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Hab-o Shefa, a Persian Medicine Compound for Maintenance Treatment of Opioid Dependence: Randomized Placebo-Controlled Clinical Trial

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Abstract

Objectives: The major problem in maintenance treatment of opioid use disorder is craving and relapse. The utilization of herbal compounds and complementary therapy for treatment of disease and addiction has been widely expanding. Considering the significant effect of Hab-o Shefa in detoxification phase, this clinical trial has explored the influence of this compound on maintenance treatment of opioid-dependent patients. This product is made of four herbs, including *Datura stramonium* L., *Rheum palmatum* L., *Zingiber officinale* Roscoe, and *Acacia senegal* L.

Design: The authors conducted a two-group parallel randomized double-blind clinical trial on 81 opioid-dependent patients within 12 weeks. After medically assisted detoxification, participants were assigned randomly to Hab-o Shefa ($n=41$) and placebo ($n=40$). Outcome measures included craving assessed by craving beliefs questionnaire, self-reported opioid use, and lapse (any opioid-positive urine test) according to urinalysis and addiction severity index-lite questionnaire, retention in treatment, and depression and anxiety scores on the Hamilton's anxiety and depression scales.

Results: Forty-one participants completed the study for 12 weeks, 21 subjects in the drug group and 20 subjects in the placebo group. The rates of opioid-positive urine tests and self-reported opioid use were significantly lower in Hab-o Shefa group ($f=8.41$, $p=0.001$). Hab-o Shefa also indicated a significant superiority over placebo in the effect of treatment by time interaction for craving ($f=5.91$, $p=0.001$), depression ($f=3.40$, $p=0.01$), and anxiety ($f=2.58$, $p=0.035$). The retention time was 66.6 days for drug group and 59.6 days for placebo one. Although the causes for dropping out in two groups were different, there was no significant difference ($p=0.623$). The side effects of the two groups were not significantly different.

Conclusion: Results indicated that Hab-o Shefa could be useful for opioid maintenance treatment, and it can also be considered as a new promising drug for prevention of craving and relapse.

Keywords: opioid, addiction, craving, Persian medicine, maintenance treatment

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Introduction

Opioid dependence is one of the major health concerns and social issues in most societies.[1] Opioids are among the three most commonly used substances in the world and they have also been the most problematic abused substances in Iran.[2] Generally, for addiction treatment, there are four main goals: reducing the symptoms of withdrawal, managing and controlling craving, stopping the rewarding effects of drugs, and treating comorbidities such as depression and anxiety.[3]

Although various methods have been suggested to attenuate withdrawal symptoms, a long-term treatment for at least 1 year or even more after detoxification phase is required.[4] The main problem of treatment is relapse, which is defined as two or more consecutive lapses. Craving, described as a strong desire for substance use, is one of the main reasons for relapse.[5] Based on several studies, some drugs have been found to reduce craving such as naltrexone and baclofen, but no drug has been specifically approved by the Food and Drug Administration as anticraving drug.[4,6]

Moreover, the comorbidities are estimated to be up to 65% among opioid-dependent patients, which play an important role in relapse.[7] Maintenance treatments for opioids have little effect on comorbidities.[8] Finally, despite the existing therapeutic approaches and their positive effects, there is a treatment gap difference between prevalence of disease and the number of patients under treatment in the treatment of addiction.[2,9]

Most recently, the utilization of traditional medicine for the treatment of addiction has been widespread in many countries. In the history, Persian medicine (PM) dates back to 10,000 years ago, which was one of the burgeoning schools of medicine.[10] PM with several thousands of articles, famous scientists, and verbal sources in different languages can be helpful in the treatment of various diseases and in the development of new drugs by using modern technology.[11–14] Some of the physicians in PM were the pioneers of neurology, psychiatry, and psychology.[15,16] Some of the first psychiatric hospitals were established by them.[17] Imad al-Din Mahmud, a famous PM physician, has penned the first comprehensive book in history on the topic of opium and its pertinent issues.[18] In the mentioned book and other PM literature, various methods such as replacement therapy with single product and herbal compounds for the treatment of opiate addiction were expressed. One of them is a herbal remedy called Hab-o Shefa.[19] This product is made of four herbs, including *Datura stramonium* L., *Rheum palmatum* L., *Zingiber officinale* Roscoe, and *Acacia senegal* L. Herbal remedies can be an appropriate solution to this problem due to their high acceptance by the public and society, little side effects, high influence, availability, and affordability.[20,21]

In recent investigations, Hab-o Shefa's effects on opioid withdrawal symptoms and pain were studied.[19,22–24] The toxic consideration of Hab-o Shefa in the study of animal toxicology did not exhibit any toxicity sign, also in another randomized clinical trial (RCT), no significant side effect was observed.[19,22] In the double-blind clinical trial performed in the authors' research center on the effect of Hab-o Shefa on detoxification treatment of 90 opiates addicts, Hab-o Shefa was more effective than clonidine in controlling subjective opioid withdrawal symptom, clinical opioid withdrawal symptom, depression, and anxiety.[22]

Considering the results of this product in detoxification phase, the aim of this study was to investigate the preliminary effect of this product on the rates of lapse, craving, anxiety, and depression in maintenance treatment for those with opioid use disorder.

Materials and Methods

Study overview

This study was registered in the Iranian Registry of Clinical Trial (RCT No. RCT2015101024446N1) and was licensed by Shahed University Research Ethics Committee (No. 1233/4) on March 9, 2015.

At the beginning of the study, the objectives, advantages, and the probable disadvantages of the process were comprehensively explained to the participants.

It was also mentioned that their cooperation is voluntary and in case of rejection, they can resume their routine treatment. Moreover, it was elaborated that they could quit their cooperation at any time they would like to. The first participant was enrolled on July 2015 and the last participant was discharged on March 2017. All subjects enrolled voluntarily and signed the informed consent.

Study design. This was a semiexperimental randomized parallel group and double-blind clinical trial. After detoxification, the subjects were treated for 12 weeks and evaluated for outcomes in four times: before the onset of the medication (pretest), 4 weeks (post-test 1), 8 weeks (post-test 2), and 12 weeks (post-test 3) after the onset of treatment. The participants of negative naloxone challenge test (NCT) were asked to complete the demographic information form, addiction severity index-lite (ASI-Lite) questionnaire, craving beliefs questionnaire (CBQ), and Hamilton's anxiety and depression scale. Patients were allowed to take acetaminophen and antihistamine if needed, but they were excluded from the study if continuous medication was necessary (for instance, in the case of remaining the symptoms of the disease or being afflicted to a disease that requires continuous treatment).

Detoxification and intervention

To initiate the study, first a complete description of research and its purpose was provided for the selected subjects. After consents of patients, they underwent detoxification by administration of clonidine, nonsteroid anti-inflammatory drugs such as diclofenac sodium, chlordiazepoxide, hyoscine, and acetaminophen over a period of 10–14 days. Then the drugs were gradually quitted within a week. At the end of detoxification, morphine urine test was performed and then, if negative, to determine the opioid dependence, the NCT was performed by intravenous administration of naloxone (0.8 mg). This test was indicative of opioid dependency, drug interferences that cause the morphine test result to be positive or false-negative have no effect on the result.

Subjects and location

The participants were selected for this trial from a residential center of addiction treatment in Isfahan, Iran (Its name was Navide Zendegi). The addiction therapist visited subjects and performed physical and psychologic examination. The

number of patients in this period was 164. Subjects were selected using purposive sampling, a method that is selected for opting participants of the study with specific characteristics based on the inclusion and exclusion criteria.

Inclusion and exclusion criteria

In this study, the inclusion criteria were as follows: Diagnostic and Statistical Manual of Mental Disorders-IV criteria for addiction, age between 18 and 65 years, desire to participate in the study, healthy condition, and signed informed consent. The following exclusion criteria were considered: addiction to alcohol, positive history of other psychiatric disorders, taking psychiatric drugs such as sodium valproate and lithium, pregnancy and breast feeding, serious medical diseases such as glaucoma, urinary retention, epilepsy, Parkinson, brain disease, heart and renal disease, allergic reaction to medical herbs, and incidence of side effect.

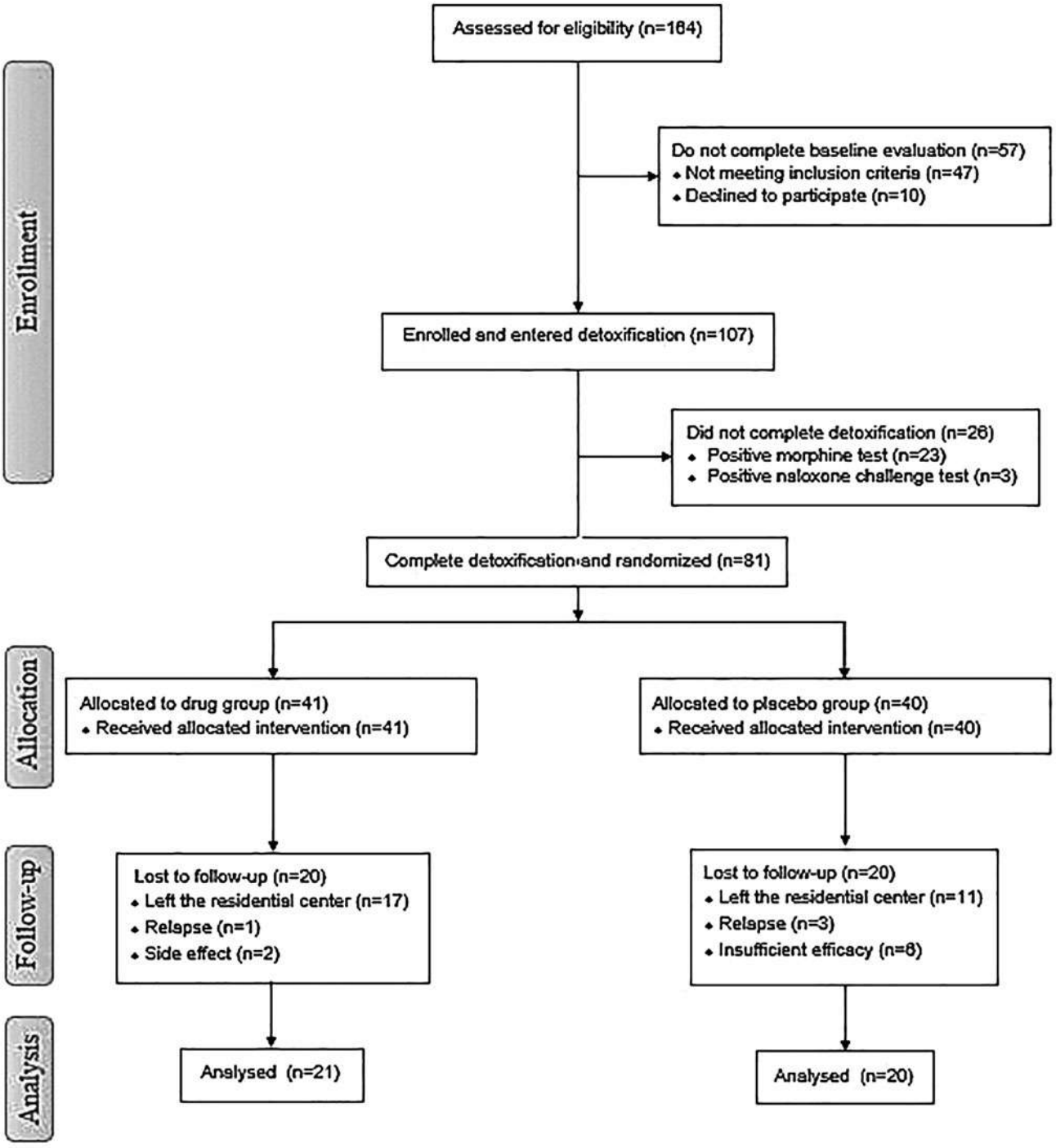

FIG. 1. Participant flow (Consolidated Standards of Reporting Trials diagram).

Plant material

The combination of Hab-o Shefa includes *Datura stramonium* L. seed at a rate of 43.3%, root of *Rheum palmatum* L. at a rate of 27.9%, *Zingiber officinale* Roscoe rhizome at a rate of 14.4%, and *Acacia senegal* L. at a rate of 14.4%. *D. stramonium* is the main ingredient of this compound. Dry plant was purchased from Vazir Nezam Company in Tehran, Iran, and was identified in the Herbarium Center of School of Pharmacy, Tehran University of Medicinal Sciences, under the voucher numbers PMP-779 for *Datura stramonium* L. (solanaceae), PMP-250 for *Rheum palmatum* L. (polygonaceae), PMP-251 for *Zingiber officinale* Roscoe (zingiberaceae), and PMP-842 for *Acacia Senegal* L. (leguminosae). The products were completely floured and mixed according to the ratio mentioned earlier and prepared by the third person who was blind to the composition of drug as 500 mg capsules in the pharmaceutical laboratories of traditional medicine in Shahed University of Tehran, Iran. For placebo, powdered sugar was selected and prepared in capsules of the same shape and weight. The initial dose was 500 mg per day, with a daily increase of 500 mg to three capsules per day (eventually after 3 days).

Randomization

The selected patients randomly allocated to the study groups and the desired drugs (Hab-o Shefa or placebo) by using random number table that were encoded by computerized random numbers without any mention of names. They were distributed by a third person who had no direct contact with the patients and the investigator. The allocation ratio was 1:1, with 41 patients in the intervention group and 40 patients in the control group. The duration of the drug consumption was 12 weeks. Patients and prescribing doctor were not aware of the contents of capsules.

Assessments

The outcome measures in this study were the number of opioid negative urine test, craving, depression, anxiety, and retention in treatment. Craving measures beliefs about the craving substances and it has been assessed with CBQ, which is a self-report scale. The questionnaire contains 20 questions each of which is scored on a scale of 1–7 degrees (from strongly disagree to strongly agree).[25,26] Hamilton Rating Scale for Depression was employed to assess depression[27] and Hamilton Anxiety Scale was applied for assessment of anxiety.[28] Treatment retention is the number of days that the participant remains in the study from the beginning of the medication until the last day of the study.[29] The validity and reliability of all tools employed to fulfill this study have been evaluated and verified in Persian.[30–33]

Participants were examined each month and rated for symptoms typically pertinent to pharmacologic side effects of Hab-o Shefa by a score sheet, including headache, weakness, blurred vision, dyspnea, palpitation, dysuria, urinary retention, tremor, vertigo, and nausea. Each item was rated as present (1) or absent (0). Vital signs, including blood pressure, temperature, pulse rate, and respiration rate, were also recorded monthly.

Statistical analysis

Craving, anxiety, and depression were analyzed using SPSS version 16. For this purpose, repeated measures analysis of variance (ANOVA) was applied. Before performing repeated measures ANOVA, the normal distribution of the dependent variables was evaluated by the Kolmogorov–Smirnov test. Furthermore, so as to evaluate the assumption of sphericity matrix-dependent variables, Mauchly's test sphericity was utilized. The results revealed that the assumption of sphericity for anxiety, depression, and craving was established. All statistical tests were two-sided and were considered significant at $p < 0.05$.

Table 1. Baseline Demographic and Clinical Characteristics of Participants

	Hab-o Shefa	*Placebo*	p*
Age, mean (SD)	33.9 (6.32)	35.85 (7.54)	0.375
Married, *n* (%)	13 (62)	10 (50)	0.443
Unemployed, *n* (%)	2 (9.6)	1 (5)	0.679
High-school education or less, *n* (%)	16 (76.2)	15 (75)	0.91
Years of opioid use, mean (SD)	10.76 (5.7)	10 (3.7)	0.623
Lifetime IDU, *n* (%)	6 (28.6)	7 (33.3)	0.83

*By independent *t* test.
IDU, intravenous drug use; SD, standard deviation.

Results

Characteristics of the participants, recruitment, retention in treatment, and follow-up

Figure 1 illustrates recruitment, enrollment, and follow-up of participants in this study. Out of 164 participants who were initially examined, 107 eligible patients were enrolled and detoxified. Among them, 26 failed to successfully complete the detoxification process. The 81 remained subjects were randomly allocated to two groups and received either drug or placebo. Finally, a total of 41 participants completed the study for 12 weeks: 21subjects in the drug group and 20 subjects in the placebo group.

Demographic and clinical characteristics of participants are demonstrated in Table 1. There is no significant difference between the two groups in these parameters.

The mean retention time in the Hab-o Shefa group for 84 days of study was 66.6 ± 30.28 days and it was 59.60 ± 34.80 in the placebo group. Independent *t* test analysis indicated that there was no meaningful difference between the two groups ($p = 0.623$). The reasons for dropping out differed in two groups (Table 2). In the drug group, ineffectiveness of

Table 2. Reasons for Dropout in Hab-o Shefa and Placebo

	Hab-o Shefa (N = 41), n *(%)*	*Placebo (N = 40),* n *(%)*	*Total (N = 81),* n *(%)*
Left the residential center	17 (85)	11 (55)	28 (70)
Drug side effect	2 (10)	—	2 (5)
Relapse	1 (5)	3 (15)	4 (10)
Insufficient efficacy	—	6 (30)	6 (15)
Total	20 (48.8)	20 (50)	40 (49.4)

Table 3. Results of Morphine Urine Test and Self-Reported Opioid Use

	Positive morphine urine test			*Self-reported days of opioids use*		
Time	*Hab-o Shefa*	*Placebo,* n *(%)*	p	*Hab-o Shefa*	*Placebo*	p
4th Week	0	1 (5)	0.306	0	0.25 ± 1.12	0.312
8th Week	0	7 (35)	0.003	0	3.55 ± 7.41	0.017
12th Week	0	14 (70)	0.001	0	7.15 ± 9.05	0.001

the drug was not the reason for dropping out and in case of a person (5%) interruption was due to relapse. In the placebo group, 30% of dropping out was due to insufficient efficacy (which was reported by participant) and in three persons (15%) interruption was due to relapse.

Effects on substance use

The results of morphine tests and self-reported opioid use are demonstrated in Table 3. The analysis by Mann–Whitney *U* test indicated that in the 8th and 12th weeks, the frequency of lapse rates in the placebo group was significantly higher than that of the Hab-o Shefa group. The self-reported opioid use also confirmed these findings so that with the passage of time, the self-reported opioid use in the Hab-o Shefa group was 0. However, it increased in the control group over time ($f = 8.41$, $p = 0.001$).

The effects on craving, depression, and anxiety

To evaluate the efficacy of Hab-o Shefa on craving, anxiety, and depression in subjects, repeated measure ANOVA was employed. The results are presented in Table 4. The results demonstrated that all dependent variables in four stages of evaluation followed normal distribution. The results were considered for a selection of the test effects among the subjects.

Craving. The results of the test of pairwise comparisons with Bonferroni's correction indicated that the craving rate decreased significantly only in the Hab-o Shefa group. These results revealed that the Hab-o Shefa caused the reduction of craving over time ($f = 4.10$, $p = 0.002$). Also, the effect of treatment by time interaction indicated that the changing trend in craving over time in the Hab-o Shefa group was different from that of the placebo group ($f = 5.91$, $p = 0.001$). Thus, the craving score decreased in the Hab-o Shefa group, whereas in the placebo group it decreased in 4th week but increased in the 8th and 12th weeks.

Depression. There was a significant effect of time on depression ($f = 2.96$, $p = 0.021$). With this regard, the results of the test of pairwise comparisons with Bonferroni's correction demonstrated that the depression rate in placebo group increased significantly in 4th and 8th weeks compared with that of the 12th week. In contrast, the level of depression in the Hab-o Shefa group has not changed over time. Also, the effect of treatment by time interaction indicated that the trend of change in depression over time in the Hab-o Shefa group was different from that of placebo group ($f = 3.40$, $p = 0.010$).

Anxiety. The results of the test of pairwise comparisons with Bonferroni's correction displayed that the anxiety rate changed only in the placebo group. In contrast, the level of anxiety in the Hab-o Shefa group did not change over time. So, there was a significant categorical effect of time ($f = 2.40$, $p = 0.021$). Also, the effect of treatment by time interaction disclosed that the trend of change in anxiety over time in the Hab-o Shefa group was different from that of placebo group ($f = 2.58$, $p = 0.035$). On the contrary, although the change in anxiety level in the placebo group until week 8 was almost constant, it increased significantly in week 12.

Table 4. Effects of Treatment-Group Assignment on Craving, Depression, and Anxiety

	Pretest (mean ± SD)	*4th Week (mean ± SD)*	*8th Week (mean ± SD)*	*12th Week (mean ± SD)*	*Main effect of time*	*Main effect of time × treatment*
Craving						
Hab-o Shefa	71.55 ± 20.27	61.40 ± 11.38	59.05 ± 13.68	50.60 ± 9.89	$F = 4.1$*,	$F = 5.91$*,
Placebo	68.65 ± 19.48	58.01 ± 21.81	64.25 ± 19.17	71.50 ± 22.21	p** = 0.002	p** = 0.001
p-Value***	0.647	0.338	0.63	0.003		
Depression						
Hab-o Shefa	10.45 ± 7.82	6.3 ± 3.9	6.55 ± 5.55	6.35 ± 4.48	$F = 2.96$*,	$F = 3.4$*,
Placebo	9.1 ± 4.45	7.35 ± 4.42	8.45 ± 5.15	12.3 ± 5.77	p** = 0.021	p** = 0.01
p-Value***	0.253	0.217	0.126	0.001		
Anxiety						
Hab-o Shefa	11.8 ± 8.96	10.7 ± 4.93	12.1 ± 7.28	11.75 ± 5.63	$F = 2.4$*,	$F = 2.58$*,
Placebo	9.9 ± 5.01	11.8 ± 5.4	10.4 ± 5.12	16 ± 9.28	p** = 0.042	p** = 0.035
p-Value***	0.413	0.5	0.388	0.04		

*The effects of the test subjects with the assumption of sphericity.
**By repeated measure analysis of variance.
***By independent *t* test.
ES, effect size.

Discussion

The objective of this study was to investigate the effect of Hab-o Shefa on the rates of lapse, retention in treatment, craving, anxiety, and depression in maintenance treatment of people with opioid use disorder. This is the first time that this study has been conducted for evaluation of this component in maintenance treatment. The results showed that this compound has reduced the rates of lapse, self-reported opioid use, craving, depression, and anxiety.

The index of lapse rates in this study has suggested that the rate of lapses in the placebo group is significantly higher than the Hab-o Shefa group. Also, the results of the ASI-Lite questionnaire have unraveled that the Hab-o Shefa group did not have any history of self-reported opioid use during the study, whereas in the placebo group an increase in the number of days of consumption was evident. Although there has not been any similar study on Hab-o Shefa, studies on the effect of other drugs in opioid maintenance therapy such as baclofen, olanzapine, and extended-release naltrexone have disclosed similar results in terms of the positive morphine urine test and self-reported opioid use.[30,34,35] One of the fascinating points in this study was the significant difference of self-reported opioid use and rates of lapse between placebo and Hab-o Shefa after the first month. The two groups showed similar results in the first month. To explain such results, it can be inferred that one of the reasons for the negative morphine urine test and self-reported opioid use in the placebo group in the week 4 is the placebo effect that was eliminated after this period and consequently the rates of lapse were increased in the placebo group. Thus, the Hab-o Shefa despite lack of agonistic effects on opioid receptors led to significant reduction in the rates of lapse and self-reported opioid use.

Shih-ku Lin who reviewed the drugs for craving states that among naltrexone, acomprosate, topiramate, disulfiram, baclofen, *n*-acetyl cysteine and bupropion that were presented as anticraving drugs, only naltrexone and baclofen effectively reduced craving in opioid addicted patients.[36] The possible cause of anticraving effect of naltrexone may be lack of pleasure in the use of opioid. However, the mechanism of baclofen is unclear.[4] The results also demonstrated that Hab-o Shefa significantly reduced craving scores compared with that of placebo (Table 4). The mechanism(s) of Hab-o Shefa in reduction of craving is not clear yet. However, the most important alkaloids of *Datura stramonium* L. (main ingredient of Hab-o Shefa) are scopolamine and hyoscyamine that have anticholinergic effect.[37] In this regard, Liu et al. have reported that administration of scopolamine in opioid addicts, not only did reduce physical symptoms in detoxification, but also had significant anticraving effect compared with the effect of methadone.[38]

The results indicated that the depression and anxiety scores in the placebo group increased significantly during the week 12. On the contrary, these scores in the Hab-o Shefa group did not change over time. The mechanism(s) of Hab-o Shefa in reducing depression and anxiety are yet to be identified. In case of its main alkaloid, scopolamine, several studies on animals and human beings have displayed evidence of antidepressant effects of scopolamine.[39–42] In tandem with these results, increasing cholinergic activity can induce depression-like behaviors in human beings and animals, consequently reducing cholinergic activity may be associated with alleviated depressive symptoms.[43–47]

Study limitations

This study had some limitations. One of the limitations was the high rate of dropping out during the study. Many patients were discharged from the center after treatment's period and had no access to the study. The next limitation was the small sample size. Failure to follow-up after termination of intervention to evaluate the efficacy or possible side effects was another limitation. Moreover, false-negative urine morphine test was a limitation, of course, for both groups.

Conclusions

The results of this study have provided the primary evidence to support the hypothesis that Hab-o Shefa is useful in opioid maintenance treatment and its associated parameters, particularly craving. In terms of relapse prevention, it can be a new promising drug. Further studies are required to elucidate the underlying mechanism(s) of Hab-o Shefa on craving. It is recommended for future studies to be conducted with larger participants and in outpatient centers. In addition, the patients could be followed up, for example, 6 months after completion of treatment to determine the product stability effects.

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Statement of Ethics

The Iranian Registry of Clinical Trial number and Ethics Committee license of this study was RCT2015101024446N1 and No. 1233/4 on March 9, 2015, respectively.

Authors' Contributions

Ab.M. performed experiments and cowrote the article; Az.M. and M.N. designed the experiments and cowrote the article; F.G., H.A., and R.J.H. cowrote the article; S.F. did the data analysis.

Author Disclosure Statement

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