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Review

The Perspective of Traditional Persian Medicine on Botanicals Effective in Quitting Opium Addiction: A Review

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Abstract

Traditional Persian medicine (TPM) is a set of theoretical and practical sciences that are used in the diagnosis, prevention, and treatment of physical, mental, or social disorders. This holistic medical system can provide solutions for some diseases, including drug addiction, that modern medicine, only offers symptomatic treatment. Since the addiction prevalence in the 16th century, Persian medicine scholars have introduced various ways to quit it. In this study, we investigated if Persian medicine has treatment options to quit opium addiction. We studied the main textbooks of TPM that specifically talked about addiction. Our study was conducted according to a systematic prioritization in traditional medicine. Additionally, scientific databases such as PubMed, ScienceDirect, Scopus, and Google Scholar searched for plant active ingredients in current pharmacology. By this method, forty-nine drugs were found, and nine drugs with herbal origin obtained the highest score in addiction treatment. Since the main purpose of the study is finding new drugs theoretically effective in quitting opium addiction; we sought to find evidence of that effectiveness in modern pharmacology and we found them in most prioritized drugs. Prioritizing traditional drugs can lead to find new drugs which also have evidence of effectiveness in modern studies. Therefore, they could be introduced as novel natural remedies for disease. The list of drugs obtained in this study can be the basis for conducting in vitro and in vivo studies for design and development of new drugs in the treatment of opium addiction. In fact, traditional medicine could have a special place in quitting opium addiction, and this capacity should be further exploited.

Keywords: Addiction; Traditional persian medicine; Herbal remedies

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Introduction

Opium addiction is one of the major concerns of the global health system [1], imposing a high economic cost on nations. While the abuse of opium and its derivatives is increasingly expanding in human societies, definitive and correct treatment is considered urgent [2]. Experience over the past few decades has shown that conventional drugs used to quit opioid addiction, with their entire efficacy, have undesirable side effects. In some cases, they have caused addiction themselves [3]. Traditional drugs contain natural substances that can be effective in treating addiction [4,5]. Traditional Persian Medicine (TPM) is a set of theoretical and practical sciences used in the prevention, diagnosis, and treatment of physical and mental disorders, including addiction, which modern medicine limits to symptomatic treatment alone [6]. Persian medicine scholars have been familiar with the therapeutic uses and side effects of opium and addiction and quitting it. They have proposed various treatment options for quitting opium addiction: 1) to increase the period between opium consumption 2) the arranged reduction of the opium dose [7,8] 3) to replace opium with a single drug (natural opiate) or compound drug (opioid) and then taper off them [9-11]. Making medicinal drugs based on doctrines of various types of traditional medicines that have been used for centuries is called reverse pharmacology. A salient feature of this approach is the combination of knowledge learned from traditional or folk medicine and modern technology to provide better and safer products [12-14]. Over the past centuries, traditional medicine texts have cited numerous therapies and medications that make it challenging to choose one drug as the most appropriate option. This seems to be an essential challenge. Solutions have also been suggested to optimally utilize these resources, including software systems designed for Ayurvedic medicine resources and traditional Chinese medicine [15,16]. Also, prioritizing the drugs recommended in traditional medicine sources seems a practical, low-cost, and effective way to find the best drug to treat addiction. In TPM, for the first time, drugs recommended in epilepsy were prioritized with two principles: to be emphasized and to be repeated in traditional medicine sources over centuries [17]. Then, this way was used in other studies to prove its efficacy to find new drugs [18-21]. Since systematic research with a fixed and specific method about drugs that are useful in stopping addiction from the perspective of TPM has not been done, so the subject was selected to search for single or compound drugs effective in quitting addiction in outstanding resources. In TPM, single drugs are mixed to make compound drugs due to several reasons: 1) Balancing the strength of the drug 2) Increase the potency of the ingredients through the synergistic effect 3) Toxicity elimination of some components 4) Cover up the unpleasant taste [9].

Methods

This study is a library review study and includes sources that have considered opioid addiction as a disease and mentioned different strategies for treating addiction and its complications. These

manuscripts have been written from the beginning of the 16th century (time of the onset of the addiction epidemic in Iran) to the end of the nineteenth-century (time of the decline of Persian medicine). This study is based on a systematic method that has been proven in prioritizing drugs in TPM [19].

• Determining the references: Since addiction was not identified as a disease with personal and socially destructive effects before the epidemic, in the early sources of TPM, there is no mention of the problem of addiction despite the familiarity with opium and its side effects and how to treat them. So we selected reliable sources that were written after that time and from different geographical areas. The TPM texts included Afyunieh (Imad al-Din Mahmud ibn Mas'ud Shirazi 16th century [8]) Tuhfat al-mu'minīn (Hakim Mumin Gilani 1669 AD [22]); Qarabadin-e-Kabir (Mohammad Hossein Aghili Alavi Khorasani 1816 AD [9]); Kholasat al-tajarib (Baha al-DawlahRazi 1501 AD [23]); Bikh-e-chini (Imad al-Din Mahmud ibn Mas'ud Shirazi 1614 AD [8] and Makhzan al-adviyah (Mohammad Hossein Aghili Alavi Khorasani 1804 AD [24]). The primary basis of this research is the Book of Afyuniyah, the most important Iranian medical treatise on opium addiction and its treatment. It was compiled by Hakim Imad al-Din Mahmud ibn Mas'ud Shirazi in the 16th century. This era coincided with the spread of specific diseases and no treatment, including addiction.

• Finding the traditional equivalent: Since the term 'addiction' has not been used in Persian medicine literature, the terms of its equivalents and the symptoms mention, have been identified. Our keywords in searching sources were:" treatment of getting used to opium", "recurrence", "opiates", "opioid", "opiate", "withdrawal" and also concepts that implicitly referred to the problem of addiction were recorded.

• Finding the keywords studied: By reviewing the sources, keywords related to the drugs effective in quitting opium addiction were identified. Our keywords in searching sources were mentioned above. Our searches were in the Persian language, so we translated our keywords for the article presenting.

• Search Resources: At this point, all sentences that directly or implicitly referred to quitting addiction were noted.

• Revision: In the next step, the names of all drugs that were solely effective in some withdrawal side effects were removed from the list.

• 2-6-Preparing a data list: All drugs and their information were collected in a single set.

• Finding the synonyms and categorizing: Since drugs were sometimes used in different names throughout the centuries, synonyms of each drug were found then each drug with the more popular name was noted.

• Final scoring: According to the description of each drug in the treatment of addiction, scoring was performed. The use of comparative or superlative adjectives in describing drugs have different scores as mentioned in table 1.

• Prioritization: The sum of the scores was finalized to prioritize the drugs based on the scores given [17,19,25]. The score points, terms, and idioms used in traditional medicine sources to describe the effects of each drug in quitting opium addiction are listed in Table 1.

• In the end, recent studies about the herbal ingredients in relation with the treatment of opium addiction were studied in databases such as PubMed, Scopus, ScienceDirect, and Google scholar from the inception until the end of the study. The results were compared and confirmed with the recent evidence on the herbs' related active ingredients and therapeutic mechanisms of action.

Results

According to the terms used to describe the advantages in the treatment of addiction, points and scores were assigned based on the expression and description of each drug (Table 1). Among the forty-nine drugs that have been found in treating addiction, nine drugs with the herbal origin had the highest score (Table 2,3). Among them four are single and five are compound drugs. All of them were alphabetically listed in table 4.

As shown in table 1, the descriptions in each book about the effect of each drug on the treatment of opium addiction were considered.

According to the scores, Habb-e-khorramgyah, Habb-e-Harmal, Tiryaq-e-Farooq, jollab, Barsh-e-Abolbarakat were among compound drugs and, Bikh-e-chini, Jadvar, Bazrolbanj, and Heltit in single drugs scored the highest points, respectively. Relevant explanations are given in table 2 and table 3.

Table 1. Score points, terms, and idioms used in traditional medicine sources to describe the effects of each drug in quitting opium addiction.

Scoring	Terms and idioms used in traditional medicine sources
1	Substitution; almost good and relatively fast; effective; beneficial; instead; spurious; not bad; advantageous; helpful; lucrative
2	Very easy way; being able to quit; suitable; quit opiate habit; the most beneficial; very useful; favorable; lieutenant
3	The best rules for quitting the opium; experienced; ablative; best and most effective spices; extreme quality; many people have been able to quit with it; fast and effective; unparalleled; the best replacements

Table 2. Endpoint score and Ingredients of compound drugs

Compound drug	Ingredients	Rating based on resources	Final Score
Habb-e-khorramgyah	Tar, *Agrostemma githago* L., *Crocus sativus* L., *Ipomoea nil* (L.) *Roth, Hyoscyamus niger* L., *Cinnamomum verum* J.*Presl, Myristica fragrans Houtt*., *Strychnos nux-vomica* L., *Fraxinus excelsior* L., and honey	Afyunieh (+3) Qarabadin-e-Kabir (+8)	+11
Habb-e-Harmal	*Peganum harmala* L., *Polygonatum orientale* Desf., *Fraxinus excelsior* L., tail fat	Afyunieh (+3) Qarabadin-e-Kabir(+3)	+6

Tiryaq-e-Farooq	*Laurus nobilis* L., *Mentha aquatica* L., *Gentiana cruciata* L., *Commiphora myrrha* (Nees) Engl., *Crocus sativus* L., white pepper, *Cinnamomum verum* J.Presl, wine, honey and viper meat	Afyunieh (+1) Qarabadin-e-Kabir (+3)	+4
Jollab	Rose water, fine sugar, *Crocus sativus* L	Afyunieh (+2) Kholasat al-tajarib (+2)	+4
Barsh-e-Abolbarakat	*Nardostachys jatamansi* (D.Don) DC., *Crocus sativus* L., *Anacyclus pyrethrum* (L.) Lag., *Amomum subulatum* Roxb., *Hyoscyamus niger* L., *Veratrum album* L., *Euphorbia antiquorum* L., white pepper, opium	Afyunieh (+2) Qarabadin-e-Kabir (+1)	+3

The information about the ingredients of compound drugs is shown in table 2.

Table 3. Endpoint score of single drugs

Traditional name	Scientific name	Family	Part of plant that used	Rating based on resources	Final Score
Bikh-e-chini	*Smilax glabra* Roxb.	Smilacaceae	Rhizome	Afyunieh (+3) Qarabadin-e-Kabir (+3) Makhzan al-adviyah (+2) Bikh-e-chini (+4) Tuhfat al-mu'minīn (+3)	+15
Jadvar	*Curcuma zedoaria* (Christm.) Roscoe.	Zingiberaceae	Rhizome	Afyunieh (+3) Qarabadin-e-Kabir (+3) Makhzan al-adviyah (+2) Bikh-e-chini (+4) Tuhfat al-mu'minīn (+3)	+13
Bazrolbanj	*Hyoscyamus niger* L.	Solanaceae	Seeds	Afyunieh (+3) Qarabadin-e-Kabir (+4)	+7
Heltit	*Ferula assa-foetida* L.	Apiaceae	Gum	Makhzan al-adviyah (+3) Kholasat al-tajarib (+2)	+5

The information about the endpoint score of single drugs is shown in table 3.

Table 4. Medicaments used for addiction treatment and other symptoms of dependence and their underlying mechanisms of action

Traditional name (Simple or Compound drug)	**Pharmaceutical form**	**Traditional usage**	**Known applications**	**Active ingredients**	**Ref.**
Barsh-e-Abolbarakat (C)	Electuary	Antidote	Unknown	-	-
Bazrolbanj (S)	Tablet	Abstinent therapy of opium addict, Sedative	Antinociceptive, Spasmolytic, antidiarrhoeal, antisecretory, bronchodilatory, Hypnotic	Hyoscyamine, scopolamine, tropane alkaloids	[38-40]

Bikh-e-chini (S)	Powder	Tonic	anti-anxiety, sedative	Flavonoids, phenolics, phenylpropanoid glycosides, steroidal saponins	[53-57]
Habb-e-khorramg-yah (C)	Tablet	Addiction treatment, skin problems, diarrhea, urinary retention, jaundice	Expectorant, Stimulant	githagin, agrostemmic acid triterpenes, saponins	[35-37]
Habb-e-Harmal (C)	Tablet	Quitting addiction, Reduced morphine withdrawal symptoms, anti-inflammatory and analgesic morphine symptoms	Antinociceptive, Antibacterial, anti-inflammatory, analgesic effects	beta-carboline and quinazoline alkaloids	[44-47]
Heltit (S)	Tablet	Addiction treatment, Antidote, Disinfectant	Antispasmodic analgesic, anti-inflammatory anthelmintic antioxidant	monoterpenes (α- and β-pinene), free ferulic acid, valeric acid, umbelliferone, , traces of vanillin	[62,63]
Jadvar (S)	Capsule	Antidote, Treatment of abdominal pain, Spasms and other smooth muscle disorders, Colds, Flu and as an anti-inflammatory in rheumatism	Reducing physical dependence on morphine, Significantly reduced morphine withdrawal symptoms, powerful analgesic, anti-inflammatory, Spasmolytic, General strengthening, Impotence	more than 10 sesquiterpenes	[58-61]
Jollab (C)	Syrup	Tonic, Addiction treatment, Treatment of Psychosomatic diseases	Analgesic, Reduce the symptoms of opioid withdrawal, anti-inflammatory, Antioxidant	terpenes, glycosides, flavonoids, anthocyanins, carboxylic acid	[48-50]
Tiryaq-e-Farooq (C)	Electuary	Antidote, Addiction treatment	Analgesic, anti-spasmodic, Detoxifier	phenolic compounds, linalool, alpha-pinene, beta-pinene, alpha terpinene	[51]

Various activities of drugs affecting the treatment of opium withdrawal are listed in the table above. The single drug is abbreviated as (S) and the compound drug is abbreviated as (C).

Discussion

Nowadays, limited information is available on the management of opium withdrawal. Many pharmacological modalities of detoxification including alpha-2 adrenergic agonists, buprenorphine, methadone, opioid antagonists, and symptomatic treatments have been used for opiate dependence [26,27]. Since the discovery of new drugs is a costly and time-consuming process, previous studies did not support using any specific pharmacological approach for the management of opium withdrawal [26,27]. One of the best ways to provide effective med-

icines is to use products that have been used in various traditional medicine doctrines for a long time. Based on TPM, natural substances and herbal drugs can play an essential and effective role in promoting health and disease prevention [28,29]. Many discoveries have been made about the healing effects of plants in modern-day applications [18,19,21,30]. In TPM, different therapeutic methods for quitting opioid addiction are proposed [31-33]. Studies on TPM texts provide valuable information for comparing and ranking natural remedies used in diseases including addiction [34, 35]. Other studies have also compiled effective drugs to treat addiction withdrawal [35,36]. In this study, the prioritization of effective compounds in treating addiction has been fully accomplished. By carefully evaluating the various drugs that are effective in the treatment of addiction and ranking them, nine single and compound drugs have the highest scores. According to table 2 (compound drugs), the first ranking is related to the Habb-e-khorramgyah. The main ingredient of the compound drug is khorramgyah, but there is no consensus on the scientific name of this plant. It must be mentioned that the suggested scientific names are *Agrostemma githago* L. and *Aster amellus* L., which are very similar in chemicals but from different families. *Agrostemma githago* L. (corncockle) contains githagin and agrostemmic acid and has been used for skin problems, such as warts and tumors, diarrhea, urinary retention, and jaundice in the past [37]. *Aster amellus* L. is also used in other traditional medicines. The plant root contains triterpenes and saponins [38] and it was shown that saponins have great efficacy in withdrawal syndrome because of their impact on the central and peripheral nervous system [39]. Other effective components are Bazrolbanj or henbane (*Hyoscyamus niger* L.), and Saffron (*Crocus sativus* L.).5*Hyoscyamus niger* L. is also used as a single drug. Hyoscyamine, scopolamine, and other tropane alkaloids have been found in this plant that shows pharmacological effects like antisecretory, spasmolytic, hypnotic, sedative, and antidiarrheal properties which make it a suitable drug to treat addiction. It is also used for abstinent therapy of opium addict persons [40-42]. Research shows that saffron and its active ingredients have analgesic and anti-inflammatory effects and reduce the symptoms of opioid withdrawal [43-45]. In the case of Habb-e-Harmal (Harmal tablet) which contains *Peganum harmala* L. as the major ingredients, beta-carboline and quinazoline alkaloids are important compounds of this plant. There are several studies on its antinociceptive effect and also on its role in quitting addiction [46-48]. In one study, the results show the significant effect of oral administration of Harmal powder in reducing the incidence of non-enumerable and enumerable morphine symptoms [47,49]. In TPM, the anti-inflammatory and analgesic effects of Harmal have been mentioned [47]. However, its use in opioid withdrawal drugs needs further study [48]. Jollab is a syrup that is recommended by TPM in many psychosomatic diseases. The main components of Jollab are Saffron (*Crocus sativus* L.) and rose water. Rose water that is an aqueous extract of *Rosa* × *damascena Herrm*., has widely used in formu-

lations of TPM medicines. This plant has some active ingredients such as terpenes, glycosides, flavonoids, anthocyanins, carboxylic acid. Suppressive effects of its essential oil on morphine withdrawal syndrome in mice have been reported [50-52]. Tiryaq-e-Farooq is a type of antidote used in many cases of poisoning. Due to many different compounds that have come to light under the name of Tiryaq-e-Farooq, it is hard to decide the main effective component of this preparation. Although viper meat is one of the main components of Tiryaq-e-Farooq, because plants were studied in this project, *Laurus nobilis* L. (another main component) was considered. However, it seems that *Laurus nobilis* L., which has analgesic effects with the active ingredients of phenolic compounds and linalool and also antispasmodic effects with alpha-pinene, beta-pinene, and alpha terpinene, plays the main role in the anti-addictive effect of Tiryaq-e-Farooq [53]. Also, Barsh-e- Abolbarakat is a kind of antidote used in the poisoning. It is challenging to decide on the main component that will play a key role in quitting opiate addiction, so it may be a subject for future research. The Bikh-e-chini is a single drug known in the pharmaceutical market as "Chinese wood", "Chinese root" and "tufuling". The medicinal part of the plant is the rhizome and the underground stem. This plant belongs to the Liliaceae family [54]. The active ingredients that have isolated and identified in this plant are several flavonoids [55], phenolics [56] and phenylpropanoid glycosides [57], and steroidal saponins [58]. The methanol extract of the rhizome of *Smilax glabra* Roxb. enhances antioxidant activities in cell culture. Some research showed that these phytochemicals can play an anti-anxiety and sedative role [59]. Jadvar is another single drug scientifically called *Curcuma zedoaria* (Christm.) Roscoe. Some researchers isolated more than 10 sesquiterpenes from the rhizome of *C. zedoaria* which has powerful analgesic and soothing effects and can help to control pain. It is a general tonic and also used to treat impotence. It is used as an antidote and repellent of toxins from the body, as well as to relieve the symptoms of arthritis, increase energy, relieve fatigue and pain caused by inflammation [60]. Studies have shown that the methanolic extract of *C. zedoaria* significantly reduced morphine withdrawal symptoms in mice [61-63]. Another single drug Heltit is an oleo-gum-resin extracted from *Ferula assa-fetida* L., a plant of the Apiaceae family. Active ingredients consist of monoterpenes (alpha- and beta-pinene), free ferulic acid, valeric acid, umbelliferone, and traces of vanillin [64]. In one study, Heltit has positive effects on the symptoms of morphine withdrawal syndrome by interfering with neurotransmitters in the nervous system [65].

Conclusion

Natural substances have a variety of effects on the body. Some of them have long been used for the treatment of diseases. But there are a lot of questions because of the novelty of this method in treating addiction. Eventually, the prioritization method for finding suitable drugs, based on the definitions of common medicine, is reliable and efficient [66]. Since the main purpose of the study is finding new drugs that are theo-

retically effective in quitting opium addiction; we try to extract and prioritize the drugs from TPM sources. The results support the efficacy of TPM medicines for the treatment of opium addiction treatment. This study represents new herbal medications that worth evaluating pharmacologically and clinically, in the field of opium addiction treatment, to confirm the effects and to consider any probable unwanted effects.

Conflict of Interest

None

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None.

References

[1] McClung CA. The molecular mechanisms of morphine addiction. Rev Neurosci 2006; 17:393-402.

[2] Pu L, Bao G, Xu N, Ma L, Pei G. Hippocampal long-term potentiation is reduced by chronic opiate treatment and can be restored by re-exposure to opiates. J Neuro Sci 2002;22:1914-1921.

[3] Sordo L, Barrio G, Bravo M, Indave I, Degenhardt L, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ 2017;357:j1550.

[4] Valipour R, Shekari A, Setareh M. Identification of medicine components in herbal drugs for addiction treatment; a case study of zanjan city. Sci J Forensic Med 2019;25:61-64.

[5] Kerachian N, Alaee H, Gharavi-Naini H, Pilevarian A, Moghim A. Effects of alcoholic extract of avena sativa, hypericumper foratum, passifloraincarnata and lavandulaofficinalis on symptoms of morphine withdrawal syndrome in rats. Iran J Psychiatry 2007;10:313-322.

[6] World Health Organization. The promotion and development of traditional medicine: report of a WHO meeting [held in Geneva from 28 November to 2 December 1977]. World Health Organization. 1978; 8-13. https://apps.who.int/iris/handle/10665/40995.

[7] Moosavyzadeh A, Jafari Hajati R, Ghaffari F, Khatami S, Vakili Zahir N, et al. From daturastramonium l to hab-o-shefa: manuscript, animal and clinical studies for the treatment of addiction. J Med Plants 2020;19:4-16.

[8] Shirazi IM, Afyunieh Choopani R, Sadeghpour O, Panahi V. Eds. 1st ed. Traditional Persian Medicine Press. Tehran 2011.

[9] Aghili Khorasani Shirazi MH. Qarabadin-e-Kabir. 1st ed. Mahmoudi Press. Tehran 1970.

[10] Arzani A. Qarabadin Qaderi. 2nd ed. Iran University of Medical Sciences Press. Tehran 2007.

[11] Nazem Jahan MA. Qarabadin-e-Azam, 2nd ed. Iran University of Medical Sciences Press. Tehran 2004.

[12] Surh YJ. Reverse pharmacology applicable for botanical drug development – inspiration from the legacy of traditional wisdom. J Tradit Complement Med 2011;1:5-7.

[13] Patwardhan B, Mashelkar RA. Traditional medicine-inspired approaches to drug discovery: can Ayurveda show the way forward? Drug Discov Today 2009;14:804-811.

[14] Patwardhan B, Vaidya ADB. Natural products drug discovery: accelerating the clinical candidate development using reverse pharmacology approaches. Indian J Exp Biol 2010; 48:220-227.

[15] Naseri M. Traditional iranian medicine (TIM) and its promotion with guidelines of world health organization. Daneshvar Med. 2004;11:53-66.

[16] Huang L, Li F, Sheng J, Xia X, Ma J, et al. Drug combo ranker: drug combination discovery based on target network analysis. Bioinformatics 2014;30:i228-236.

[17] Naseri M. Study of antiepileptic drugs in Iranian traditional medicine [PhD thesis]. Department of Medical Sciences, Shahid Beheshti University of Medical Sciences, Iran; 1993.

[18] Mozaffarpur SA, Khodadust M, Shirafkan H, Yousefi M, Mirzapor M. Introducing a model for prioritization of drugs, based on iranian traditional medicine references. Med Hist 2014;6:11-28.

[19] Mozaffarpur SA, Naseri M, Kamalinejad M, Shams MA, Memariani Z, et al. Nine steps to discover new medicines from traditional sources: the example of persian medicine. J Altern Complement Med 2020;26:365-368.

[20] Ghaffari F, Alijaniha F, Fallahi F. Single remedies for khafaghan in iranian traditional medicine. Journal of Islamic and Iranian Traditional Medicine 2013;4:1-11.

[21] Khodaei SA. Explanation of Qharhe according to Persian Medicine, and effect of topical products of Myrtuscommonis and Punicagranatum on diabetic ulcer [PhD thesis]. Department of Medical Sciences, Shahed University of Medical Sciences, Iran; 2018.

[22] Momen Tonekaboni MM. Tohfat al Momenin. 1st ed. Moasese Nashre Shahr Press. Tehran 2008.

[23] Razi Nourbakhshi B. Kholasat al-Tajarob (The Summary of Experience). 1st ed. Sahba Danesh Press. Tehran 2009.

[24] Aghili SMH. Makhzan-Al' Advieh. 1st ed. Tehran University Press. Tehran 2008.

[25] Zargaran A, Zarshenas M, Hosseinkhani A, Mehdizadeh A. Jawarish, a Persian traditional gastrointestinal dosage form. Pharm Hist 2012;42:24-25.

[26] Amato L, Davoli M, Minozzi S, Ferroni E, Ali R, et al. Methadone at tapered doses for the management of opioid withdrawal. Cochrane Database Sys Rev 2013;2013:CD003409.

[27] Gowing L, Farrell MF, Ali R, White JM. Alpha2-adrenergic agonists for the management of opioid withdrawal. Cochrane Database Sys Rev 2014;2014:CD002024.
[28] Eldahshan OA, Elsakka AMA, Singab AN. Medicinal plants and addiction treatment. Med Aromat Plants 2016;5:260.
[29] Arulsamy A, Kumari Y, Shaikh MF. Reverse pharmacology: fast track path of drug discovery. Pharm Pharmacol Int J 2016;4:358-359.
[30] Edens E, Massa A, Petrakis I. Novel pharmacological approaches to drug abuse treatment. Curr Top Behav Neurosci 2010;3:343-386.
[31] Mahdizadeh S, Khaleghi Ghadiri M, Gorji A. Avicenna's Canon of Medicine: a review of analgesics and anti-inflammatory substance. Avicenna J Phytomed 2015;5:182-202.
[32] Inanlou M, Bahmani B, frhoudian A, Rafiee F. Addiction recovery: a systematized review. Iran J Psychiatry 2020;15:172-181.
[33] Naseri M, Vakili Zahir N, Khatami S, Mizani A. Scientific Reassessment of Old Medical Sources Can be a Futuristic Approach for New Opium Addiction Drug. Proceedings of the 8th National Congress on Medicinal Plants. 2019 April 24,25; Tehran.
[34] Nazari M. Explanation of addiction and its treatment methods traditional Iranian medicine and investigation of effect of Habb-o-Shefa on control of withdrawal symptoms of opioid dependency: A randomized, double blind, controlled clinical trial in acute detoxification [PhD thesis]. Department of Medical Sciences, Shahed University of Medical Sciences, Iran; 2015.
[35] Moosavizadeh SA. Explanation of healthy lifestyle and treatment in opioid dependent patients according to Persian medicine and effect of Habb-o-shefa in maintenance treatment [PhD thesis].Department of Medical Sciences, Shahed University of Medical Sciences, Iran; 2018.
[36] Khatami S, Naseri M, Moosavizadeh SA, Ghaffari F, Bahaaddin Z, et al. Effective mufradah drugs in treating addiction to opium in selective sources of the traditional persian medicine. Journal of Islamic and Iranian Traditional Medicine 2019;10:147-156.
[37] Polito L, Bortolotti M, Maiello S, Battelli M G, Bolognesi A. Plants producing ribosome-inactivating proteins in traditional medicine. Molecules 2016;21:1-27.
[38] Burgess ES. Studies in the History and Variations of Asters-Part I: History of Preclusian Botany in Its Relation to Aster. In: Memoirs of the Torrey Botanical Club. Torrey Botanical Society. 1902.
[39] Nah SY, Bhatia KS, Lyles J, Ellinwood EH, Lee TH. Effects of ginseng saponin on acute cocaine-induced alterations in evoked dopamine release and uptake in rat brain nucleus accumbens. Brain Res 2009;1248:184-190.
[40] Zhang L, Yang B, Lu B, Kai G, Wang Z, et al. Tropane alkaloids production in transgenic Hyoscyamusniger hairy root cultures over-expressing putrescine N-methyltransferase is methyl jasmonate-dependent. Planta 2007;225:887-896.
[41] Zimmerman G, Njunting M, Ivens S, Tolner E, Behrens CJ, et al. Acetylcholine-induced seizure-like activity and modified cholinergic gene expression in chronically epileptic rats. Euro J Neurosci 2008;27:965-975.
[42] Alizadeh A, Moshiri M, Alizadeh J, Balali-Mood M. Black henbane and its toxicity–a descriptive review. Avicenna J Phytomed 2014;4:297-311.
[43] Shams J, Molavi S, Marjani S, Kamalinejad M, Sahraei H, et al. Reduction of morphine tolerance by the Crocus sativus extract in female mice as assessed by tail flick. Proceedings of 18th Iranian Congress of Physiology & Pharmacology. 2007 Aug 26-30; Mashad, Iran.
[44] Hosseinzadeh H, Younesi HM. Antinociceptive and anti-inflammatory effects of Crocus sativus L. stigma and petal extracts in mice. BMC Pharmacol 2002;2:7-15.
[45] Hosseinzadeh H, Shariaty VM. Antinociceptive effect of safranal, a constituent of Crocus sativus (saffron), in mice. BMC Pharmacol. 2007;2:498-503.
[46] Aslam N, Wani AA, Nawchoo IA, Bhat MA. Distribution and medicinal importance of peganumharmala-A review. Int J Advance Res 2014;2:751-755.
[47] Moloudizargari M, Mikaili P, Aghajanshakeri S, Asghari MH, Shayegh J. Pharmacological and therapeutic effects of Peganumharmala and its main alkaloids. Pharmacogn Rev 2013;7:199-212.
[48] Sulieman AME, Alghamdi AA, Veettil VN, Ibrahim NA. Antimicrobial activity of harmal plant (Peganumharmala L.) extract, ha'il region, saudi arabia. J Microbiol Res 2016;6:40-46.
[49] Patel K, Gadewar M, Tripathi R, Prasad SK, Kumar Patel D. A review on medicinal importance, pharmacological activity and bioanalytical aspects of beta-carboline alkaloid "Harmine". Asian Pac J Trop Biomed 2012;2:660-664.
[50] Mlcek J, Rop O. Fresh edible flowers of ornamental plants - A new source of nutraceutical foods. Trends Food Sci Tech 2011;22:561-569.
[51] Abbasi Maleki N, Abbasi Maleki S, Bekhradi R. Suppressive effects of rosadamascena essential oil on naloxone- precipitated morphine withdrawal signs in male mice. Iran J Pharm Res 2013;12:357-361.
[52] Sardari FA, Azadi A, Mohagheghzadeh A, Badr P. Gulqand; a nutraceutical from sugared petals. Trad Integr Med 2018;3:180-185.
[53] Caputo L, Nazzaro F, Souza LF, Aliberti L, De Martino L, et al. Composition of Essential Oil and Its Biological Activities. Molecules 2017;22:930.
[54] Heydari M, Hashempur MH, Ayati MH, Quintern D, Nimrouzi M, et al. The use of Chinese herbal drugs in Islamic medicine. J Integr Med 2015;13:363-367.
[55] Du QZ, Li L, Jerz G. Purification of astilbin and isoastilbin in the extract of smilax glabra rhizome by high-speed counter-current chromatography. J Chromatogr 2005;1077:98-101.
[56] Ng TB, Yu YL. Isolation of a novel heterodimeric agglutinin

from rhizomes of Smilax glabra, the Chinese medicinal material tufuling. Int J Biochem Cell Biol 2001;33:269-277.
[57] Chen T, Li JX, Xu Q. Phenylpropanoid glycosides from Smilax glabra. Phytochem 2000; 53:1051-1055.
[58] Shams Ardakani MR, Rahimi R, Javadi B, Abdi L, Khanavi M. Relationship between temperaments of medicinal plants and their major chemical compounds. J Tradit Chin Med 2011;31:27-31.
[59] Farzaei MH, Bahramsoltani R, Rahimi R, Abbasabadi F, Abdollahi M. A systematic review of plant-derived natural compounds for anxiety disorders. Curr Top Med Chem 2016;16:1924-1942.
[60] Lobo R, Prabhu K, Shirwaikar A, Shirwaikar A. Curcuma zedoaria Rosc. (white turmeric): a review of its chemical, pharmacological and ethnomedicinal properties. 2009;61: 13-21.
[61] Ullah HA, Zaman S, Juhara F, Akter L, Tareq SM, et al. Evaluation of antinociceptive, in-vivo & in-vitro anti-inflammatory activity of ethanolic extract of Curcuma zedoaria rhizome. BMC Complement Altern Med 2014;14:346.
[62] Talebi Keyasari F, Miladigorji H. Effect of medicinal plants in the treatment of opium addiction Review of laboratory studies. J North Khorasan Uni Med Sci 2013;4:157-165.
[63] Zafar S, Ahmad MA, Siddiqui TA. Protective role of delphinium denudatum (jadwar) against morphine induced tolerance and dependence in mice. J Ethnopharmacol 2001;78:95-98.
[64] Mahendra P, Bisht S. Ferula asafoetida: traditional uses and pharmacological activity. Pharmacogn Rev 2012;6:141-146.
[65] Khanavi M, Maadani S, Farahanikia B, Eftekhari M, Sharifzadeh M. Effect of the methanolic extracts of different parts of Ferula assa-foetida on naloxone-induced withdrawal behavior in morphine-dependent mice. Avicenna J Phytomed 2017;7:426-435.
[66] Tobinick EL. The value of drug repositioning in the current pharmaceutical market. Drug News Perspect 2009;22:119-125.