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Original article

# Antidepressant Effect of a Polyherbal Syrup Based on Iranian Traditional Medicine

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## Abstract

**Background and objectives:** Depression is a common and costly public-health disease. It has been considered in Iranian traditional medicine and many herbal combinations have been used for healing depressive-like disorders. Traditional herbal medicines should be converted into common dosage forms for patient acceptance and easier usage. **Methods:** In the present research, a poly herbal syrup containing *Echium amoenum*, *Lavandula angustifolia*, *Melissa officinalis*, *Cuscuta chinensis*, *Vitis* sp., *Prunus domestica* and *Alhagi camelorum* was formulated and its physicochemical characteristics including physical appearance, pH, viscosity, density, dried residue, physical stability and microbiological levels were evaluated. Furthermore, the antidepressant activity was determined by tail suspension test (TST) and also the effect of the formulation on the serum levels of dopamine and adrenaline was assessed in mice. **Results:** The syrup showed to be stable regarding physical changes and microbiological quality control tests. It significantly reduced the time of immobility in TST ($p<0.05$) and increased the serum levels of dopamine ($p<0.001$) more considerable than the positive control group fluoxetine ($p<0.01$). Compared with the saline control group, the serum level of adrenaline in the syrup low dose (3 mL/kg) and fluoxetine groups increased but in high dose of the syrup (6 mL/kg) significantly decreased ($p<0.05$). **Conclusion:** Regarding the modern evidences about the plants used in the poly herbal syrup and physiochemical stability and the considerable results of the in vivo experiments, it could be suggested as a suitable antidepressant agent.

**Keywords:** neurotransmitters; Iranian traditional medicine; Persian medicine; tail suspension test

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## Introduction

The use of herbal drugs has been widely extended in traditional and complementary systems of medicines to treat various diseases [1]. Usage of complementary therapies is widespread between sufferers from mood disorders and among them, depression and anxiety are the most common reasons for the usage of complementary and alternative medicine [2]. Iranian traditional medicine (ITM), also called Persian medicine, owns one of the richest systems of medication, which has been progressed over thousands of years [3]. Depression is a prevalent, chronic and recurring disorder and is also resistant to treatment, which imposes wide costs to patients and the health systems [2]. Depression will be the second pioneer illness in the world in the year 2020 according to the World Health Organization (WHO) [4]. At the moment, common drugs for

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depression are selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and lithium salts and stimulants. These drugs have some disadvantages such as slow onset of action, poor response, high price, easy recurrence of the disease and several side effects [4-6]. Thus, new antidepressants free from these restrictions and also with higher efficacy and lower adverse effects, toxicity and cost are still needed. Depression has been considered in ITM too [7, 8]. Among diverse prescriptions in ITM, a combination of ox-tongue flower, lavender, lemon balm, dodder, large raisins, plum and camel thorn (equal ratio) have been used in the form of "Matbookh" according to "Tebb-e-Akbari*"* prescription for improving depressive like disorders called "Malikhoolia" [9]. Traditional formulations should be converted into new dosage forms for better patient acceptance and easier usage and the prepared syrup could be simply used by patients in the period of depression treatment compared to the traditional "Matbookh" formulation which needed to be prepared for each turn of use. In the present study a polyherbal syrup was formulated and its antidepressant activity was determined by using TST in mice, moreover serum levels of dopamine and adrenaline were measured.

## Material and Methods

### Ethical considerations

The animals were handled in accordance with the guidelines of the NIH Animal Care and Use Committee [10]. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran with the code No. IR.SBMU.RETECH.REC.1397.215, 2018.

## Chemicals

Sodium benzoat and fluoxetine (Sigma-Aldrich, USA), Folin-Ciocalteu (Merck, USA) and dopamine and adrenalin ELISA kits (CUSABIO, Germany) were used in the study. Other reagents were of analytical grade.

## Plant material

Plants required for preparation of the syrup were procured from a local market in Tehran. The samples were identified by botanists at the Herbarium of Traditional Medicine and Materia Medica Research Center (TMRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran. Herbal market samples of *Echium amoenum* Linn. petals, ox-tongue flower, (Boraginacea) (No.459), leaves and flowers of *Lavandula angustifolia* Mill., lavender, (Labiatae) (No.457), aerial parts of *Melissa officinalis* Linn., lemon balm, (Labiatae) (No.458), aerial parts of *Cuscuta chinensis* Lam., dodder, (Cuscutaceae) (No.463), fruits of *Vitis sp*., large raisins, (Vitaceae) (No.461), fruits of *Prunus domestica* Linn., plum, (Rosaceae) (No.462) and manna of *Alhagi camelorum* Fisch.,camel thorn, (No.457) were kept at the Herbarium of TMRC for future references.

### Analysis of plant materials

Quality assessments of each plant material were performed according to pharmacopeia [11-13].

### Formulation of the poly herbal syrup

A decoction was provided from the plant material in equal ratio (9 g each plant). Briefly, petals of ox-tongue flower, leaves and flowers of lavender and aerial parts of lemon balm were heated with distilled water (plant: water 1:7 w/v). When boiling started, crushed plum and large raisins were added to the mixture and boiling continued for 20 min. The mixture was filtered afterwards dodder covered in a cotton cloth was suspended in the mixture for 3 min. The extract was then centrifuged and concentrated by heating till the volume reached to 45 mL. Finally, camel thorn manna was added to the mixture. Considering that the prepared syrup tasted bitter due to *Cuscuta chinensis*, and that camel thorn manna alone was not enough to cover the taste, various sweeteners and flavoring agents including brown sugar, honey, masking flavor, sucralose, lemon and orange essential oils were examined to cover the unpleasant taste of the syrup; among them, sucralose showed to be the best taste covering agent. Therefore, sucralose (0.1% w/v) was added as the masking agent to improve the taste of the syrup. Also sodium benzoate (0.015%) as a microbial preservative was added

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### Physicochemical evaluation of poly herbal syrup

#### Physical examination

Macroscopic characteristics like color, odor, taste and appearance of the syrup were analyzed.

### Crystallization evaluation

Three samples of the syrup were placed in a refrigerator (4 °C) for two weeks and were checked for any sediment thereafter.

**Cap locking**
The syrup was poured into three 60 mL bottles, and the bottles were turned upside down at room temperature. The opening behavior was considered after one week. Cap locking would be confirmed if the cap could not be unlocked simply.

**Dried residue**
Five mL of the final formulation was placed in an oven (110 °C). Two hours later, the sample was weighed after cooling in a desiccator. It was exposed to heat again for 30 min and the process was repeated as mentioned above to reach a steady weight and dried residue was computed. This protocol was repeated 3 times [14].

**Sedimentation**
Three samples were centrifuged at 5,600 rpm for 15 min. The sediment was separated from the solution and dried at 120 °C in an oven for 36 h. It was weighted after cooling.

**pH**
PH of the prepared syrup was determined with a Mettler-Toledo AG, Seven easy apparatus (Switzerland) after calibration with buffers with pH 4 and 7. Three measurements were done at room temperature and their average was reported.

**Density**
Density of the final product was measured in triplicate at room temperature using a 10 mL pycnometer.

**Viscosity**
The viscosity was recorded by placing 600 mL of the product in a Brookfield viscometer type Dv2 Rv (USA); Spindle No.2 with 30 gear speed at room temperature. The test was performed three times[15].

**Temperature stability**
Three samples of 60 mL syrup were placed in refrigerator (4°C) and three others were placed in incubator (40° C). Fourteen days later, the samples were replaced. After 28-days cycle, the samples were evaluated for apparent changes such as uniformity, sedimentation, taste, odor and color.

**Microbial evaluations**
Total Viable Count (TVC) was performed as recommended by WHO. Also, the presence of specific microorganisms (*Escherichia coli* and *Salmonella sp.*) was evaluated [14].

**Total phenolics content**
Total phenolics content was measured by using pyrogallol calibration curve and Folin-Ciocalteu reagent according to British Pharmacopeia [12]. One mL of the syrup was diluted to 10 mL with distilled water. Two hundred µL of Folin-Ciocalteu reagent was added to 50 µL of the diluted syrup (50 µL syrup and 350 µL distilled water), then 2 mL distilled water was added to the combination. The solution was diluted with sodium carbonate (29% w/v) to 5 mL. After 30 min in the dark, the absorbance of all samples was determined at 760 nm. All measurements were performed three times at room temperature.

**Animals**
Six-week-old male BALB/c mice (Pasteur Institute of Iran), weighing 25-30 g, were used in the experiments. The animals were given a period of one week to adjust to the new environment (22±2 °C, 45-60% humidity and 12/12-h light/dark cycle). The animals were fed ad libitum.

**Experimental groups and drug treatments**
The mice were divided into 4 experimental groups (five in each group). Saline control group was administered with 10 mL/kg normal saline (0.9% NaCl). Model groups were treated with 3 and 6 mL/kg of the syrup, respectively and positive control group received fluoxetine at the dose of 3.5 mg/kg [16]. All groups were treated once a day for 14 days via intra-gastric gavage (i.g.) 60 min before TST.

**Tail suspension test (TST)**
The method of the present study was described by Stéru et al. TST is a sensitive and well-designed model for measurement of antidepressant efficacy. It is simple, fast and predictive about antidepressant action of drugs in humans [17,18]. The mice were hung individually using a sticking tape about one cm from the tip of the tail with a clamp (2 cm from the tip of the end) in a box (25 × 25 × 30 cm) in a dark room with minimal background noise for 6 min during videotaped sessions. The syrup was administered half an hour before the test session via gavage. The immobility time due to tail

suspension was recorded by a video camera and a blind observer scored the videotapes for the whole 6 min. The mice were considered immobile when they hung passively and were completely motionless. The collected data were reported as the mean of immobility time (in second ± SEM) [19,20].

**Measurement of serum dopamine and adrenalin levels**

Instantly after behavioral test, the mice were anesthetized using diethyl ether and blood sample were collected from their heart. The serum was separated by centrifugation at 5,000 rpm for 5 min and further evaluated using dopamine and adrenalin ELISA kits (CSB-E08661m; CUSABIO and CSB-E08678r; CUSABIO, respectively) pursuant to the manufacturer's instructions. All samples were analyzed in triplicate and serum levels were reported in (pg/mL).

**Statistical analysis**

All data were represented as (mean±SEM). Data were analyzed using one-way Analysis of Variance (ANOVA) followed by Tukeys test for comparison between all treatment groups using GraphPadInstat program. The data for locomotor activity scores were subjected to student's paired t-test. Probabilities of less than 5% ($p<0.05$) were considered statistically significant.

## Results and Discussion

The results of analysis of the plants, used in the poly herbal syrup have been reported in table 1. They were in acceptable range noted for each plant monograph in pharmacopoeia. The results of the quality assessments tests have been mentioned in table 2 which were acceptable regarding the physical parameters. No contamination or microbial growth regarding total viable count for bacteria and fungi was observed. Also, no growth was detected for *Escherichia coli* and *Salmonella sp*. In microbial evaluation. Both doses of 3 and 6 mL/kg significantly reduced the immobility time in the TST as compared to the saline control group ($p<0.05$) and the reduction was more considerable than the positive control group fluoxetine, demonstrating a significant antidepressant effect (figure 1).

Both doses significantly increased the concentration of dopamine in mice serum more considerable than the positive control group fluoxetine ($p<0.05$) demonstrating a significant antidepressant effect (figure 2). The serum levels of adrenaline in the low dose group and fluoxetine increased but in high dose significantly decreased ($p<0.05$) (figure 3).

In line with increasing popularity of herbal remedies and their widespread use in the treatment of depression due to the better acceptance and lower adverse effects, several investigations have been performed on the efficacy of the herbal ingredients of our poly herbal syrup. Some examples have been mentioned here. In a clinical trial on depression and anxiety *Echium amoenum*, proved to have antidepressant activity [21]. Moreover, Antidepressant effect of *Lavandula angustifolia* , has been reported in several studies [4].

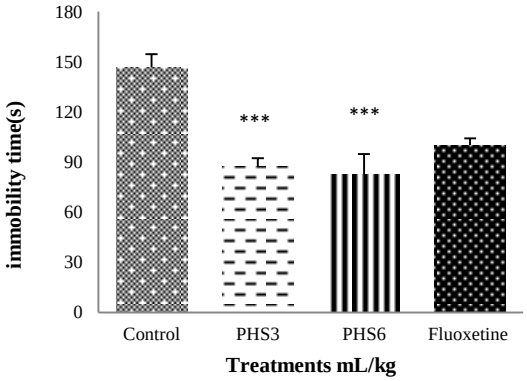


**Figure 1.** Effects of administration of poly herbal syrup (3 and 6 mL/kg; PHS3 and PHS6, respectively), fluoxetine (positive control group 3.5 mg/kg) and 0.9% NaCl (as saline control group 10 mL/kg) on immobility time in male BALB/c mice. Data have been expressed as mean ± SEM ($n$=5). ***: statistical difference in comparison to saline control $p$<0.001

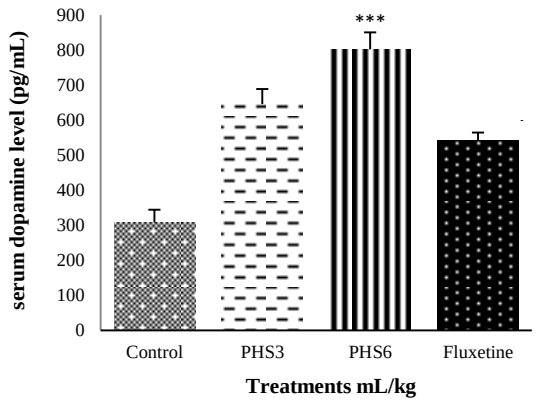


**Figure 2.** Effects of administration of poly herbal syrup (3 and 6 mL/kg; PHS3 and PHS6, respectively), fluoxetine (positive control group 3.5 mg/kg) and 0.9% NaCl (as saline control group 10 mL/kg) on dopamine serum levels in male BALB/c mice. Data have been expressed as mean ± SEM (n = 5). ** and *** statistical difference in comparison to saline control $p < 0.01$ and $p < 0.001$, respectively.

**Table1.** Quality assessment results of *Echium amoenum*, *Lavandula angustifolia*, *Melissa officinalis*, *Cuscuta chinensis*, *Vitis* sp., *Prunus domestica* and *Alhagi camelorum*

| Plant material | Total ash % | Acid insoluble ash % | Loss on drying % | Essential oil % and color | Foreign materials % | Alcohol soluble extractive | Water soluble extractive |
|---|---|---|---|---|---|---|---|
| *Echium amoenum* | 10.0±0.2 | 1.1±0.1 | -* | - | - | - | - |
| *Lavandula angustifolia* | 7.7±0.2 | 0.7±0.1 | - | 0.3±0.20 | - | - | - |
| *Melissa officinalis* | 11.8±0.3 | - | 6.6±0.2 | 0.2±0.01 | 1.6±0.1 | - | - |
| *Cuscuta chinensis* | 8.6±0.3 | 3.3±0.1 | - | - | - | 8.4±0.2 | 15.2±0.3 |
| *Vitis sp.* | 2.1±0.1 | 0 | 10.3±0.4 | - | 0.6±0.01 | 25.7±0.2 | 71.7±0.5 |
| *Prunus domestica* | 2±0.1 | 0 | 2.2±0.1 | - | - | 12.0±0.1 | 50.0±0.5 |
| *Alhagi camelorum* | 2.77±0.1 | - | 1.2±0.1 | - | - | - | - |

*: not determined

**Table2**. Results of laboratory stability testing of the poly herbal syrup

| Parameters | Results |
|---|---|
| Color | Brownish black |
| Odor | Characteristic |
| Taste | Bitter |
| Appearance | Semi-clear liquid |
| Crystallization evaluation | None |
| cap locking | None |
| Density | 1.07g/mL |
| Viscosity | 39.2 cp |
| pH | 4.31±0.02 |
| Dried residue | 27.5 ±0.14% |
| Total phenolics content | 80.4±0.05 (mg/100 mL) (as pyrogallol) |

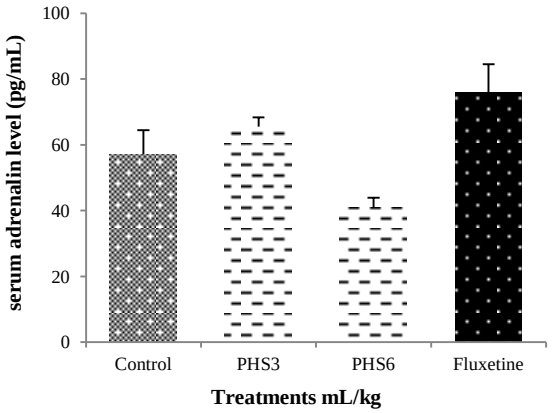


**Figure 3.** Effects of administration of poly herbal syrup (3 and 6 mL/kg; PHS3 and PHS6, respectively), fluoxetine (positive control group 3.5 mg/kg) and 0.9% NaCl (as saline control group 10 mL/kg) on adrenaline serum levels in male BALB/c mice. Data have been expressed as the mean ± SEM ($n$ = 5). **##:** statistical difference to positive control $p <$ 0.01

Researches have confirmed that the mechanism of action in some herbal medicines, such as lavender, with mood elevating effects, may be modulation of neurological pathways (GABAergic systems) [22].Previous researches have shown that the methanol extract of *Mellisa officinalis* L. represented MAO-inhibitory activity because of its flavonoids [23]. The antidepressant-like effects of *M. officinalis* leaves ethanol extract has been also reported in the forced swim test [24]. In addition, *Cuscuta chinensis*, has markedly reduced immobility times in tail suspension test and forced swimming test in mice, compared to imipramine and fluoxetine; the mechanism was suggested to be similar to TCAs or SSRIs and SNRIs [25]. In a clinical trial conducted in Shiraz University about *Cuscuta plantiflora* and *Nepeta menthoides* , 43 patients with major depression were enrolled and devided to two groups, one receiving *Cuscuta plantiflora* and the other *Nepeta menthoides.* Both groups demonstrated significant reduction in total Beck Depression Inventory scores at the end of the trial [26]. Cheng et al. have shown that Tiansi Liquid, a basic traditional Chinese medicine, containing *Morinda officinalis* and *Cuscuta chinensis* had antidepressant-like effects, due to the presence of some flavonoids and chemical ingredients such as kaempferol and quercetin with the mechanism of increasing the levels of NE, dopamine and 5-HT [27]. Aslam et al. have examined the antidepressant effect of *Vits vinifera* juice (4 mL/kg and 8 mL/kg) in mice (forced swimming test and tail suspension test). They have demonstrated that *V. vinifera* increased the levels of serotonin and noradrenalin in the brain tissue [28] while Solanki et al. have proved that grape powder (15 g/L for 3 weeks) in the single-prolonged stress (SPS) rat model prevented SPS-induced increase in corticosterone levels in plasma and reversed behavioral deficits (anxiety and depression) [29]. Also, in ITM texts grape *(V. venifera)* has been prescribed for depression management [30]; whereas, *Alhagi Camelorum* manna has been one of the beneficial sweeteners recommended as a non-pharmacological intervention for depression in ITM [31].

The results of this investigation showed that the syrup represented satisfactory physicochemical characteristics. Physical stability and

microbiological tests indicated that the syrup was stable with no growth of pathogenic microorganisms. It was standardized on the basis of total phenolics content. Both doses of the syrup significantly reduced the immobility time in the TST even more considerable than fluoxetine. TST is extensively used as an animal model of depression to evaluate new antidepressants and there is a which has been shown to be correlated to clinical [20]. Both doses significantly increased dopamine in mice serum more than fluoxetine. Many studies in animal models support the role of dopamine in depression and numerous hypotheses have confirmed that dysfunction of dopamine systems might contribute to depression [32]. The serum levels of adrenaline in high dose of the syrup significantly decreased. Previous reports showed that plasma levels of adrenaline increased in depressed patients with chronic fluoxetine treatment. The plasma level of adrenaline is associated with blood pressure and heart rate; chronic fluoxetine treatment could cause increasing the plasma catecholamines, mild hypertension and tachycardia in rats as well [33]. Since the high dose of the syrup in our study decreased adrenalin serum level in mice, it could be a good candidate as an antidepressant without side effects. The results of the present investigation demonstrated that the poly herbal syrup possibly has a dose-dependent antidepressant activity which makes it valuable for treatment of depression probably due to dopaminergic reuptake inhibition similar to bupropion [34]. It can be an appropriate choice as a herbal origin antidepressant agent that can significantly reduce anxiety levels, regarding its traditional usage and acceptable results of the experiment. The next step would be evaluating the syrup in clinical trials.

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## Author contributions

Maryam Hamzeloo-Moghaddam designed and supervised all the experiments and edited the final copy of the manuscript; Leila Ara carried out quality control of the plants; Sara Zakerin and Maedeh Rezghi performed the formulation and animal studies as well as quality control of the syrup; Homa hajimehdipoor analyzed the data; Sara Zakerin prepared the draft of the manuscript.

## 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

ITM: Iranian traditional medicine; PHS: poly herbal syrup; TST: tail suspension test; AD: adrenalin; DA: dopamine; WHO: World Health Organization