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Review

The medieval Persian manuscript of *Afyunieh*: the first individual treatise on the opium and addiction in historyAbdolali Moosavyzadeh^a, Farzaneh Ghaffari^b, Seyed Hamdollah Mosavat^c, Arman Zargaran^d, Azarakhsh Mokri^e, Soghrat Faghihzadeh^f, Mohsen Naseri^{g,*}^a Department of Iranian Traditional Medicine, Faculty of Medicine, Shahed University, Tehran 33191-18651, Iran^b School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran 15167-45811, Iran^c Research Center for Traditional Medicine and History of Medicine, Shiraz University of Medical Sciences, Shiraz 71356-44144, Iran^d Department of History of Medicine, School of Traditional Medicine, Tehran University of Medical Sciences, Tehran 16687-53961, Iran^e Psychiatry Department and National Center for Addiction Studies, Tehran University of Medical Sciences, Tehran 14176-53761, Iran^f Department of Biostatistics and Epidemiology, Faculty of Medicine, Zanzan University of Medical Sciences, Zanzan 45371-38791, Iran^g Traditional Medicine Clinical Trial Research Center, Shahed University, Tehran 14179-53836, Iran

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ABSTRACT

According to historical evidence, the abuse of opium has been reported all over the globe—specifically throughout Eastern nations—since the sixteenth century. Before that, opium had mostly been applied as medication. Reference has been made in traditional Persian medical literature to the method of cultivation, properties, side effects and toxicity. In sixteenth century Iran, during the reign of the Safavids, opium abuse began. It was from then that prominent Persian scholars started to think of solutions to this societal problem. One of the most famous scholars was Imad al-Din Mahmud ibn Mas'ud Shirazi, who composed a book concerning addiction—*Afyunieh*, a comprehensive book on the topic of opium and all issues of opium. Furthermore, he recommended methods for reducing opium dose as well as substitution with other medications that had a narrower range of side effects, in order to eradicate dependency upon opium and opium-derived materials. This is most likely the first book that comprehensively addressed opium and discussed drug rehabilitation methodology, in traditional Persian medical literature. In this historical review, the authors have introduced the book *Afyunieh*, which presents methods for treating addiction to and giving up opium; the text comprises a synthesis of the author's opinions, professional experience and references to the work of other famous physicians.

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1. Introduction

Opium is the gum or sap extracted from the opium poppy plant (*Papaver somniferum* L.) [1]. The history of human opium use is long. There is evidence of opium poppy cultivation in some Neolithic cultures (10,000–4000 BCE) in Europe [2]. The first evidence of its medicinal use dated back to the Sumerians (3000 BCE), who lived in Mesopotamia [3]. Poppy cultivation and the use of its extracts were transferred from the Sumerians to the people of other nations, especially the Assyrians, Babylonians, Egyptians, Greeks, Persians and Romans [3].

The medicinal effects of opium, as well as its adverse effects, were known to various civilizations in the ancient era to some extent. The sedative and hypnotic properties of opium poppy extract were clearly mentioned in the Ebers papyrus, deemed to be one of ancient Egypt's and the world's oldest medical texts (dating back to circa 1500 BCE) [4,5]. In the Iliad and the Odyssey, the Greek mythical texts harking back to the 9th century BCE, Homer discussed the side effects of opium consumption. He warned soldiers against consuming drinks containing poppy extract because they caused forgetfulness and indifference to pain [6]. In all of the eras mentioned above, it is evident that people believed in the holistic and mythical healing effects of the opium poppy plant [7]. Later, circa 460 BCE, Hippocrates claimed that there were no mythical or magical effects of the opium poppy plant, and its extract properties could be explained through biological and medical phenomena. Consequently, he tried to remove the opium poppy plant from the halo of sanctity and mystery, and he made every effort to promote its use as a drug in medicine [8].

Ancient Persia was another great and important civilization in the world. It seems that the opium poppy was well known in this culture from antiquity. It was called as *Gāokerenā* in the Avestan language, a Persian language that dates back to at least 3000 years ago [9]. It was used as an analgesic and anesthetic for pain control during surgery [10]. In the first century CE, Pedanius Dioscorides—the Roman physician, pharmacologist and botanist and the author of *De Materia Medica*, a five-volume encyclopedia on herbal medicine and related medicinal substances—referred to detailed specifications of the poppy plant and methods for preparing its extract as well as its medicinal use. He claimed that the opium poppy had a

cold nature, was a sedative agent, and was a suitable drug to treat insomnia and restlessness [11]. In the Islamic Golden Age (the 9th–12th century CE) [12], Persian physicians greatly expanded medical knowledge, especially in the fields of pharmacy and pharmacology [13–15]. They knew about opium and wrote about its medicinal applications in their medical manuscripts. In the *Kitab al-Maliki*, or the *Complete Book of the Medical Art*, written by Haly Abbas (949–982 CE) [16], a Persian physician, opium's toxicity and overdose symptoms, in addition to its therapeutic uses, were presented [17]. Moreover, Rhazes (865–925 CE) [18] discussed opium and its medicinal applications. Especially, Avicenna (980–1037 CE) explained opium's effects, side effects, and symptoms of intoxication in his famous book *Canon of Medicine* [19,20]. It seems that Avicenna's view of opium was different from prior scholars. He believed that the nature, properties, and effects of opium could be discovered by experience and not only by syllogism [21].

Although there is evidence of opium use in ancient and medieval civilizations, there were no manuscripts or treatises that comprehensively undertook the discussion of opium and its effects, formularies, addiction and side effects until the 18th century [22]. Therefore, finding historical manuscripts on this subject can be important to clarify the history of opium abuse and toxicology. In this study, we introduce a book written about opium, *Afyunieh*, by a Persian physician Imad al-Din Mahmud ibn Mas'ud Shirazi in Safavid era (1501–1722 CE).

1.1. Safavid dynasty

The Safavid dynasty (1501–1722 CE) (Fig. 1) was one of the most important Iranian kingdoms in history. It was founded by King Ismail in the early 16th century. Great Empires ruled Persia from at least 3000 years ago.

Safavid kings restored the great Persian Empire (for nearly 230 years) again during the Islamic era. They were among the most important governments in Western Asia and stopped Ottoman Empire expansion at their borders [23]. Under this powerful government in Iran, a respected military and powerful foreign policy, culture, science and art flourished in addition to security and economic prosperity, and commercial, agricultural and industrial developments.

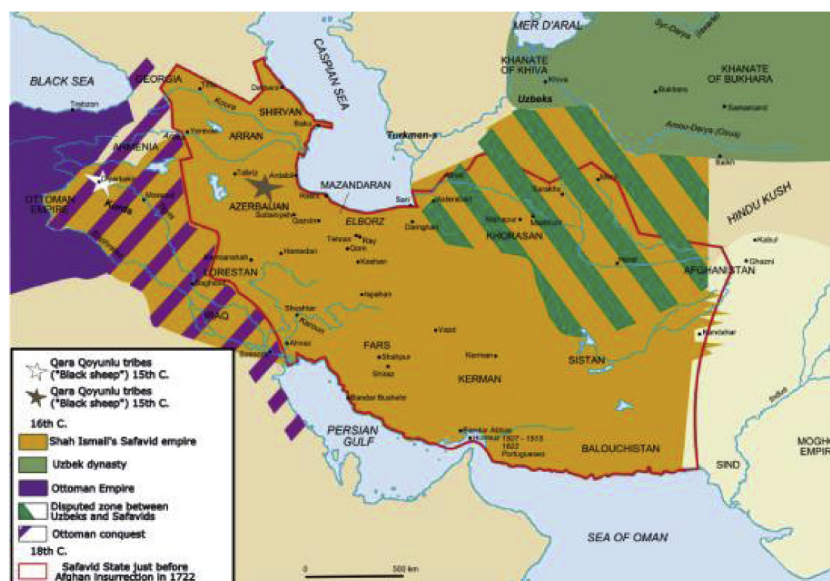


Fig. 1. Safavid Empire (1501–1722 AD). Copyright from: <https://commons.wikimedia.org/w/index.php?curid=1170537>.

1.2. Opium abuse in the Safavid era

Although opium was known to the Persian physicians from antiquity, its abuse as a social complication began during the Safavid era in Iran [24,25]. The prevalence of opium abuse increased among Iranians in that time, and this abuse was also prevalent among governors all around the country. It is believed that the East India Company was the main dealer of opium in Iran because of its high-beneficial trade. The strong analgesic and euphoric effects of opium contributed to its appeal, in addition to religious prohibition of drug abuse and consumption of alcohol during the Safavid [24,25]. The spread of opium abuse during this era raised concerns among physicians and the government due to complications including the medicinal effect, abuse, addiction, opium cessation, withdrawal effects, among others. In this atmosphere, Imad al-Din Mahmud started to write his manuscript, *Afyunieh*, on the subject of opium.

1.3. Imad al-Din Mahmud

Imad al-Din Mahmud was a Persian physician in the 16th century. He lived in Shiraz, in the south of Iran, during the Safavid era [26]. He was born in a family that was famous for medicine and lived most of his life in Mashhad (in the North-East of Iran) [27]. Because of his competence and proficiency in medicine, he became court physician to King Tahmasp (1525–1578 AD), the second king of the Safavid dynasty. He also worked at the court of Abdullah Khan Ustajlu (1549–1565 AD), ruler of Shirvan (in the North-East of Iran). After disobeying a command of the ruler, he was sentenced to spend a night in a pool in the cold and snowy weather. He was saved from death that night using opium [28]. Following his own clinical experiences, and given the prevalence of opium abuse among the people, he embarked upon writing a treatise in Persian, called *Afyunieh*, about opium and its therapeutic uses, side effects, dependency and addiction recovery [29]. Although some historians believe that he was a recovered addict, there is no strong support for this theory. Other treatises—such as *Chob Chini*, an important treatise on *Smilax china* L., an herb for the treatment of syphilis [29], *Tarkibate Shahieh* (royal compound), a treatise on compound remedies [30], and an unnamed manuscript on anatomy—are also attributed to him. Another important manuscript is *Sharh Tashrih al-Qanun*, a unique, detailed commentary on the chapter of anatomy in the *Canon of Medicine* [29]. *Atashak*, the first Persian-language treatise on syphilis, and *Sam Shenasi* (toxicology), are other treatises of Imad al-Din Mahmud, translated into English by Cyril Elgood in the mid 12th century CE [31,32].

2. The book of *Afyunieh*

Afyunieh [33] is the most important treatise written by Imad al-Din Mahmud in the Safavid era on opium use and abuse (Fig. 2). It was very popular in his time [27]. The word of *Afyunieh* is derived from *Afyun* (Persian equivalent of opium), which means related to opium. He used his own clinical experiences for writing this book. Currently, this book is corrected and republished as a part of Iranian national project entitled “Multicenteric project to revive the written heritage of traditional Persian medicine” in 250 pages by Choopani et al. [33] (Fig. 3). This book comprises an introduction and 15 chapters (Table 1). In the introduction to the treatise, Imad al-Din Mahmud categorized people of his time into three groups based on their attitude toward opium consumption. The first group of people denounced the use of opiates and did not consume opium under any circumstances. The second group consumed opiates regularly as a treatment or a hobby. The last group used



Fig. 2. The first page (right) and last page (left) of *Afyunieh*.



Fig. 3. The cover of corrected and republished *Afyunieh* [33].

opiates only for medicinal purposes. The last category was considered by Imad al-Din Mahmud to be very rare.

The first three chapters of this treatise include detailed description of the nature, characteristics, benefits, side effects, and identification methods of pure opium. In the fourth chapter of *Afyunieh*, the author discussed opium poisoning and toxicity. The causes of intoxication and opium addiction are mentioned in subsequent chapters. Finally, treatment of opiate addiction, seemingly the most important chapter of *Afyunieh*, is addressed.

Table 1
The content of the book of *Afyunieh*.

Number of chapter	Title	Main goals of chapter
Introduction	–	Categorizes people of his time into three groups based on their attitudes toward opium consumption
1	Description of opium and its nature in scientist's views	Main points about opium and its nature and how opium is obtained from the poppy plant
2	Pure opium characteristics and methods for examining it	Pure opium characteristics and different ways of differentiating pure opium from counterfeit medicine
3	Benefits and risks of consuming opium in scholar's ideas	Review and analysis of scholar's ideas about benefits and risks of consuming opium
4	Management of opium intoxication	Therapeutic methods related to opium intoxication
5	Mechanism of euphoria (<i>neshat</i>) and addiction to opium	Explanation of the mechanisms of euphoria (<i>neshat</i>) and addiction to opium by Persian medicine foundations
6	Advantage of opium	Explanation of 31 benefits of opium
7	Disadvantage of opium	Explanation of 20 negative effects of opium
8	Reducing opium side effects	Different medicinal and nonmedical ways of reducing opium side effects
9	Opium dependency treatment	List of various methods for treating opium dependency according to the principle of gradation (<i>tadreej</i>)
10	Description of the conditions that follows withdrawal of opium	Explanation of signs and symptoms of withdrawal phase
11	Treatment of withdrawal conditions	Expression of medical treatment for each sign and symptom mentioned in previous chapter
12	How to eat opium during illness	The quantity and the using time of opium and other modifiers according to any disease
13	Opium eating before or after a meal	Many points regarding opium eating and its relation to eating and advantage of any situation
14	Opium eating in Ramadan	Opium eating without damaging the fasting
15	Views and suggestions of Greek and Arab scholars and also his contemporaries about opium in combination with other drugs	List of pharmaceutical compounds containing opium in scholars' views and analysis of them

2.1. The content of the book of *Afyunieh*

In the first chapter of the book, he described opium and its nature by mentioning views of previous scholars like Dioscorides, Avicenna, and others. Considering the two opposite points of view about the nature (temper) of opium among the followers of deductions and experimentalism, he explained his own theory. At the end of the chapter and after describing how opium was obtained from the poppy plant, he explained the reasons and importance of main points, such as the reason for cutting in the early morning.

In the next chapter, Imad al-Din Mahmud suggested different ways of differentiating pure opium from counterfeit medicine based on the tools of his time. Then, he talked about how long opium could be stored and also the characteristics of the container in which opium was kept. At the end of the chapter he discussed how opium could be used in combination with other ingredients. Throughout the chapter he also cited other scholars and physicians.

In Chapter 3, Imad al-Din Mahmud reviewed the ideas of different scholars about the benefits and risks of consuming opium and gave a general analysis of it. At the end of the chapter, there is a list of alternatives (substitutions with similar effects) to opium (e.g., *Hyoscyamus niger*) and their equivalent quantities.

Chapter 4 discusses therapeutic methods related to opium intoxication. Different views of scholars have also been used in this chapter. The chapter ends with the author's prescriptions for treating opium intoxication.

The main content of Chapter 5 is the use of Persian medicine theories to explain the mechanisms of euphoria (*neshat*), depression and their relationship to opium from opium use. In Imad al-Din Mahmud's view, the main mechanism of euphoria and addiction was a rapid qualitative and local change in one's spirit and inner heat. He had also mentioned other reasons for addiction to opium in other chapters of the book.

At the beginning of Chapter 6, Imad al-Din Mahmud addressed people who denied the benefits and therapeutic applications of opium and believed they were unwise people who did not base their opinions on scientific reason. Although Imad al-Din Mahmud reviewed the ideas of the other scientists about the benefits of

opium in Chapter 3, in this chapter he discussed 31 benefits of opium with details. He considered pain reduction as the most important benefit of opium. The other benefits of opium he described were: hypnotics, reduction in sleep, enthusiasm and exhilaration in performing tasks, anti-diarrheal effects, coryza and cough reduction, and helping to lose weight. He mentioned two opposite effects of opium, sleep inducement and reduction in sleep in this list. Another interesting point of this chapter is the effects of opium on sexual activity and the reduction in sexual desire (as opposed to common beliefs). Current findings supported Imad al-Din Mahmud's theory on the effects of opium on sexual activity [1]. At the end of the chapter he discussed one of his clinical cases who had suffered from severe diarrhea (*zaheer*) and described how opium had made a great improvement in his treatment.

He mentioned 20 negative effects of consuming opium in Chapter 7. Physical weakness, difficulty in cognition, tendency for solitude and isolation from people, thinness, visual and hearing loss are some of opium's negative effects. The chapter is clarified by a short list about opium harms at the end. Like other chapters, Imad al-Din Mahmud tried to develop a practical guide using clinical cases.

Chapter 8 of the book is a companion to Chapter 7, because in this chapter the author tried to introduce different medicinal and nonmedicinal ways for reducing opium's negative effects. Of course, in many cases, besides suggesting various medicines, he mentioned that reducing opium use was the best way of dealing with those negative effects. One interesting point of the chapter is Imad al-Din Mahmud's focus on opium tolerance. He explained it as: "...and it is clear that everyone tries to obtain the euphoria and as they like to get the first day experience which would not be achieved unless with increasing their opium use, and therefore the intake increases so much that the body becomes pretty weak and the desired quality will not be achieved."

Chapter 9, which is the richest part of the book after the last chapter, introduces various methods of treating opium addiction. We will discuss this chapter in a separate section.

In Chapter 10, Imad al-Din Mahmud described the conditions that follow withdrawal from opium (*tarke-afyun*) and explained the causes of each symptom in detail. This condition can be consid-

ered as “acute withdrawal syndrome.” The symptoms he described were: feeling of suffocation and shortness of breath, runny nose, insomnia, pain of joint and other areas, anorexia, stomach ache and colic, backache, headache, coughing, vocal difficulty, diarrhea, fever and anxiety.

Like Chapter 8, Chapter 11 tries to complete the previous chapter and elaborate on the medical treatment of withdrawal conditions.

Chapter 12 of the book describes some of the illnesses that an addict might face and suggests some points about the quantity and the duration of use of opium and other modifiers. At the beginning of the chapter, Imad al-Din Mahmud referred to one of his case studies, a ruler who had been suffering from an illness and was told to make a balance in his opium dosage and finally he died because he did not follow Imad al-Din Mahmud’s instructions. He believed that in some cases, the best approach was opium dose reduction or even cessation. Based on his own experience, Imad al-Din Mahmud disagreed with the notion that sudden cessation of opium would cause death.

Imad al-Din Mahmud had considered nutritional regimens in the context of taking opium in Chapter 13. It discusses whether opium should be taken before or after the food. He suggested 12 reasons for taking opium before food and 2 reasons for using opium after it. Overall, it seemed that he preferred opium use before eating.

Chapter 14 deals with one of the religious orders of Islam that fasted during Ramadan. In the month of Ramadan, Muslims avoid some activities and none of them is eating or drinking during daylight hours. Many patients addicted to opium thought that because they had to take opium several times a day, fasting would be

impossible for them. Imad al-Din Mahmud proposed a few solutions for that issue which was a great innovation for his time [34]. One solution was the gradual reduction in daily opium doses. In this method, the person tried to reach one or two doses per day during the months before Ramadan. The next solution was the use of rectal products and slow-release oral products. He stated at the end of this chapter that he did not use any outside references to write this chapter.

The last chapter of the book is the most detailed and comprehensive chapter. In it, he discussed the compound formularies (like a pharmacopeia) which contained opium as an ingredient. He also explained their clinical issues and made reference to the work of other physicians, in this chapter.

He also discussed other herbal intoxicants as well as how medicinal herbs, like saffron, possessed enlivening effects. Then, he introduced a drink called *Jollab*. Finally, he claimed he has used coffee occasionally to treat opium dependency, and when coffee was unavailable, he developed a mixture based on his own experience that contained many elements and had few side effects. He stated that the mixture needed some small modifications when prescribed for people of different tempers.

2.2. Approaches to treating opium addiction in Afyunieh

According to Imad al-Din Mahmud, there were three methods for the treatment of opium addiction (Fig. 4). The first was increasing the time between opium consumption (*taa-veegh*). The second was the regular reduction in the opium dose (*taghleel*). The third—and, according to the author, the best—method was replacing opium with drugs similar or dissimilar to opium (*taa-veez*) and

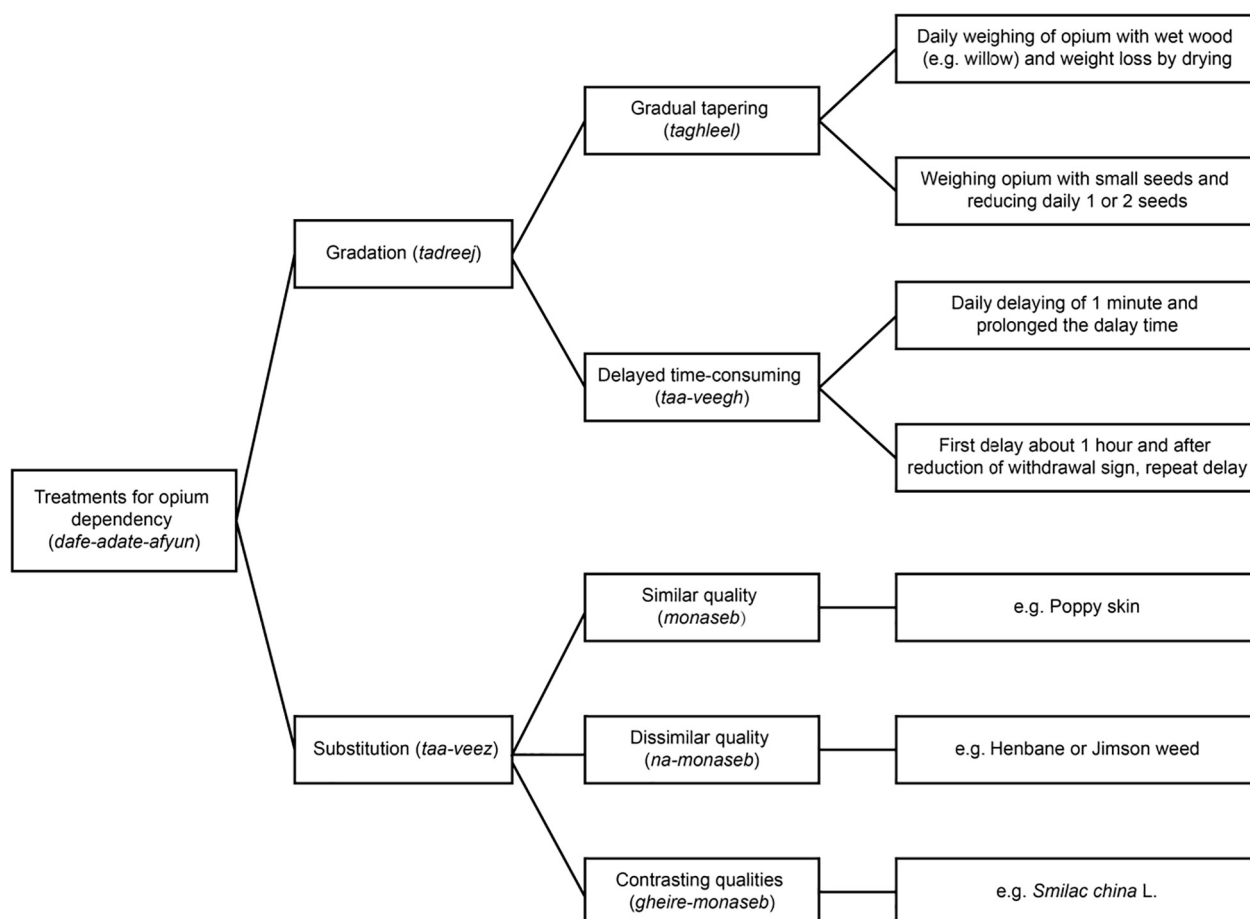


Fig. 4. Different methods proposed for the treatment of opium addiction from Imad al-Din Mahmud’s book.

Table 2
Alternatives for opium mentioned in the *Afyunieh*.

Scientific name	Common name	Name in <i>Afyunieh</i>	Recommended by Imad al-Din Mahmud
<i>Hyoscyamus niger</i> L.	Henbanes	<i>Bazr-ol-banj</i>	Yes
<i>Conium maculatum</i> L.	Hemlock	<i>Shokaran</i>	No
<i>Mandragora officinarum</i> L.	Mandrake	<i>Lofah</i>	No
<i>Datura stramonium</i> L.	Devil's snare	<i>Joz-e-masel</i>	No
<i>Smilax china</i> L.	China root	<i>Bikh-e-chini</i>	Yes
<i>Cannabis sativa</i> L.	Hemp	<i>Qonnab</i>	No
<i>Strychnos nux-vomica</i> L.	Poison nut	<i>Kachaleh</i>	Yes
–	Wine	<i>Khamr</i>	No
–	Tar	<i>Qatran</i>	No
–	Castor testicle	<i>Jond-bidastar</i>	Yes
<i>Papaver somniferum</i> L.	Poppy	<i>khaskhaash</i>	Yes
<i>Crocus sativus</i> L.	Saffron	<i>Za'feran</i>	Yes
<i>Peganum harmala</i> L.	Harmal	<i>Sepand</i>	Yes
<i>Boswellia sacra</i> Flueck.	Olibanum	<i>Kondor</i>	Yes
<i>Coffea arabica</i> L.	Coffee	<i>Qahveh</i>	Yes

then tapering off these drugs. Several herbs that could be viable alternatives to opium were mentioned in detail in *Afyunieh* (Table 2). Imad al-Din Mahmud also discussed withdrawal symptoms and their remedies. In the last chapter of *Afyunieh*, Imad al-Din Mahmud identified other herbs, such as saffron and coffee that cause pleasure and drunkenness.

3. Discussion

Afyunieh, was a comprehensive book on the topic of opium. In this book, all issues of opium were discussed such as morphology of the opium poppy plant, the opium harvesting techniques, identifying pure opium, therapeutic effects and side effects of opium as well as methods to reduce these unwanted effects. Furthermore, there was a comprehensive discussion of how to treat opium addiction with different therapeutic strategies.

Despite the long history of opium use, the history of its widespread abuse and addiction seemed to be short [35]. Although opium was mentioned by some previous scholars, these references were small parts of other books, like the Avicenna's (980–1037 CE) [36] descriptions in the *Canon of Medicine* in the 10th century CE [19], or focused only on a special aspect of opium, like the treatises on the use of opium as a recreational drug (aphrodisiac) [37]. Therefore, it seems that this book can be considered as the first comprehensive work, focused on all aspects of opium relevant at that point in history. The first scientific book entirely about opium in the West, entitled *Mysteries of Opium* was published more than one century later, in 1700 [22]. Later, in the 19th century, the addictive nature of opium was reported by Western physicians, and therapeutic strategies for drug dependent patients were developed in the mid-20th century [38,39].

On the other hand, the value of this book increased its content, which combined Imad al-Din Mahmud's own experiences with knowledge from physicians and scholars that preceded him. Opium abuse started to be prevalent in Iran during the Safavid era (the 16th century CE) [40] and this social problem seems to have prompted Imad al-Din Mahmud to compose this work. Imad al-Din Mahmud himself stated that his motivation for writing this manuscript was to create a comprehensive book on the subjects of opium, covering all aspects, including both clinical uses and harms. It can be considered an important link that chained the medical history, particularly in the field of addiction and substance abuse.

It is interesting that effectiveness of some of the herbs and drugs proposed in *Afyunieh* for the management of addiction has been studied in contemporary medicine for the same purpose. For example, one of the compound herbal formulations that are

mentioned in *Afyunieh* is the *Hab-o shefa* pill. *Hab-o shefa* is a combination of *Datura stramonium*, *Rheum palmatum*, *Zingiber officinale* and *Acacia arabica*. In an animal study and a clinical trial of Nazari et al. [41,42], the efficacy of this drug in controlling morphine withdrawal symptoms was evaluated. They concluded that control of withdrawal symptoms and depression in *Hab-o Shefa* group was better than the other groups.

Conflicts of interest

There are no conflicts of interest.

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