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Antidepressant Effects of a Reformulated Traditional Tablet

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Abstract

Background: Herbal medicines are preferred over chemical medications for a wide range of mental disorders such as depression. "*Monzej-e soda*" is a polyherbal combination that has been used in Iranian traditional medicine for several years to cure different mood disorders with similar signs to depression. Traditional formulations should be reformulated to reach pharmacopoeial standards as modern medicines.

Objectives: In this study, "*Monzej-e soda*" was reformulated and its quality control and antidepressant evaluations were performed to present a standard and efficacious formulation.

Methods: The aqueous extract of the mixture of *Echium amoenum, Lavandula angustifolia, Melissa officinalis, Foeniculum vulgare, Ziziphus jujuba, Cordia myxa, Glycyrrhiza glabra, Fumaria parviflora, Adiantum capillus-veneris*, and *Alhagi* spp. manna was dried with the spray drying method. Dried extract and various ingredients at different ratios were used to produce 13 experimental tablet formulations and several pre- and post-formulation tests were performed to select the best formulation. The formulation was evaluated physico-chemically. The accelerated stability test was performed on the tablets, as well. Moreover, the antidepressant effect of tablets was evaluated by the forced swimming test. The serum levels of serotonin (5-HT), noradrenaline (NA), and brain-derived neurotropic factor (BDNF) were measured in rats. Finally, histopathological examinations were performed on the liver, kidney, and spleen.

Results: Among different formulations, the best one was a combination of dried extract (490 mg), maltodextrin (189 mg), colloidal silicon dioxide (21 mg), and croscarmellose sodium (2%). The hardness, weight, friability, disintegration time, dissolution percentage, and total phenolic content were 6.98 kg/cm^2, 715.76 mg, 0.7%, 12.0 min, 97.46% in one hour, and 31.4 mg/tab, respectively. No significant changes were seen in the product in the accelerated stability test. The polyherbal tablet produced significant antidepressant effects through the decrease in immobility time, which was mediated via an increase in NA and 5-HT levels. It had no effect on the BDNF level. In addition, tablets had no toxic effects on the liver, kidney, and spleen.

Conclusions: "*Monzej-e soda*" tablet can be considered a suitable antidepressant drug and used in patients after passing clinical trial tests.

Keywords: Depression, Forced Swimming Test, Iranian Traditional Medicine, *Monzej-e soda*, Tablet

1. Background

Depression is the most prevalent and one of the leading causes of disease burden worldwide, which has been considered in various publications (1, 2). Nowadays, a variety of antidepressants have been widely used to treat depression, including tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors, monoamine oxidase inhibitors, noradrenergic and specific serotonergic antidepressants. While most of the mentioned antidepressants can cause several adverse effects such as sexual dysfunction, body weight gain, and sleep disorder, the effectiveness of the mentioned antidepressant drugs does not exceed 40% - 50% that is unsatisfactory. Therefore, novel antidepressants with higher efficacy and safety are still necessary (3, 4).

Nowadays, the use of Complementary and Alternative Medicine (CAM) therapies has expanded widely among patients with psychiatric disorders (5, 6). The World Health Organization (WHO) has promoted its traditional medicine strategy and accepted different alternative treatments for diseases, such as herbal therapy and traditional

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medicine (7). Medicinal plants as valuable pharmaceutical resources have been used to cure many kinds of diseases, like psychiatric disorders and they usually cause lower side effects than synthetic and chemical drugs (8). Herbal drug synergism has a significant role in the therapeutic effects of herbal formulations with regard to each individual herbal component (9). Iranian traditional medicine (ITM), also called Persian medicine, is a potential source to find new drugs for diseases such as depression. One of the prescriptions in ITM is "*Monzej-e soda*" that is a combination of 10 herbal components including *Echium amoenum* L., *Lavandula angustifolia* Mill., *Melissa officinalis* L., *Foeniculum vulgare* Mill., *Ziziphus jujuba* Mill., *Cordia myxa* L., *Glycyrrhiza glabra* L., *Fumaria parviflora* Lam., *Adiantum capillus-veneris* L., and *Alhagi* spp. Fisch. manna and it is a well-known formulation used to treat a broad range of mood disorders with similar signs to depression (10). Traditional formulations need to be standardized and converted to modern dosage forms to facilitate patient reception and consumption (11). The oral route is a favorite method of administration of medicines for systemic effects. Among them, tablets are more popular than liquid dosage forms because of their self-administration, easy manufacturing, more stability, uniformity, and correct potency, fewer microbial problems, and better flavor masking (12).

2. Objectives

Considering the necessity of producing plant-based medicines for the treatment of depression and the achievement of standard pharmaceutical dosage forms, this research aimed to prepare and evaluate a polyherbal tablet called "*Monzej-e soda*" in ITM. Moreover, the antidepressant effect of the formulated tablet was evaluated by using the forced swimming test and measuring the serum levels of serotonin, noradrenaline, and brain-derived neurotrophic factor in rats to present a qualified formulation for depression.

3. Methods

3.1. Ethical Considerations

All methods were carried out according to the National Institutes of Health (NIH) animal care and use committee guidelines (13).

3.2. Plant Material

All herbal ingredients were purchased from a local herbal market in Tehran. The samples were authenticated 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* Mill. fruits, *Alhagi* spp. Fisch. manna, *Echium amoenum* L. petals, *Cordia myxa* L. fruits, *Glycyrrhiza glabra* L. rhizomes, *Melissa officinalis* L. aerial parts, *Fumaria parviflora* Lam. aerial parts, and *Adiantum capillus-veneris* L. whole plant, were saved at the Herbarium of TMRC for future references.

3.3. Chemicals

Sodium carbonate was provided from Sigma, Germany. Folin-Ciocalteu, pyrogallol, Maltodextrin, Colloidal silicon dioxide, and Croscarmellose sodium were purchased from Merck, Germany. Other chemicals used in the experiment were of analytical grade.

3.4. Instrumentation

The hardness of the tablets was assessed using a hardness tester (Model TBH28, Erweka, Germany). Friability of tablets was determined by a Pharma-test friabilator (Model TAR, Erweka, Germany). The disintegration time of tablets was measured using a disintegration tester (Model ZT3, Erweka, Germany). Dissolution behavior was investigated with dissolution testers (Kavosh Co., Iran). The tablets were pressed with an Excentric Tabletting Machine EKO model single-punch tablet machine (Erweka, Germany). The UV absorption was measured by a UV-Vis spectrophotometer (Shimadzu, Japan).

3.5. Physicochemical Analysis of Plant Materials

The physicochemical tests of the herbals were carried out according to the pharmacopeia monograph for all plants including loss on drying, total ash, acid insoluble ash, foreign matter, alcohol soluble extractives, and content of a marker of each plant (14).

3.6. Extract Preparation

According to the ITM prescription (10), *Cordia myxa* and *Alhagi manna* (six parts), *Glycyrrhiza glabra* (five parts), *Lavandula angustifolia, Melissa officinalis, Echium amoenum, Fumaria parviflora, Foeniculum vulgare*, and *Adiantum capillus-veneris* (three parts), and *Ziziphus jujuba* (one part) were coarse powdered separately and mixed. The combination was extracted with distilled water (1:15) by using a decoction method at 90°C for two hours. Afterward, the mixture was filtered and the aqueous extract was dried by using 27% maltodextrin and 3% colloidal silicon dioxide with a spray drier instrument. Finally, a creamy colored powder was obtained with specific herbal taste and odor.

3.7. Preformulation Studies

For developing the tablet formulations, 13 experimental formulations were prepared with the mixture of the dried extract and ingredients containing microcrystalline cellulose, lactose monohydrate, and croscarmellose sodium at different ratios (F1 - F13) (Table 1). Then, in preformulation studies, the flowability of all formulations was evaluated based on the angle of repose, Carr's Index, and Hausner's ratio to determine the best formulation (15).

3.8. Preparation and Evaluation of Polyherbal Tablets

Regarding the preformulation studies, the five best formulations were prepared with the direct compression method in the caplet form. The pharmaceutical quality control tests were performed on F1, F2, F5, F6, and F8 tablets based on the United States Pharmacopoeia (16) including the uniformity of weight, hardness, friability, disintegration time, dissolution behavior, and the assay of total phenolic content. The dissolution test was carried out by apparatus II (paddle) on randomly selected six tablets from the select formulation accepted by friability and hardness tests. Each tablet was individually placed in the dissolution vessel each containing 900 mL of distilled water as the dissolution medium and maintained at 37 $\pm$ 0.5°C and 50 rpm. A 15 mL volume sample was withdrawn, refilled with a fresh and equivalent medium at predetermined intervals (15, 30, 45, and 60 min), and maintained at the same temperature and the amount of dissolved total phenols of each withdrawn sample was thereafter calculated using UV spectroscopy at 760 nm (14). According to the USP Pharmacopeia, the acceptance level for the dissolution test of herbal tablets in 60 min was 75% (Q) + 5% of marker compounds in each tablet (16).

To determine total phenolic compounds in each tablet, the Folin-Ciocalteu method was used according to the British Pharmacopeia (14). Ten tablets were powdered. Then, an exactly weighed powder, equivalent to one tablet, was diluted in 100 mL distilled water. Quantification was performed based on the standard curve of pyrogallol. The results were expressed as mg of pyrogallol equivalent per each tablet. All procedures were performed three times at room temperature.

3.9. Stability Studies

The stability study of the optimized formulation was carried out at accelerated stability conditions as per the ICH guidelines. Forty tablets were packed in a polyethylene container and were stored at 40 $\pm$ 2.0°C and 75 $\pm$ 5% RH in a stability chamber for six months. Afterward, the samples were tested for physicochemical properties and microbial levels (17).

3.10. Evaluation of Antidepressant Activity of Polyherbal Tablets

3.10.1. Animals

We used 8 - 10-week-old male Wistar rats (Pasteur Institute of Iran), weighing 220 - 250 g. The animals were kept on one week to adjust to the new environment (22 $\pm$ 2°C, 45 - 60% humidity, and 12-h light/dark cycle) with free access to food and water.

3.10.2. Experimental Groups and Drug Treatments

The rats were divided into six experimental groups of eight animals each. The control group received distilled water (N). The tablet (T) group was cured with 285 mg/kg of the Tablet (based on daily dosages of traditional use). The positive control group was treated with fluoxetine (F) at a dose of 20 mg/kg. The Sham (SH) group was treated with only tablet excipients. All groups were treated once daily for 21 days via intra-gastric gavage (i.g.).

3.10.3. Forced Swimming Test (FST)

The studies were done on rats according to a method by Porsolt et al. (18). The rats were placed in plexiglass cylinders (height 40 cm, diameter 18 cm) containing 30 cm of water, maintained at 23 - 25°C. The rats were submitted to two sessions: the first session for 15 min (pretest) and the second session 24 h later for five minutes. After 15 min in water, the rats were removed, allowed to completely dry, and returned to their home cages. They were again placed in the cylinder 24 h later for 5 min and their behavior was videotaped and then analyzed by two independent observers who were blinded to the treatment. After each swimming, the water in the cylinder was refilled with fresh water for a test with another rat. The rat seemed to be immobile when it ceased struggling and passively floated in the water, doing those movements that were needed to keep its head above water.

3.10.4. Neurotransmitters Analysis

Immediately following the swim exposure, each rat was anesthetized using ketamine-xylazine and the blood was collected from the heart. The blood was centrifuged at 5,000 rpm for 5 min and the serum was collected and stored at -20°C until further analysis. The serum was evaluated using serotonin, noradrenaline, and BDNF ELISA kits (ab133053; Abcam, CSB-E07022r and CSB-E04504r; CUSABIO, respectively) according to the manufacturer's instructions. Each sample was analyzed three times and serum levels were informed in ng/mL.

3.11. Pathological Studies

At the end of the experiment, the kidney, liver, and spleen were taken from rats for toxicity assessment. The tissues were fixed in formalin 10% and dehydrated in graded

Table 1. Constituents of Polyherbal Formulations and Flowability Characteristics

No.	Herbal Powder (mg)	Maltodextrin (mg)	Colloidal Silicon Dioxide (mg)	Microcrystalline Cellulose(mg)	Cros Carmellose Sodium (mg)	Lactose Monohydrate (mg)	Angle of Repose (°)	Carr's Index (%)	Hausner Ratio
F1	490	189	21	-	-	-	30.32	10.68	1.10
F2	490	189	21	-	14	-	29.14	9.07	1.07
F3	490	189	21	-	35	-	30.25	10.33	1.10
F4	490	189	21	-	70	-	29.61	10.18	1.09
F5	490	189	21	126	14	-	32.83	15.69	1.16
F6	490	189	21	105	35	-	32.47	14.29	1.15
F7	490	189	21	70	70	-	31.29	13.95	1.15
F8	490	189	21	140	-	-	34.45	14.81	1.16
F9	490	189	21	70	-	70	34.18	15.17	1.18
F10	490	189	21	-	-	140	34.63	15.74	1.17
F11	490	189	21	-	14	126	33.29	15.52	1.17
F12	490	189	21	-	35	105	34.03	14.76	1.16
F13	490	189	21	-	70	70	31.87	13.85	1.15
Function	Active ingredient	Glidant	Glidant	Binder, Direct compression excipient	Disintegrant	Binder, Direct compression excipient	-	-	-

series of alcohol, cleared in xylene, and embedded in paraffin wax. Sagittal sections (3 - 5 μm thick) were prepared and stained with hematoxylin-eosin (H & E) and photographed under 100 $\times$ magnification by an Optika light microscope.

3.12. Statistical Analysis

All data were presented as mean $\pm$ SEM. Data were analyzed using the one-way Analysis of Variance (ANOVA), followed by Turkey's test using GraphPad Prism 8. We considered $P < 0.05$ statistically significant.

4. Results

4.1. Analysis of Plant Materials

The results of the physicochemical analysis of raw herbal materials were in accordance with the requirements (14).

4.2. Preformulatuion Studies

Table 1 shows the constituents of polyherbal formulations in preformulation studies provided by using a required amount of dried extract and a suitable amount of excipients at different ratios (F1 - F13), along with the results of preformulation studies. The results showed that the flowability of all formulations was suitable.

4.3. Evaluation of Polyherbal Tablets

All the 13 experimental formulations were prepared but among them, formulations F3, F4, and F7 showed low hardness and high friability because of using a high amount of croscarmellose sodium (5 and 10%). Thus, these formulations were refused. Also, the color of lactose-containing tablets changed over time and turned into dark brown, indicating incompatibility between lactose monohydrate and the other formulation constituents; so, formulations F9 - F13 were omitted, too. According to the formulation studies, F1, F2, F5, F6, and F8 were further evaluated (Table 2).

The results of the drug release profile of five different formulated polyherbal tablets are noted in Table 3. The released total phenols, as the marker of polyherbal tablets, were more than 75% (Q) + 5% after 60 min, which was in agreement with the USP principles. Among different formulations, F2 was chosen as the best one.

4.4. Results of Stability Studies

The obtained results of accelerated stability studies demonstrated that the optimized tablet formulation showed no significant changes in physicochemical and microbial characteristics during six months. The reduction in the total phenolic contents as the marker of polyherbal tablets was 1.1%, which was in agreement with the ICH requirements (17).

4.5. Effect of Polyherbal Tablet on Depression in FST

The effects of administering polyherbal tablets on Wistar rats in the FST are shown in Figure 1. Polyherbal tablets significantly decreased immobility time compared to the control group after 21 days of treatment ($P < 0.001$).

4.6. Effects of Polyherbal Tablets on Serum Levels of 5-HT, NA, and BDNF

The continuous treatment for three weeks with polyherbal tablets increased 5-HT ($P < 0.01$) and noradrenaline

Table 2. Physicochemical Properties of Polyherbal Tablets

Tests	Formulations				
	F1	F2	F5	F6	F8
Appearance	Creamy color, smooth, biconvex oval tablet	Creamy color, smooth, biconvex oval tablet	Creamy color with white spots, smooth, biconvex oval tablet	Creamy color with white spots, smooth, biconvex oval tablet	Creamy color with white spots, smooth, biconvex oval tablet
Length (mm)	19.45	19.46	19.45	19.44	19.45
Width (mm)	8.32	8.33	8.34	8.32	8.33
Thickness (mm)	6.12	6.14	6.51	6.51	6.50
Weight (mg)	700.32	715.76	841.63	842.48	842.86
Friability (%)	0.70	0.76	0.66	0.79	0.60
Hardness (kg/cm^2)	7.31	6.98	7.75	6.76	8.04
Disintegration time (min)	14.31	12.08	14.58	14.15	16.31
Dissolution (%) in 60 min	96.24	97.46	95.83	96.88	94.26
Assay of total phenolics (mg/tab) as pyrogallol, mean ± SD	31.35 ± 0.13	31.47 ± 0.21	31.08 ± 0.22	31.27 ± 0.17	31.09 ± 0.12

Table 3. Drug Release Profile of Five Different Formulated Polyherbal Tablets

Time (min)	Released Total Phenolics as Pyrogallol (%)				
	F1	F2	F5	F6	F8
15					
Min	45.44	47.15	42.57	45.32	40.88
Max	46.87	48.08	43.71	46.97	43.14
Mean	46.15	47.34	43.36	46.66	42.65
30					
Min	63.11	67.67	61.02	64.17	60.13
Max	64.26	68.34	62.95	64.84	61.96
Mean	63.59	68.18	62.41	64.50	61.41
45					
Min	82.22	84.69	80.72	83.37	80.95
Max	83.78	86.64	82.61	84.46	82.57
Mean	83.36	85.37	81.28	84.15	81.23
60					
Min	95.73	97.21	94.46	95.45	93.81
Max	96.68	98.13	96.31	97.87	95.41
Mean	96.24	97.46	95.83	96.88	94.26

($P < 0.001$) in serum compared to the control group but BDNF remained unchanged (Figures 2-4).

4.7. Histopathology

The histopathological study of prepared polyherbal tablets showed a normal structure and the absence of any gross pathological lesion in the kidney, liver, and spleen. Macroscopic views of the organs of rats revealed no abnormalities in the color or texture, compared to the control group (Figure 5).

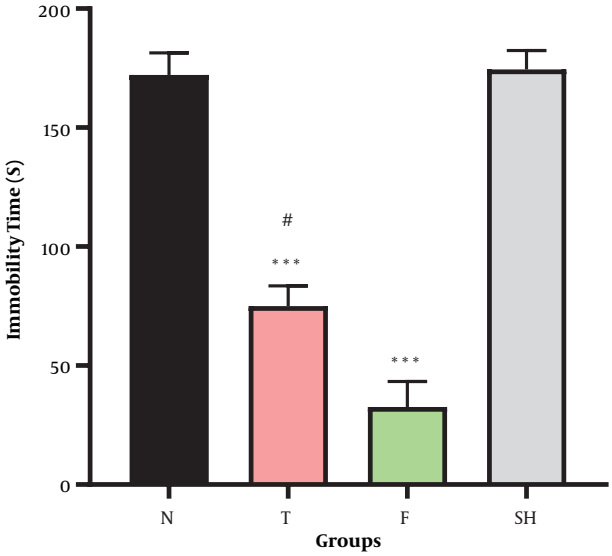

Figure 1. Effects of polyherbal tablet (258 mg/kg), fluoxetine (positive control group 20 mg/kg), distilled water (as the control group) and sham on immobility time in male Wistar rats. Data were been expressed as mean ± SEM (n = 8). *** A significant difference compared to control at P < 0.001, # A significant difference compared to positive control at P < 0.05.

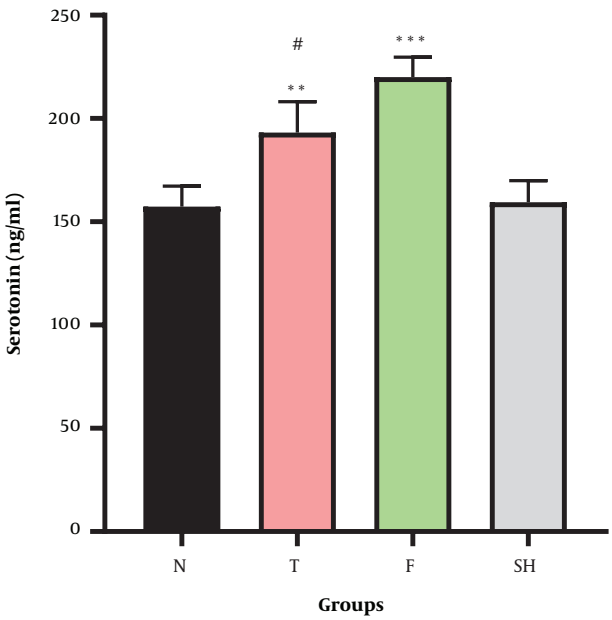

Figure 2. Effects of polyherbal tablet (258 mg/kg), fluoxetine (positive control group 20 mg/kg) and distilled water (as the control group) and sham on the serotonin serum level in male Wistar rats. Data were expressed as mean ± SEM (n = 8). ** and *** A significant difference compared to control at P < 0.01 and P < 0.001, respectively, # A significant difference compared to positive control at P < 0.05.

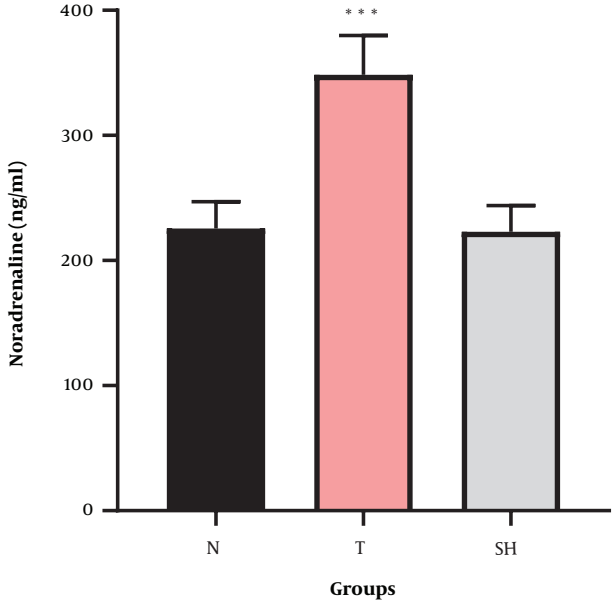

Figure 3. Effects of polyherbal tablet (258 mg/kg), distilled water (as the control group) and sham on the noradrenaline serum level in male Wistar rats. Data were expressed as mean ± SEM (n = 8). *** A significant difference compared to control at P < 0.001.

5. Discussion

Regarding the wide use of traditional medicine, the reformulation of drugs to modern dosage forms is necessary. In the present research, "*Monzej-e soda*" tablets were reformulated pursuant to ITM and its antidepressant effect was established. The angle of repose as a characteristic of the cohesion of particles was good in all formulation series. Carr's index and Hausner ratio are indirect methods to predict the powder flowability. Carr's index up to 16 was considered acceptable as a flow property (15). Hausner's ratio was related to the inter-particle friction and all formulations had a ratio of approximately 1.20, indicating a good flow and compressibility. Hence, the outcomes of preformulation studies exhibited good flow properties and good packing ability. Therefore, all of the formulations were pressed to determine the appropriate formulation and considered for further studies. The weight variation was narrow (maximum 5%) in each formulation series. All formulations had suitable hardness (60 - 80 N) and friability (less than 1%). Disintegration time for all the formulated tablets was less than 20 min that is suitable for herbal tablets. Disintegration time is one of the most significant tests in tablets' quality controls and the usage of disintegrants in natural products is unavoidable, as many of these combinations may cause powders and extracts to be sticky (19). The dissolution behavior of all tablets was acceptable. Several factors may influence dissolution results, such as the disintegration rate and the nature of the excipients (20). Tablet hardness and disintegration time

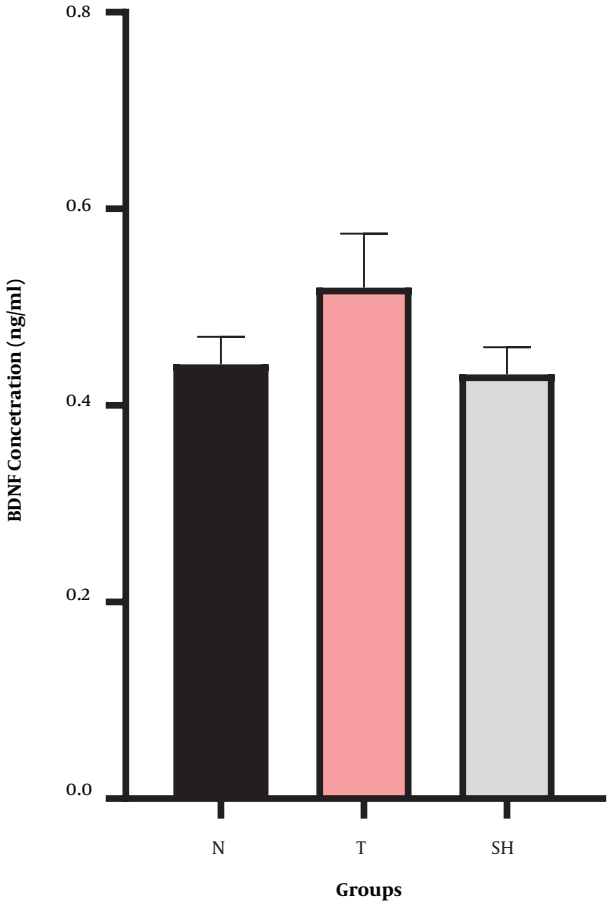

Figure 4. Effects of polyherbal tablet (258 mg/kg), distilled water (as the control group) and sham on the BDNF serum level in male Wistar rats. Data were expressed as mean ± SEM (n = 8).

were also significantly dependent on the amounts of disintegrants. Totally, considering the results, by reducing microcrystalline cellulose and increasing croscarmellose sodium, we observed reductions in tablet hardness and disintegration time (F2 and F6). Thus, F2 (2% croscarmellose sodium) exhibited the lowest disintegration time and suitable dissolution (release of 97% total phenolics) with the least excipients was selected as the final formulation. It exhibited a limited weight variation that demonstrated the uniform distribution of active ingredients and ensured that the tablet included an appropriate amount of medication and maintained good quality and performance. The final formulation contained only three excipients that reduced the costs and difficulties in industrial-scale production. Drug stability had a major role in the safety and efficacy of the medicine. Stability studies were done to realize the effects of different temperature and humidity conditions on the formulation (16). The results of the accelerated stability test of the mentioned tablets were in agreement with requirements.

The FST is an accepted behavioral test in rodents and there is a significant correlation between clinical potency and the potency of antidepressants in this model. Thus, FST is usually used to evaluate antidepressant drugs (21). Polyherbal tablets could significantly increase climbing more than swimming. In contrast, fluoxetine increased swimming without affecting climbing behavior in rats. The dysregulation of the central nervous system (CNS) is related to neurotransmitters like serotonin and noradrenaline which have a major role in the pathogenesis of mental illnesses including depression. Currently, the most efficacious treatment of major depression is an increase in serotonin and/or noradrenaline (22). There are several types of antidepressants, divided into three general categories: monoamine reuptake inhibitors, monoamine oxidase inhibitors, and monoamine receptor antagonists. All these medicines elevate the synaptic concentrations of noradrenaline and serotonin. Although various medications have various relative selectivity for noradrenaline and serotonin systems, these two neurotransmitter pathways work in parallel and in a coherent manner to make the same final antidepressant response (23). The results of the present investigation revealed significant enhancement in 5-HT and NA in serum levels of rats treated with polyherbal tablets compared to the control group, indicating the involvement of the serotonergic and noradrenergic systems in the antidepressant effect of polyherbal tablets but dominant behavior of rats was climbing that indicated that the NA pathway was more effective than 5-HT in the antidepressant effect. No change was found in BDNF, which established that the antidepressant effect of the tablet was not mediated through BDNF. "*Monzeje soda*" is a famous polyherbal compound in ITM used for many therapeutic purposes such as depressive disorders; it consists of 10 herbal materials, some of which have demonstrated antidepressant effects individually in previous studies. For example, in a clinical study on depression and anxiety, *Echium amoenum* showed antidepressant activities (24, 25). The antidepressant effect of *Lavandula angustifolia* has been reported in several studies (26-28). The antidepressant effects and heart palpitation relief of *Melissa officinalis* leaves' ethanolic extract were demonstrated in the forced swim test (29, 30). The antidepressant effect of *Glycyrrhiza glabra* has been proven, as well (21, 31, 32). In a similar investigation, the effect of 24 days of oral administration of abnormal "*Monzej-e soda*" (ASMq), which had some similarity with our product, was observed by measuring the serum levels of neuroendocrine in depression animal models. The mechanism of its antidepressant effect was to improve the dysfunc-

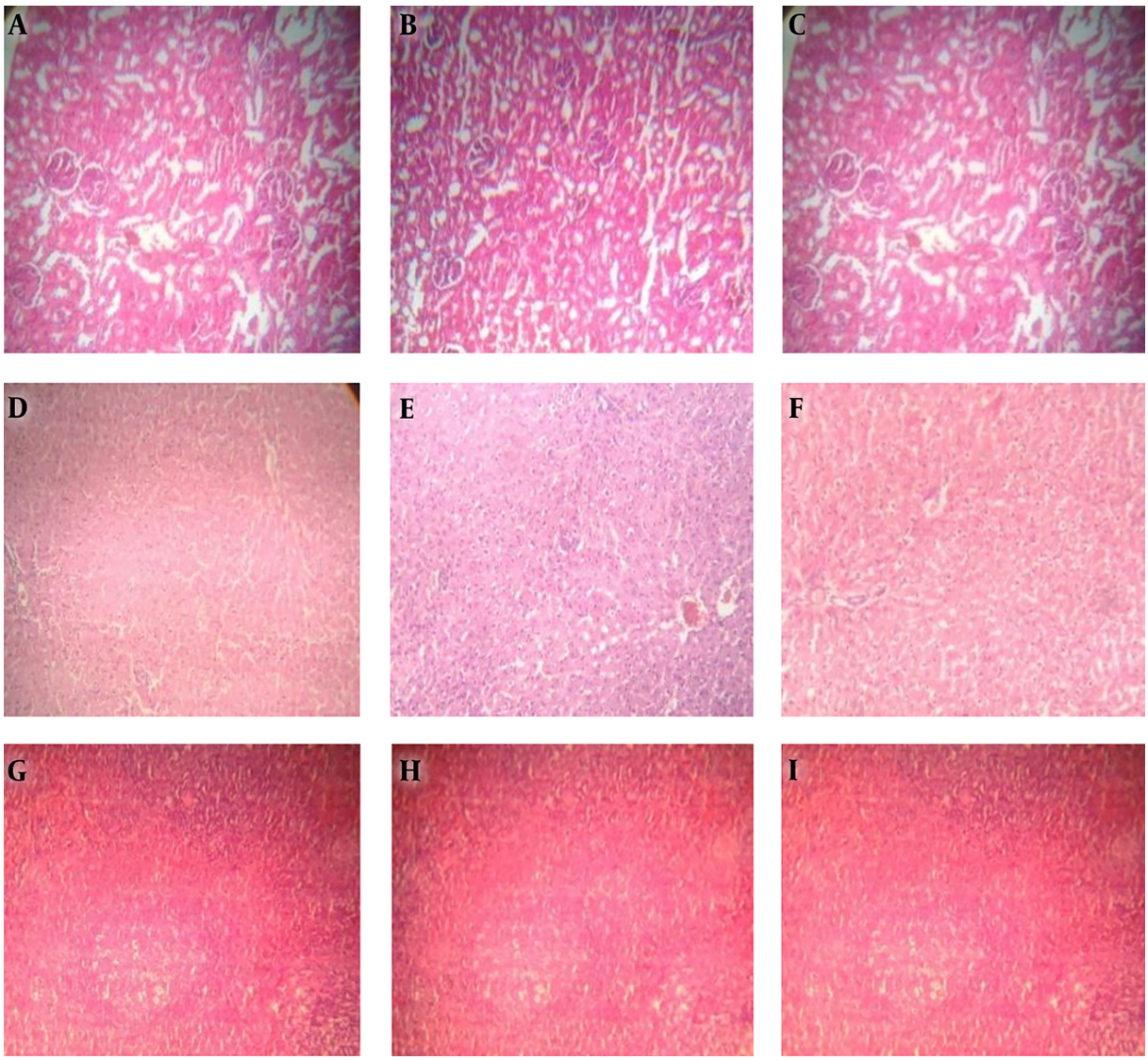

Figure 5. Microscopic views of: the kidney in normal (A), tablet (B) and fluoxetine (C) groups, showing no structural change in the shape of renal corpuscles and convoluted tubules; the liver in normal (D), tablet (E) and fluoxetine (F) groups, showing no structural change in hepatic cord and portal vein; the spleen in normal (G), tablet (H), and fluoxetine (I) groups, showing no structural change in white and red pulps.

tion of the Hypothalamus-Pituitary-Adrenal Axis (HPAA) (33). Also, in another study, biological syndromes were improved in the depression animal model by ASMq after 24 days of oral administration (34). Regarding recent studies on the antidepressant effects of "*Monzej-e soda*" ingredients, a combination of them should have the same effect, as well. Moreover, the synergetic effects of ingredients may possibly occur. But, it should be mentioned that this product is used in ITM as a decoction and it is possible that tablet formulation, especially spray drying procedure, may change some components and their biological effects; therefore, it is necessary to evaluate the effect of every novel dosage form after reformulation from traditional to modern dosage forms. The results of our research demonstrated the antidepressant effect of the prepared tablets. Regarding the complex mixture of the "*Monzej-e soda*" tablet, which contains various secondary metabolites, especially polyphenolics, flavonoids, saponins, and anthocyanins, various pathways could be involved in antidepressant properties, which are necessary to be investigated in further studies.

5.1. Conclusion

The present research confirmed that the formulated polyherbal tablet based on ITM produced an antidepressant effect via a significant increase in the serum levels of serotonin and noradrenaline that could be a good choice for depression after passing clinical trials.

Footnotes

Authors' Contribution: Sara Zakerin performed the research, collected, analyzed, and interpreted the data, and drafted the manuscript. Homa Hajimehdipoor designed and supervised all the experiments and participated in revising the manuscript. Seyed Alireza Mortazavi supervised the formulation of the tablets. Masoumeh Sabetkasaei supervised the pharmacology section. Rasool Choopani and Shirin Fahimi helped in the extraction of the manuscript from traditional references.

Conflict of Interests: The authors declare no conflict of interest.

Ethical Approval: The study protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran, with code No. IR.SBMU.RETECH.REC.1396.532.

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