alleviate disorders for many years and the entrance of new herbal medicines in the pharmaceutical industry has been hot topics in the last decades [4,7]. Boraginaceae family includes approximately 100 genera and consists of active ingredients including mucilage, anthocyanins, flavonoids, naphthoquinones, cyanidins and pyrolizidine alkaloids. This family is medicinally used as astringent, wound healing, antimicrobial, antioxidant, anticancer, anti-inflammatory, immunomodulatory, emollient, sedative and antianxiolytic in the form of infusion or poultices. *Asperugo procumbens* L. is the only species of *Asperugo* genus in Boraginaceae family. *A. procumbens* is native to eastern and central Europe, Egypt, west Asia and North America. It is known as “madwort” in English, “Allaf-chasbak” in Persian and “Badranjbuyeh” in Iranian traditional medicine (ITM). In ITM the name of Badranjbuyeh referred to the genus of *Hymenocrater*, *Dracocephalum*, *Asperugo*, and *Melissa* [8,9]. *A. procumbens* with usually paired axillary flowers and enlarging calyx after flowering differs in many respects from more typical borage family plants. The plant is an herb with a slender stem that can grow up to 20-70 cm long (figure 1) [10,11].



Figure 1. The *Asperugo procumbens*, Boraginaceae family [8]

In ITM *A. procumbens* is used as a mild sedative with mood elevating activities for treatment of skin infections and herpes, to strengthen heart and the nervous system. It is, also, useful in all kinds of phlegmatic, hiccup, refreshing and mouth aromatics [12-15]. The antidepressant and sedative-hypnotic potential of *A. procumbens* hydro alcoholic extract had been well established in mice by our team [4]; therefore, in this study we aimed to evaluate the antidepressant activity of *A. procumbens* hydro alcoholic extract in comparison with fluoxetine in the form of a clinical trial.

Material and Methods

Ethical considerations

This double blind clinical trial had been performed in Sari city for 6 weeks (Mazandaran province, Iran). The protocol of the research was designed base on the Declaration of Helsinki and approved by the Ethics Committee of the Mazandaran University of Medical sciences (83-127, 2004-03-02) and Iranian Registry of Clinical Trials (IRCT138709051457N2, 2010-11-02). All patients had been informed from details of the study and signed the consent form optionally.

Preparation of the plant material

Asperugo procumbens was purchased from a grocery in Sari. The plant scientific name was identified and authenticated by the Department of Pharmacognosy, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran. The dried powder of *A. procumbens* was extracted by percolation method in ethanol 70° (plant- solvent ratio was 1:10). The extract was evaporated in a rotating evaporator and solidified under freeze-drier. From 100 g of the air-dried and powdered aerial parts of the plant, 20 g dried extract was obtained (the yield = 20%). Each capsule contained 2 mg of flavonoid.

Total flavonoid assay and drug preparation

The identification of flavonoids in the extract was performed by the cyanidine test [16]. Total flavonoid content was measured by the aluminum chloride colorimetric assay [17]. Ten g of the extract was transferred to the flasks and 20 mL acetone, 2 mL hydrochloric acid and 1 mL of hexamethylenetetramine 0.5% were added. The mixture was protected from light during the procedure and refluxed on a water bath for 30 min. After cooling, the final volume was made up

to 100 mL with acetone. Twenty mL of acetone and 20 mL water were treated with 15 mL ethyl acetate three times. The ethyl acetate phase was washed twice with 50 mL water and made up to 50 mL (P). Two mL of $AlCl_3$ ethanolic was added to 10 mL of the above mixture and made up to 25 mL with methanol/ acetic acid to produce the test solution (T).

The second 10 mL aliquot of P was diluted to 25 mL with acetic acid methanolic solution (C). After 30 min, the absorbance of T was recorded at 420 nm against C. The same procedure was repeated for 30 and 40 mL of S [18]. Total flavonoid content was calculated using equation ($DAB10 = \text{German pharmacopoeia}$). The total flavonoid was assessed three times for *A. procumbens* extract.

The similar capsules in size, shape and color to fluoxetine were filled with 400 mg of dried extract (2 mg total flavonoid).

Patients

18- 65 years old volunteers who had depression disorders were selected from Sari, Iran. Thirty outpatients who met the DSM-IV-TR criteria for major depressive disorder based on the clinical interview with the score of 18-25 on the Hamilton Depression Rating Scale (HDRS) were enrolled to the trial.

Intelligence quotient (IQ) less than 70, positive history of bipolar mood disorder (BMD), psychostimulator agents consumption in the last two weeks, serious medical diseases, allergy and sensitivity to *A. procumbens*, psychotic features, suicidal ideas, suicidal attempt history, pregnancy, positive history of cognitive dysfunction, clinically deterioration, abnormally in paraclinical test (U/A, CBC, T3, T4, TSH, AST, ALT, ALP, K, Na) were proved as exclusion criteria. Patients were randomly divided in two groups in which group one received 10 mg fluoxetine with the same LOT number (Abidi Pharmaceutical Co, Tehran, Iran) and the second received 400 mg of *A. procumbens* capsules twice daily for one week and continuing the treatment three times a day for 5 weeks. Also, famotidine (40 mg/d) or dimeticone (120 mg/d) were prescribed in GI problems and lorazepam (1 or 2 mg/d) in the case of insomnia.

Patients were visited by the psychiatrist to evaluate the clinical symptoms and possible side effects through a checklist every 2 weeks. Also, the 17-item was HAM-D assessed at the baseline

and after 1, 2, 4, and 6 weeks of the medication. The mean decrease in HAM-D score from baseline was considered as the main outcome measure of depression response to the treatment.

Statistical analysis

Chi-square test was used for qualitative variables, and T-test and Fisher's exact test (two sided) was performed for quantitative variables.

Results and Discussion

From 30 selected patients, 25 completed the trial; 3 patients dropped out from fluoxetine group and 2 persons from *A. procumbens* group. 76% of the participants were female. The mean of the age was 33.33 years in fluoxetine group and 34.76 in *A. procumbens* group. Regarding the basic demographic data including age and gender, marital status, occupation and education level, no significant differences were identified between two groups (table 1).

Table 1. Baseline demographic characteristics of two group's patients

Demographic	Fluoxetine	<i>Asperugo procumbens</i>	P
Age (mean±SD)	33.33±11.84	34.76±10.66	N/S
Marital status	Married : 75% (9) Single: 25% (3)	Married : 100%(3) Single: 0	N/S
Gender	Male (4)-33.34% Female (8)-66.64%	Male (2);18.38% Female (11);84.61%	N/S
Occupation	Employed : 58.33%(7) Unemployed:41.66%(5)	Employed: 38.64%(5) Unemployed: 61.53%(8)	N/S

There were no significant differences in the HDRS between the two groups at week 0 (baseline) ($t=1.03$, $P=0.16$). Depressive symptoms were significantly decreased in both groups; but the difference between two groups was not significant at the 2nd and 4th weeks ($t=0.31$, $P=0.76$; and $t=0.89$, $P=0.38$, respectively). However, fluoxetine had a higher antidepressant effect than *A. procumbens* after 6 weeks (table 2). The mean score changes of two groups have been shown in figure 2. As shown in table 3, 10 kinds of side effects were observed in fluoxetine group. The main side effects in fluoxetine group were confusion, nausea, vomiting, headache and dry mouth. The most prevalent adverse effects of *A. procumbens* were headache, increased appetite, palpitation and constipation. The difference between fluoxetine and *A. procumbens* in the frequency of side

effects was not significant. Only two patients were prescribed additional drug (10 mg propranolol, 3 times a day for 3 weeks) for their palpitation.

Table 2. Comparison between mean score of Hamilton Depression Scale score before and after intervention

group time	<i>Asperugo procumbens</i>	fluoxetine	t	p
Baseline	24.7+3.42	22.5+4.56	1.03	0.16
After 2 weeks	15.38+6.78	14.5+5.16	0.31	0.76
After 4 weeks	12.25+6.9	10.16+4.13	0.89	0.38
After 6 weeks	11.5+7.5	6.5+1.8	2.21	0.03

Table 3. Clinical side effects reported as number (percent) in two groups of patients.

Side effects	Fluoxetine	<i>Aseprugo procumbens</i>
Confusion	5 (41%)	1 (7.5%)
Headache	4 (33%)	4 (30%)
Anxiety	2 (16.5%)	3 (23%)
Palpitation	1 (8%)	3 (33%)
Increase appetite	2 (16.5%)	4 (30%)
Decrease appetite	1 (8%)	0
Nausea & vomiting	5 (41%)	2 (15%)
Diarrhea	1 (8%)	1 (7.5%)
Constipation	2 (16.5%)	3 (23%)
Dry mouth	3 (25%)	0

In this research, the antidepressant activity of *A. procumbens* hydroalcoholic was compared with fluoxetine in human model for the first time. The majority of patients were female, as previous studies have reported a twofold rate of depression in females [19-21]. Some researchers believe that women tendency to report depressive symptoms more than men; however, some authors are considering the female gender as a risk factor [22]. According to our data *A. procumbens* possessed significant antidepressant effects on mild to moderate depression. This is in agreement with ITM textbooks such as the Canon of medicine (by Avicenna; 10th- 11th century) [13], Makhzan al -Advieh (by Aghili Khorasani-e Shirazi; 17th-18th century)¹⁵, and Al-Seidaneh Fi'l-Tibb (Abu Rayhan Al-Biruni; 10th - 11th century) [14].

The onset of action of *A. procumbens* was faster than fluoxetine at the baseline but the higher antidepressant activity was observed in fluoxetine group after the 6th week.

As mentioned previously, fluoxetine had a greater effect than *A. procumbens* after 4th week of the trial. It is likely that by increasing the dosage of *A. procumbens* or continuing the trial for more than 6 weeks, more suitable therapeutic effect may be obtained. Regarding that our research was the first clinical trial on *A. procumbens* effects, the dose selection was made

based on the ITM sources. As a result, in this dosage no important or intolerable side effects was observed and the minor side effects of two groups were almost the same.

Our previous study has demonstrated good sedative-hypnotic effects of *A. procumbens* hydroalcoholic extract in animal model and no serious side effects had been observed in mice [4]. Nowadays, complementary medicine has received significant popularity among different populations [23, 24], and many patients suffering from depression prefer to use herbal medicines. The efficacy of some other herbal remedies such as *Hypericum perforatum*, *Passiflora incarnata*, *Valeriana officinalis*, *Stachys lavandifolia* has been already demonstrated in the treatment of depression [25]. Effects of *A. procumbens* on depression can be explained by its multiple chemical constituents and its effects on variety of neurotransmitters involved in pathophysiology of depression. Flavonoids with anxiolytic activities have been used in folk medicine to depress the CNS due to their affinity to the central benzodiazepine receptors [26,27]. Norepinephrine and serotonin are the two neurotransmitters, which mostly involve in pathophysiology of mood disorders. Because of the significant effect of selective serotonin reuptake inhibitors (SSRIs) in treatment of depression, today, serotonin is well known as a neurotransmitter of biological amine type which is most of all related to depression [28]. Fluoxetine is one of the well-known SSRIs by inhibiting the uptake of serotonin by the presynaptic neurons in the brain and enhances serotonin neurotransmission through action on 5HT_{2C} receptors. It has the longest half-life in all SSRIs and may also mediate some of its effects through 5-HT_{2C} antagonism. Fluoxetine does not significantly inhibit norepinephrine and dopamine reuptake [29]. So it can be suggested that the possible mechanism of *A. procumbens* is similar to the SSRIs through serotonin system [30].

In the present study, *A. procumbens* exhibited appropriate antidepressant activity in mild or moderate cases. More clinical trials can be designed to evaluate the *A. procumbens* activity on other types of depressive disorders such as dysthymia, and bipolar depression. The antidepressant activity of many plants is attributing to the flavonoids content [28,30]. May be other active component including terpenoids,

essential oils or alkaloids are responsible for the antidepressant activity. So, further phytochemical analysis of the extract is essential for future studies.

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Author contributions

Mehran Zarghami was the study investigator; Aroona Chabra conducted the phytochemical analysis, comprehensive revision and composition of the manuscript; Mohammad Azadbakht was the study investigator, contributed to the collection of the data and critically revised the manuscript; Alireza Khalilian analyzed the data; Ali Asghar Hoseini contributed to the collection of clinical trial data

Declaration of interest

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

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Abbreviations

DR: Depression; ITM: Iranian traditional medicine; HDRS: Hamilton Depression Rating Scale; IQ: Intelligence quotient; BMD: Bipolar mood disorder