Original Article

A Herbal Syrup: Formulation and Antidepressant Effect in Male Rat

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Abstract

Introduction: Herbal medicines play a significant role in global health-care systems. In this investigation, a polyherbal syrup has been reformulated pursuant to Iranian traditional medicine and its antidepressant effect has been evaluated. **Materials and Methods:** The syrup was prepared by decocting a mixture containing: *Lavandula angustifolia*, *Melissa officinalis, Echium amoenum, Cordia myxa*, *Glycyrrhiza glabra*, *Ziziphus jujuba, Foeniculum vulgare*, *Fumaria parviflora*, *Adiantum capillus-veneris*, and *Alhagi* spp. along with glycerin and potassium sorbate. Physicochemical characteristics of the syrup were examined. An accelerated stability test was carried out for syrup as well. Moreover, antidepressant evaluations were performed by the forced swimming test using the drug as gavage (3.3 mL/kg/day) for three consecutive weeks. The serum levels of serotonin (5-HT), noradrenaline (NA), and brain-derived neurotropic factor (BDNF) were determined in rats as well. Finally histopathological examinations were done on liver, kidney and spleen. **Results:** The herbal syrup was brown in color with a special taste and flavor. Density, pH, viscosity, dry residue, and total phenolics content were 1.085 g/ml, 5.56, 5.35 cP, 15.22%, and 194 mg/100 mL, respectively. The syrup was stable during accelerated stability tests, and no significant changes were observed. The polyherbal syrup exhibited significant antidepressant effects by decreasing immobility time through increasing in NA and 5-HT levels without affecting BDNF levels. Formulated syrup also did not have any toxic effects on the liver, kidney, and spleen. **Conclusion:** The syrup could be an appropriate candidate for pharmaceutical companies after complementary tests such as toxicity and clinical trials.

Keywords: *Depression, forced swimming test, Iranian traditional medicine, syrup*

Introduction

Depression is a major global public health problem and despite the high prevalence, its cure remains difficult.[1] Existing antidepressants have a number of side effects. In addition, the efficacy of these drugs is not satisfactory. So, novel drugs with better efficacy and fewer side effects are desperately needed.[2] Today, the usage of medicinal plants in the cure of different human psychological disorders has become widespread.[3,4] Herbal drugs have an important role in health care.[5] Iranian traditional medicine (ITM) or Persian medicine has been used for many years in the diagnosis and prevention of diseases. Most treatments in traditional medical systems have been historically administered either individually or in combination forms.[6,7] One of the herbal mixtures in ITM is a combination of 10 different herbal ingredients containing *Lavandula angustifolia, Melissa officinalis, Echium amoenum*, *Adiantum capillus-veneris*, *Foeniculum vulgare*, *Ziziphus jujuba, Cordia myxa, Glycyrrhiza glabra, Fumaria parviflora*, and *Alhagi* spp. Manna, which is appropriate for a variety of mental disorders such as depression.[8] This combination should be decocted and used for at least 15 days. The traditional formulations should be converted to a modern dosage form to achieve better patient acceptance and use.[9] Syrups are one of the pharmaceutical dosage forms with suitable taste, appearance, and stability; they can be used in various patients, including children and elderly people.[10] Therefore, most of the herbal formulations traditionally used as decoction can be converted into syrup dosage form. However, the efficacy of novel dosage forms needs to be evaluated in animal models and then, during clinical trial studies. Forced swimming test (FST) is the accepted stress model of depression and most of the antidepressants that are clinically effective in humans have reduced immobility time in the animal FST.[11]

In current research, due to the need to develop herbal remedies for depression, a polyherbal syrup has been formulated according to ITM and quality control tests have been performed.

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In addition, its antidepressant activity was assessed by using FST and measuring the serum levels of serotonin (5-HT), noradrenaline (NA), and brain-derived neurotropic factor (BDNF) in rats to provide a suitable formulation for patients with depression.

Materials and Methods

Plant material

All the species for preparing the syrup were obtained from a herbal market in Tehran. The samples were identified by the botanists at the Herbarium of Traditional Medicine and Materia Medica Research Center (TMRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran. Herbal market samples (No. 465–474 HMS for *Lavandula angustifolia* Mill. Aerial parts, *Foeniculum vulgare* Mill. fruits, *Ziziphus jujuba* Lam. fruits, *Alhagi* spp. Fisch. manna, *Echium amoenum* L. petals, *Cordia myxa* L. fruits, *Glycyrrhiza glabra* L. rhizomes, *Melissa officinalis* L. aerial parts, *Adiantum capillus-veneris* L. whole plant and *Fumaria parviflora* Lam. aerial parts, respectively) were deposited at the Herbarium of TMRC for future references.

Chemicals

Sodium carbonate and potassium sorbate (Sigma-Aldrich, USA), Folin-Ciocalteu, pyrogallol, and glycerin (Merck, Germany) were applied in the study. Analytical-grade solvents were used as well.

Instrumentation

pH of the syrup was assessed with a Mettler-Toledo AG, Seven easy apparatus (Switzerland). The viscosity and rheological behavior of syrup was determined by using a Brookfield Rheometer (Brookfield, DV3 Ultra model, USA).

Quality control of the herbal materials

Quality control assessments of all herbal substances were carried out pursuant to the pharmacopeia.[12,13] For each species, at least a marker was quantified as follows: *G. glabra*: glycyrrhizin by HPLC, *A. capillus-veneris*: mucilage by gravimetry, *F. vulgare*: essential oil and anethol by volumetry and GC, *E. amoenum*: total anthocyanins by UV-Vis, *L. angustifolia*: essential oil by volumetry, *M. officinalis*: total hydroxycinnamic derivatives by UV-Vis, *F. parviflora*: total alkaloids by titration, *Z. jujuba*: pectin and total polysaccharides by gravimetry and UV-Vis, *C. mixa*: mucilage by gravimetry, and *Alhagi* spp. Manna: total polysaccharide by UV-Vis.

Formulation of the syrup

Based on the ITM reference, *Lavandula angustifolia*, *Melissa officinalis*, *Echium amoenum*, *Fumaria parviflora*, *Foeniculum vulgare* and *Adiantum capillus-veneris* (3 parts), *Cordia myxa* (6 parts), *Glycyrrhiza glabra* (5 parts), and *Ziziphus jujuba* (1 part) were powdered coarsely and were extracted by using the decoction method with distilled water for 30 min (plant: water 1:15 w/v). The mixture was filtered afterward and the powdered *Alhagi* manna (6 parts) was added to the mixture, shaken, and filtered. To access appropriate appearance and viscosity, several experimental formulations were produced by using various ingredients containing carbomer 940, carboxy methyl cellulose (CMC), hydroxy propyl methyl cellulose (HPMC), poly vinyl pyrrolidone (PVP), propylene glycol (PG), and glycerin. Potassium sorbate (0.2%) was used in the final formulation as a preservative.

Quality control of the herbal syrup

Macroscopic characteristics

Color, odor, taste, and appearance of the syrup were checked.

Crystallization evaluation

Three bottles of the syrup were placed in a refrigerator (4°C) for 14 days and then they were checked for any sediment.

Cap locking

Three 60 mL bottles of syrup were placed upside down at room temperature. The opening behavior was checked after a week. Cap locking would be approved if the cap could not be opened easily.

Dry residue

Five mL of the syrup was placed in the oven (110°C). After two hours and cooling in a desiccator, the sample was weighed. The process was repeated as described earlier to achieve a constant weight, and dry residue was calculated. This procedure was repeated three times.

Sedimentation

Three samples were centrifuged at 5600 rpm for 15 min. The sediment was removed from the solution, dried at 120°C in an oven, and weighted after cooling.[14]

pH

pH of the formulated syrup was measured at room temperature.

Density

Density of the syrup was measured in triplicate at room temperature by using a 10 mL pycnometer.

Viscosity

The viscosity was calculated by placing 600 mL of the syrup in a Brookfield viscometer; Spindle No.2 with 30 gear speed at room temperature. The test was done three times.

Total phenolics content

Since most of the species used for preparing the syrup contain phenolic compounds, total phenolics content of the syrup was considered for standardization of the product. The test was performed according to British Pharmacopoeia by using pyrogallol as the standard material and Folin-Ciocalteu as the reagent.[12,15] Quantification was carried out based on the standard curve of pyrogallol. Results were recorded as mg of pyrogallol equivalent per 100 mL of syrup. All evaluations were made three times at room temperature.

Accelerated stability test

The stability study for optimized formulation was performed at accelerated stability conditions according to ICH guidelines. Three bottles of syrup were placed at 40 ±2.0°C in a stability chamber for six months. Then, samples were checked every three months for any changes in physicochemical characteristics and microbial levels, including total aerobic microbial count, total mold and yeast count, bile-tolerant gram-negative bacteria count, and the presence of *E. coli, Staphylococcus aureus,* and *Salmonella* spp.[16]

Evaluation of antidepressant activity by FST

Animals

Wistar male rats (8–10 weeks old) (Pasteur Institute of Iran), weighing 220–250 g, were used in the study. The animals were kept for one week to adjust to the new medium (22±2°C, 45–60% humidity, and 12-h light/ dark cycle) and housed eight per cage with free availability to food and water.

Experimental and drug treatment groups

The rats were divided into six experimental groups (each group consisted of eight animals). The control group received distilled water (N). The syrup (S) group was treated with 3.3 ml/kg of the syrup (based on daily dosages of traditional usages). The positive control group received fluoxetine at the dose of 20 mg/kg. The sham group (SH) was treated with only syrup excipients. All groups were treated once a day for three weeks via intra-gastric gavage (i.g.).

Forced swimming test protocol

The study was performed on rats as per the method described by Porsolt *et al.*[17] The rats were placed individually in Plexiglas cylinders (with a diameter of 20 cm and a height of 45 cm) filled with water up to 30 cm and maintained at 25°C. Each rat was subjected to two swimming trials: In the first session (pretest), the animals were forced to swim for 15 min. Afterward, the rats were dried and returned to their cages. Then, 24 h later, the second swim session for 5 min (Test) was videotaped. Immobility was reported as the time that the rat passively floated in the water, doing those movements that are needed to keep its head above water.

Neurotransmitters analysis

Immediately after the swim test, each rat was anesthetized by using ketamine-xylazine and the blood was collected from the heart. Blood was centrifuged at 5000 rpm for 5 min. Serum was collected, stored at −20°C, and kept for further analysis. Serum was assessed by using 5-HT, NA, and BDNF ELISA kits (ab133053; Abcam, CSB-E07022r and CSB-E04504r; CUSABIO, respectively) according to the manufacturer's guidelines. All samples were analyzed in triplicate, and serum levels were reported in ng/mL.

Statistical analysis

All data were expressed as mean±SEM. Data were analyzed by using one-way Analysis of Variance (ANOVA) followed by Tukey's test for comparison between all treatment groups using GraphPad Prism 8.0 program. $P < 0.05$ was considered statistically significant.

Pathological studies

At the end of the research, the liver, kidney, and spleen were taken from rats to assess the toxicity. The tissues were fixed in 10% formalin, dehydrated in a series of alcohol, cleared in xylene, and embedded in paraffin wax. Sagittal sections (3–5µm thick) were prepared, stained with hematoxylin-eosin (H&E), and magnified by Optika light microscopy at ×100 magnification.

Results

Analysis of the plant materials

The results of analysis of the herbal materials used in the polyherbal syrup are noted in Table 1. The results were in accordance with pharmaceutical guidelines for each plant.[12,13]

Formulation studies

Among different excipients used to prepare the syrup, 16% glycerin alone was selected as the best excipient. Also because the syrup was susceptible to microbial contamination, potassium sorbate was added as an antimicrobial preservative. The final formulation of the syrup is shown in Table 2.

Determination of physicochemical characteristics of the polyherbal syrup

All physicochemical specifications of the polyherbal syrup are noted in Table 3.

Results of rheological behavior

Rheological behavior of the polyherbal syrup is shown in Figure 1.

Results of stability studies

The results obtained from accelerated stability studies showed that the selected syrup formulation exhibited no significant changes in physicochemical and microbiological specifications over six months. Total aerobic microbial counts were 2×10^1, 4×10^1, and 4×10^1 in 0, 3, and 6 months, respectively, and bile-tolerant Gram-negative bacteria count was acceptable during six months. No growth of mold, yeast, *Staphylococcus aureus*, *E. coli*, and *Salmonella* was observed in the syrup during the stability test.

Effect of polyherbal syrup on depression in FST

The effects of administering polyherbal syrup on Wistar rats in the FST are presented in Figure 2. Polyherbal syrup significantly decreased immobility time compared with the control group after three weeks of treatment ($P < 0.001$).

Effects of polyherbal syrup on serum levels of 5-HT, NA, and BDNF

The continuous treatment for 21 days with polyherbal syrup increased 5-HT ($P < 0.01$), and NA ($P < 0.001$) in serum in comparison to the control group but BDNF remained unchanged [Figures 3–5].

Table 1: Quality control assessment of polyherbal syrup ingredients

Ingredients	Total ash, %	Acid-insoluble ash, %	Foreign matter, %	Loss on drying, %	Alcohol-soluble extractive, %	Water, %	Assay, %
Glycyrrhiza glabra	6.01 ± 0.38 (NMT[a] 10)[b]	0.46 ± 0.03 (NMT 2)	–	5.95 ± 0.11 (NMT 10)	–	–	Glycyrrhizin: 7.40 ± 0.28 (NLT 4)[c]
Adiantum capillus-veneris	9.66 ± 0.3 (NMT 10)	–	9.5 ± 0.45 (NMT 10)	–	11.72 ± 0.85 [d]	–	Mucilage: 1.62 ± 0.14
Foeniculum vulgare	8.42 ± 0.25 (NMT 10)	0.71 ± 0.05 (NMT 1.5)	0.18 ± 0.01 (NMT 1.5)	–	–	–	Anethole: 80.50 ± 0.63 (NLT 80) Essential oil: 3.00 ± 0.00 (NLT 2)
Echium amoenum	8.76 ± 0.38 (NMT 10.5)	1.31 ± 0.12 (NMT 1.5)	–	–	–	–	Total antho cyanins as cyanidine-3-o-glucoside: 0.04 ± 0.00
Lavandula angustifolia	5.71 ± 0.24 (NMT 9)	–	1.06 ± 0.03 (NMT 2)	–	–	–	Essential oil: 14.5 ± 0.1 (NLT 13)
Melissa officinalis	8.84 ± 0.12 (NMT 12)	–	1.53 ± 0.07 (NMT 2)	7.30 ± 0.25 (NMT 10)	–	–	Total hydroxycinnamic derivatives as rosmarinic acid: 9.81 ± 0.53
Fumaria parviflora	11.41 ± 0.71 (NMT 15)	–	–	7.10 ± 0.16 (NMT 12)	–	–	Total alkaloids as hyoscyamine: 0.38 ± 0.00
Ziziphus jujuba	2.78 ± 0.11 (NMT 3)	0.7 ± 0.01 (NMT 0.7)	–	–	–	13.12 ± 0.92 (NMT 14.37)	Pectin: 0.57 ± 0.03 Total polysaccharide as glucose: 58.91 ± 2.12
Cordia myxa	6.74 ± 0.31 (NMT 7.2)	1.41 ± 0.01 (NMT 1.5)	–	–	–	2.75 ± 0.12 (NMT 3.15)	Mucilage: 8.31 ± 0.08
Alhagi spp. manna	2.78 ± 0.12 (NMT 3.4)	–	–	1.25 ± 0.09 (NMT 1.5)	–	–	Total polysaccharide as glucose: 60.74 ± 1.76

[a]Not more than
[b]The data in parentheses are acceptable ranges in Pharmacopoeia (BP/Iranian Herbal Pharmacopoeia)
[c]Not less than
[d]There is no acceptable range for some data

Table 2: Formulation of the polyherbal syrup

Ingredient	Percentage	Action
Ziziphus jujuba	0.6	Active constituent
Alhagi spp.	3.6	Active constituent
Cordia myxa	3.6	Active constituent
Glycyrrhiza glabra	2.8	Active constituent
Adiantum capillus-veneris	1.9	Active constituent
Melissa officinalis	1.9	Active constituent
Echium amoenum	1.9	Active constituent
Lavandula angustifolia	1.9	Active constituent
Fumaria parviflora	1.9	Active constituent
Foeniculum vulgare	1.9	Active constituent
Potassium sorbate	0.2	Preservative
Glycerin	16.0	Co-solvent, thickening agent, preservative, stabilizer, and sweetener
Water	Up to 100 mL	solvent

Histopathology

A histopathological study of polyherbal syrup demonstrated normal structure and absence of gross pathological lesions in the liver, kidney, and spleen. Macroscopic views of the organs revealed no color or texture abnormalities, compared with the control group [Figure 6].

Discussion and Conclusion

Depression is one of the most prevalent psychiatric disorders with a high incidence of relapse, chronicity, and suicide. Treatment with existing antidepressants is often accompanied by unwanted adverse effects, and some patients do not show the desired therapeutic response.[18,19] Complementary and

alternative therapies such as herbal remedies have been used widely to reduce the symptoms of depression.[20] Due to the widespread use of traditional medicine, reformulation of drugs to modern dosage forms is essential. In this investigation, to prepare the syrup, we tried to use less additional ingredients, such as coloring, flavoring, and sweetening agents, to make the final formulation more similar to the traditional form and less expensive on the industrial scale as well. Different excipients were used for making viscosity, and for providing an acceptable taste and clarity of the syrup. By using carbomer 940, CMC, and HPMC (1%), viscosity of the herbal syrup was increased but turbidity and particles appeared in the product, which indicated incompatibility between the polymers and syrup ingredients. On the other hand, by adding PVP, the syrup was found to be clear and uniform, but adequate viscosity was not obtained. Glycerin and propylene glycol improved viscosity and transparency of the syrup, but propylene glycol induced an undesirable taste in the syrup. Glycerin is a clear viscose liquid with a sweet taste that improves viscosity and appearance of the syrup; it also masks the bitter taste of the herbal agents. Therefore, it was selected as the best excipient and four different concentrations (8, 12, 16, 20%) of glycerin were also tried to choose the best one for preparing the syrup. Investigating the glycerin-based experimental formulations demonstrated that increasing glycerin ratio improved the taste, appearance, and viscosity of the syrup; however, glycerin 20% produced a very sweet flavor that was not favorable, thus a herbal syrup containing glycerin 16% was selected as the most appropriate formulation. Glycerin was used as a sweetener, co-solvent, thickening agent, stabilizer, and clarity enhancer in the syrup. The final formulation of the syrup consisted of 22% plant materials, 16% glycerin, and 0.2% preservative. The results of the quality control demonstrated that the selected syrup had good visual properties, suitable viscosity, and without cap locking and crystallization. No signs of physical changes were observed during the accelerated stability condition. The results of microbiological evaluations were in agreement with the requirements.[21] Rheology is the study of flow that indicates the viscosity specifications of powders, fluids, and semisolids. On the basis of the flow characteristics, materials are classified into two groups, Newtonians and non-Newtonians. The Newtonian flow is applied by constant viscosity regardless of shear rate. A Newtonian fluid will be plotted as a straight line, with viscosity as the slope of the line.[10] The rheogram of the syrup is linear, demonstrating Newtonian behavior.

Table 3: Physicochemical characteristics of the polyherbal syrup

Test	Result
Appearance	Dark brown
Taste	Specific
Odor	Specific
pH	5.56 ± 0.06
Density	1.085 ± 0.00 g/mL
Viscosity	5.35 cP
Dry residue	15.22 ± 0.43%
Total phenolics content as pyrogallol	194.15 ± 0.54 mg/100 mL

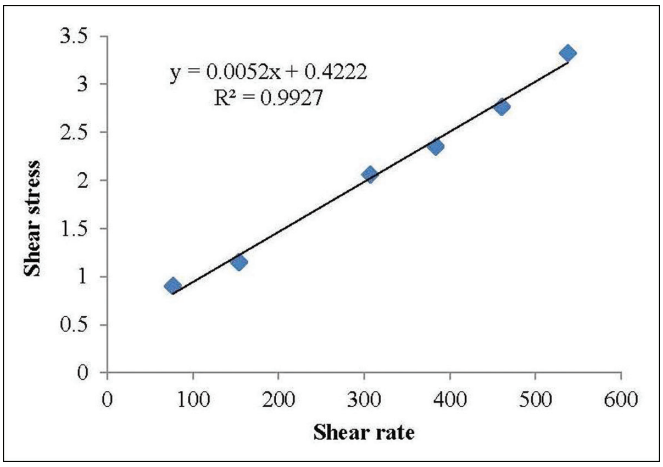

Figure 1: Rheogram of the polyherbal syrup, showing the presence of Newtonian behavior (*n* = 3)

The importance of animal models in human mood disorders such as depression has been revealed during recent progress in experimental neuroscience. It is difficult to study the true antidepressant mechanism by which antidepressants work or to find combinations with the new antidepressant. Among the different theoretical models, FST has been widely used. The FST, behavioral despair test, is beneficial to investigate the mechanism of depression and evaluation of antidepressant

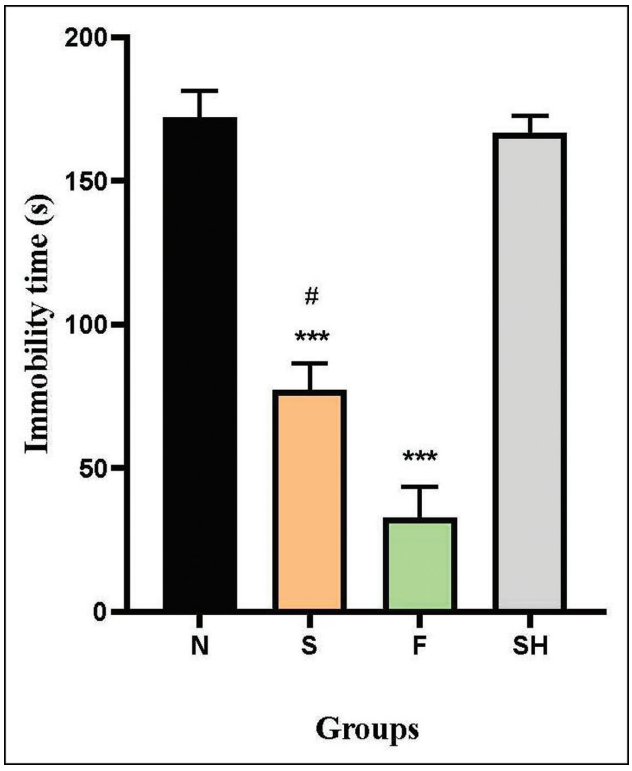

Figure 2: Effects of polyherbal syrup (3.3 mg/kg), fluoxetine (positive control group 20 mg/kg), distilled water (as control group), and sham on immobility time in male Wistar rat. Data have been reported as mean ± SEM (*n* = 8). ***Significant difference in comparison to control *P* < 0.001, #Significant difference in comparison to positive control *P* < 0.05

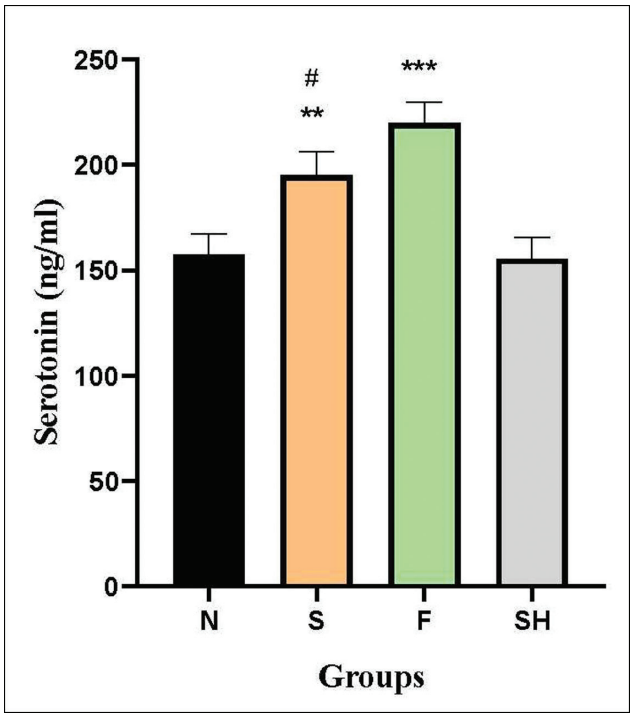

Figure 3: Effects of polyherbal syrup (3.3 mg/kg), fluoxetine (positive control group 20 mg/kg), distilled water (as control group), and sham on serotonin serum level in male Wistar rat. Data have been expressed as mean ± SEM (*n* = 8). ** and ***statistical significant difference in comparison to control *P* < 0.01 and *P* < 0.001, respectively, #statistical significant difference in comparison to positive control, *P* < 0.05

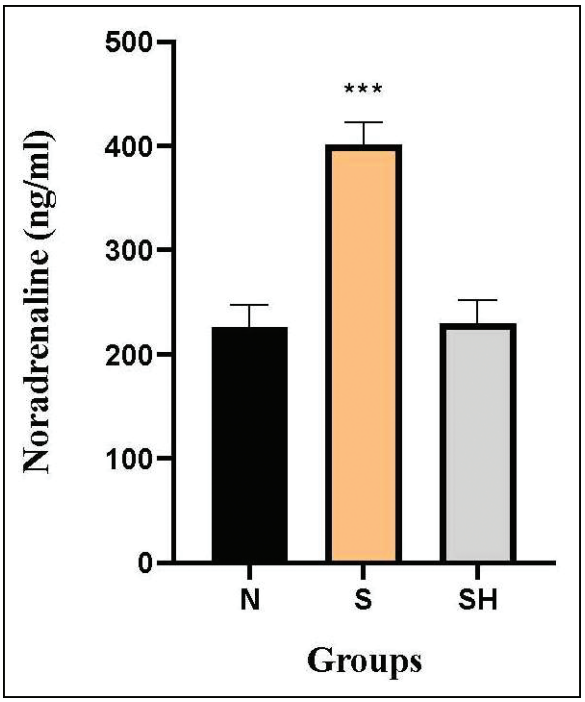

Figure 4: Effects of polyherbal syrup (3.3 mL/kg), distilled water (as control group), and sham on noradrenaline serum level in male Wistar rat. Data have been expressed as mean ± SEM (*n* = 8). ***Statistical significant difference in comparison to control *P* < 0.001

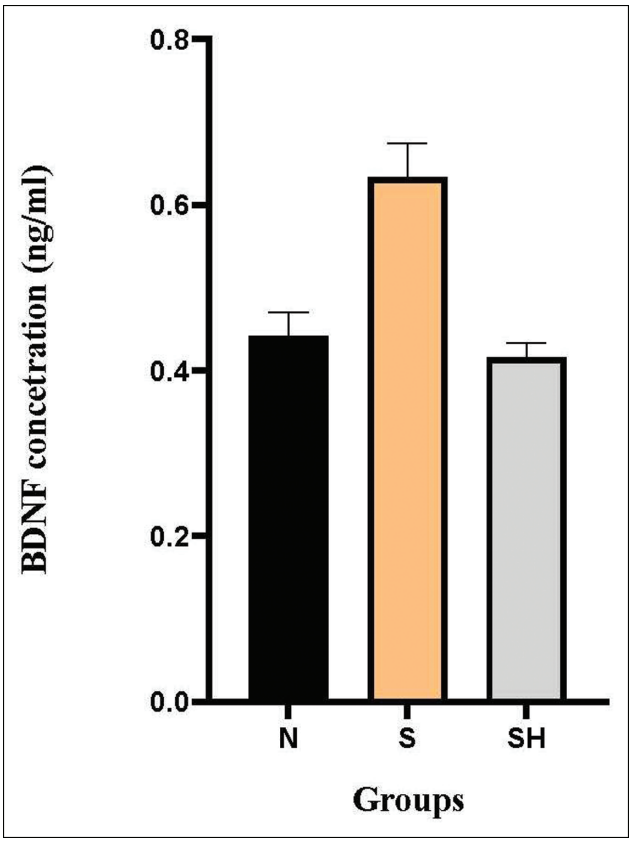

Figure 5: Effects of polyherbal syrup (3.3 mg/kg), distilled water (as control group), and sham on BDNF serum level in male Wistar rat. Data have been expressed as mean ± SEM (*n* = 8)

medicines.[22,23] In the present investigation, polyherbal syrup significantly decreased immobility time compared with the control group after three weeks of treatment. Decreased immobility time in FST is related to induced antidepressant activity. The syrup significantly increased climbing more than swimming. In contrast, fluoxetine increased swimming without affecting climbing behavior in rats. The dysfunction of the central nervous system is correlated with the neurotransmitters NA and 5-HT, which have a major role in the pathogenesis of depression. Currently, substantial experimental and clinical evidence proved that the most effective remedy of depression involves an increase in 5-HT and NA neurotransmission.[2] Different kinds of antidepressants increase the synaptic concentrations of NA and 5-HT. Although different medications have various relative selectivity for NA and 5-HTsystems, these two neurotransmitters work in parallel and in a coherent manner to make antidepressant effects.[24] In our investigation, the polyherbal syrup significantly increased 5-HT and NA levels in the rat serum in comparison to the control group. These findings indicated the potential involvement of the serotonergic and noradrenergic systems in the antidepressant effect of the formulated polyherbal syrup but the dominant behavior of rats was climbing, which indicated that the NA pathway was involved in the observed effect more than 5-HT.

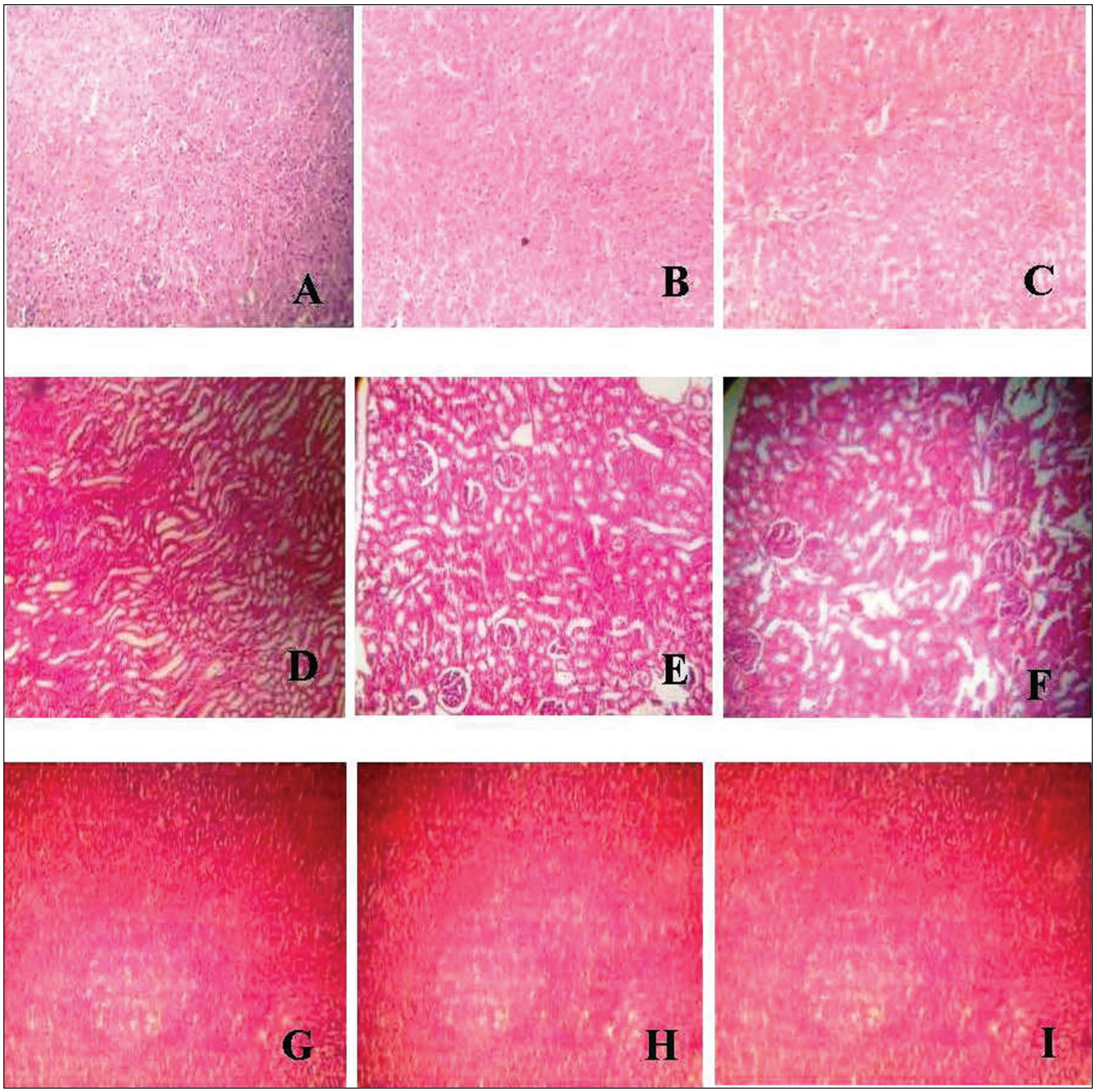

Figure 6: Microscopic views of liver in normal (A), syrup (B), and fluoxetine (C) groups: There was no structural change in hepatic cord and portal vein; kidney in normal (D), syrup (E) and fluoxetine (F) groups. There was no structural changes in the shape of renal corpuscles and convoluted tubules; spleen in normal (G), syrup (H), and fluoxetine (I) groups. There was no structural change in white and red pulps

Moreover, no significant changes were found in the BDNF level. Generally, the therapeutic effects of medicinal plants are mostly based on the synergistic property of ingredients; herbal mixtures are used instead of one species and have better activities.[25] The formulated polyherbal syrup is a well-known multi-ingredient formula in the ITM that is used for a range of mood disorders, and it consists of 10 herbal substances. In some species of the syrup, *in vivo* studies and for some other herbs, clinical trials have been done and different mechanisms have been proposed for the observed effects. For example, during a double-blind clinical trial on *E. amoenum*, it was found that an aqueous extract of the plant was effective in mild to moderate depression. In addition, *E. amoenum* increased CSF 5-HT and dopamine concentrations in rats.[26,27] During a clinical trial, a combination of *L. angustifolia* tincture and imipramine showed more anti-depression effects compared with imipramine alone. Antidepressant effects of lavender in rats have been established by FST. These effects have been attributed to antagonism on the NMDA-receptor and inhibition of 5-HT transporter (SERT).[28-30] Antidepressant properties of *M. officinalis* have been proved in FST; the aqueous extract of the plant acts similar to imipramine in reducing immobility and increasing climbing behavior.[31-33] The antidepressant-like effect of *G. glabra* seems to be mediated by the increase of brain norepinephrine

and dopamine and the inhibition of monoamine oxidase.[34,35] *Foeniculum vulgare* has shown antidepressant effects via monoamine oxidase inhibitory effects.[36,37] *Adianthum capillus-veneris* has shown a decrease in immobility time in mice, which is related to the antidepressant property.[38] Taking all of the just cited information into consideration, the species in the polyherbal syrup could have synergistic effects as well as antidepressant effects, which have been established in the *in vivo* experiments. During an examination on a herbal product, namely "Abnormal Savda Munziq (ASMq)" with some similar component to our product in depression animal models, the antidepressant effect of the product was established through improving the function of the hypothalamus-pituitary-adrenal axis (HPAA); moreover, biological syndromes of depression, including loss of body weight and reduction of the food and water intake, were improved.[39,40] Considering some similarity between ASMq and the formulated syrup, the proposed mechanisms may be considered as another mechanism for antidepressant effects of the syrup but further studies are necessary. Taken together, the present experiment revealed that the formulated herbal syrup exhibited antidepressant effects in the FST rat model, which was mediated by increasing 5-HT and NA and could be a suitable choice for depression after clinical trials.

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Financial support and sponsorship

Nil.

Conflicts of interest

The authors declare that they have no conflict of interests.

Ethical approval

All experiments were performed based on National Institutes of Health (NIH) animal care and use committee guidelines. The research 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.1397.339.

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