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Research Paper: Determination of Common Pharmaceutical Adulterants in Herbal Medicinal Products Used in the Treatment of Opioid Addiction

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ABSTRACT

Background: Opioid addiction is a serious and growing global concern. Recently, herbal medicine has been popular for the treatment of opioid abusers worldwide. Unfortunately, the adulteration of herbal remedies with undeclared synthetic pharmaceuticals has been reported. In Iran, there are few reports on the adulteration of herbal remedies by synthetic pharmaceuticals sold as opioid addiction treatment. The aim of this study was to analyze herbal products used in opioid addiction treatment for the identification of synthetic pharmaceuticals as adulterants in the remedies.

Methods: Forty commonly-used handmade herbal products for the treatment of opioid addiction were collected from herbal shops in Kermanshah (western area of Iran). After organoleptic examinations, the samples were prepared and analyzed by high-performance liquid chromatography and gas chromatography-mass spectrometry for detecting probable synthetic pharmaceutical adulterants.

Results: The chromatographic analysis of the samples showed that 90% of the products had at least one undeclared pharmaceutical ingredient as an adulterant. The majority of the samples (n=19, 47.5%) had only one undeclared pharmaceutical. Diphenoxylate (n=24, 39.3%), tramadol (n=16, 26.2), methadone (n=8, 13.2%), and the combination of these drugs were reported as common adulterants. We detected the presence of buprenorphine and sildenafil as adulterating agents in the herbal formulations for the first time.

Conclusion: According to the presence of undeclared synthetic pharmaceuticals in opioid addiction herbal products, as well as their threats to public health, awareness, in this case, is necessary.

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1. Introduction

The opioid addiction is a chronic, debilitating, and the recurring phenomenon of opioids use despite the negative medical, mental, and social consequences. Opioid addiction is one of the serious and growing social and medical problems in the world [1, 2]. It is associated with a wide range of mental and physical morbidity and mortality [2]. Pharmacotherapy, especially Opioid Agonist Therapy (OAT), is one of the most important therapeutic modalities in opioid addiction [3]. OAT with methadone and buprenorphine has proven efficacy in reducing illicit opioid use. These drugs are mu opioid receptor agonists with different pharmacodynamic and pharmacokinetic characteristics [4]. These treatments play an effective role in improving opioid abuse/addiction outcomes [5]. Unfortunately, the utilization of OAT is associated with the high risk of drug overdose, misuse, undesirable side effects, and drug interactions, especially among individuals in correctional settings or the complications of HIV disease [6, 7]. Moreover, the effectiveness of OAT is limited by difficulties at all levels of the therapeutic process, such as diagnosis, entry, and persistence of the patients on treatment; it also needs training health care professionals for the treatment and prevention of opioid abstinence syndrome during the therapy [1]. In this regard, there is an increased interest in alternative pharmacotherapy modalities for opioid addiction among health care providers and patients [8-12].

Recently, alternative medicine has been popular and self-medication with herbal medicinal products has increased worldwide [13]. Globally, traditional herbal remedies are used by many people as alternative medicine in some medical and psychiatric disorders [14]. Traditional herbal medicines and the related pharmaceutical formulations have been used for the adjuvant management of opioid addiction in different stages, including detoxification, rehabilitation, and withdrawal with lower side effects and costs [15, 16].

Unfortunately, herbal remedies used in the treatment of opioid addiction have poorly described pharmacokinetics and mechanism of action, high potential of drug interactions, and the lack of evidence-based efficacy data from well-controlled clinical trials. Severe toxicity and high risk with adulteration with synthetic chemical and pharmaceutical agents are the important limitations of the usage of herbal remedies in treatment [8]. In Iran, many unregistered herbal shops introduce herbal medicines as traditional formulations, but there are poor regulations for the safety of traditional herbal products. There are a few reports from Iran and other countries about the adulteration of herbal remedies by synthetic pharmaceuticals sold as weight loss, weight gain, and sexual enhancer products in herbal shops and through the Internet, satellite channels, and social media [14, 17-21]. However, scant studies have been performed on the determination of adulterants in herbal products used in opioid addiction treatment in Iran. The aim of this study was to analyze herbal products for the identification of synthetic pharmaceuticals as adulterants in these remedies.

2. Materials and Methods

Samples

Forty commonly-used handmade herbal products for the treatment of opioid addiction were collected from herbal shops in Kermanshah (western area of Iran). The samples were gathered from all of the herbal shops in the different regions of the city. The pharmaceutical dosage forms included tablets, capsules, powders, oral drops, and oral solutions. None of the pharmaceutical dosage forms were registered by the Ministry of Health and Medical Education of Iran. All samples were introduced to the Laboratory of Forensic Toxicology, Legal Medicine Center (Kermanshah, Iran) for the analysis of synthetic and active pharmaceutical ingredients.

Chemicals

Chloroform, methanol, acetonitrile, potassium dihydrogen phosphate, phosphoric acid, and hydrochloric acid (37%) were obtained from Merck Co. (Darmstadt, Germany). High-Performance Liquid Chromatography (HPLC) grade water was purchased from Merck Millipore. All of the used chemicals and solvents were of analytical grade.

Organoleptic examinations

For each solid pharmaceutical dosage form, organoleptic characteristics, including features of the sample, weight, size, shape, odor, and color were recorded. Also, for liquid samples, pH was determined by the pH meter (827 pH lab, Metrohm, Switzerland).

Sample preparation

For powders, the samples were homogenized and uniformed with mortar and pestle. Tablets were crushed and, then, homogenized in a mortar and pestle. For capsules, after breaking the capsules, the solid content was homogenized. All samples were grinded to fine and uni-

form powders and, then, extracted with 3 mL methanol (for each 1 mg of the sample) for 20 minutes in the test tube, using a rotator. The extract was centrifuged (5 minutes at 4000 rpm). The supernatant was collected and the top layer of the compound was injected into the analytical instruments for analyses [21]. For liquid samples, the sample was diluted with methanol and filtered by a 0.22-µm membrane filter (Macherey-Nagel, Germany) and, then, injected into the instruments.

Instrumental analysis

All of the samples were analyzed with the previously validated HPLC and Gas Chromatography-Mass Spectrometry instrumentations used for systematic toxicological analysis [22].

HPLC analysis

The HPLC system was a Knauer (Berlin, Germany) with a quaternary pump and equipped with a diode array detector (S2800). The separation was carried out on a Eurospher-100-5 C18 column (250 mm x 4.6 mm, 5 µm particle size) with a Smart 1000 pump. A mixture of acetonitrile and phosphate buffer (pH=2.3) (37:63) was used as an elution solvent in isocratic mode. A 20-µL sample was injected into the column and eluted at room temperature with a constant flow rate of 1.0 mL/min. The HPLC conditions were optimized to achieve the maximum response and the best peak shape and resolution.

Gas Chromatography-Mass Spectrometry analysis

A gas chromatograph (Clarus 680, PerkinElmer, USA) equipped with a split/splitless injector was used. The column of the GC was Elite®-5MS (5% phenyl and 95% dimethyl polysiloxane, 30 m length x 0.25 mm ID x 0.25 µm film thickness) (PerkinElmer, USA). Mass analyzer (Quadrupole, PerkinElmer, USA) was connected to the column. The injection port temperature was 250° C and the transfer line temperature was 280° C. The initial column oven was set to 60° C and held constant for one minute. The temperature program rate was 2° C/min and the final temperature was set to 280° C and the final hold for 15 minutes. The mass spectrometer was operated by electron impact (70 ev) in positive full scan mode (50-550 m/z). Wiley, National Institute of Standards and Technology, and PEST libraries were used for the qualitative analysis of the samples.

Statistical analysis

Statistical analysis was performed by SPSS V.16 (Chicago, IL, USA). The results are shown as frequency and percentages.

3. Results

The organoleptic characteristics of the samples

In the present study, 40 handmade herbal products sold in herbal shops for opioid addiction treatment were analyzed. Herbal products were formulated in different dosage forms, such as tablets (n=19, 47.5%), capsules (n=13, 32.5%), powders (n=5, 12.5%), oral drops (n=2, 5%), and oral solution (n=1, 2.5%). Table 1 summarizes the physical and organoleptic characteristics of all the products. The majority of the products (n=35, 87.5%) had an herbal odor like sumac, cumin, black cumin, fennel, cinnamon, aniseed, rosemary, clove, mint, henna, and vanilla. Five samples (12.5%) formulated in handmade capsules had not herbal odor. None of the samples had standard pharmaceutical packaging (e.g. standard labels, patient package inserts, batch number, manufacturer's name, and production and expiration dates).

General results of the chromatographic analysis of the samples

The chromatographic analysis of the samples showed that 4 (10%) samples had no synthetic pharmaceutical adulterant (oral solution, 2 oral drops, and 1 handmade capsule). Totally, 90% of the products had at least 1 undeclared pharmaceutical ingredient as an adulterant. Table 2 represents the frequency, type, and combination of pharmaceutical adulterants detected in the herbal products. The majority of the samples (n=19, 47.5%) had only 1 undeclared pharmaceutical adulterant. In 15 (37.5%) of the samples, there were 2 pharmaceutical components and in 2 samples, there was a mixture of 3 pharmaceutical components (diphenoxylate, tramadol, and sildenafil had been detected) (Table 2). Generally, diphenoxylate (n=24, 39.3%), tramadol (n=16, 26.2), and methadone (n=8, 13.2%) were reported, respectively, as the most frequent pharmaceutical adulterants in the products (Table 3).

Chromatographic analysis of "Dta India" samples

The results showed that in all of the herbal samples sold under the brand of "Dta india", at least 1 pharmaceutical adulterant has been found. The majority of the samples (67%) had 1 pharmaceutical ingredient (diphenoxylate

Table 1. Brand name, the dosage form, organoleptic characteristics, and type of adulterants in the herbal products

Product Brand Name	Dosage Form	Organoleptic Characteristics	Adulterants
Dragon	Tablets (n=19)	Gray, light, or dark brown tablets (caplets) with herbal odor and imprint codes as "VIP", "DRAGON", and "ND" or with stars logo	Diphenoxylate, Tramadol, Methadone, and Sildenafil
Dta India	Capsules (n=9)	Blue/white, gray/green, orange, and red hard gelatin capsules in different sizes sold as bulk capsules	Diphenoxylate, Tramadol, Methadone, and Sildenafil
Untitled	Capsules (n=4)	Beige or colorless handmade hard gelatin capsules sold as bulk containing 1-2 g solid powder in each capsule	Diphenoxylate, Tramadol, Methadone, and Diazepam
Untitled	Powders (n=5)	White to dark brown powders without herbal odor. Powders were wrapped in plastic bags (3-5 g/bag) and soluble in water and sold as bulk	Buprenorphine, Diazepam, Methadone, Chlordiazepoxide, and Diphenoxylate
Untitled	Oral drops (n=2)	Colorless liquid (10 mL, pH=7.2) with herbal odor in unlabeled 15-mL polyethylene bottles with dropper	ND
Zenyan (aniseed) Distilled	Oral solution (n=1)	Colorless liquid (pH=7.2) with herbal odor in labeled 1.5-L Polyethylene terephthalate bottle	ND

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ND: None Detected

or tramadol). In 22% of the samples, 2 pharmaceuticals were detected (combined with diphenoxylate and tramadol or diphenoxylate and methadone). In 11% of the samples, a mixture of diphenoxylate, tramadol, and sildenafil was detected.

Chromatographic analysis of "Dragon" samples

The results showed that in all of the herbal samples sold under the brand of "Dragon", at least one pharmaceutical adulterant has been found. The majority of the samples

Table 2. Frequency, type, and combination of pharmaceutical adulterants detected in the herbal products

Adulterant Identified	No.	%
Diphenoxylate	12	30
Tramadol	4	10
Methadone	2	5
Buprenorphine	1	2.5
Tramadol + Diazepam	1	2.5
Tramadol + Chlordiazepoxide	1	2.5
Tramadol + Diphenoxylate	5	12.5
Tramadol + Sildenafil	1	2.5
Tramadol + Methadone	2	5
Diphenoxylate + Methadone	4	10
Diphenoxylate + Sildenafil	1	2.5
Diphenoxylate + Tramadol + Sildenafil	2	5
None detected	4	10
Total	40	100

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Table 3. Cumulative frequency of detected undeclared pharmaceuticals in the herbal medicinal products

Adulterant	No.	%
Diphenoxylate	24	39.3
Tramadol	16	26.2
Methadone	8	13.2
Buprenorphine	1	1.6
Diazepam	1	1.6
Chlordiazepoxide	1	1.6
Sildenafil	4	6.5

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(50%) had 1 pharmaceutical ingredient (diphenoxylate or tramadol). In 43% of the samples, 2 pharmaceuticals were detected (combined with diphenoxylate and tramadol or diphenoxylate and methadone or diphenoxylate with sildenafil or tramadol with methadone or tramadol with sildenafil). In 7% of the samples, a mixture of diphenoxylate, tramadol, and sildenafil was detected.

Herbal-derived organic compounds

The most common organic compounds were detected in the herbal products shown in Table 4.

Figures 1, 2, 3 show the mass spectrum of diphenoxylate, tramadol, and methadone as common pharmaceutical adulterants of the herbal samples. Figure 4 shows the HPLC chromatogram and ultraviolet spectrum of sildenafil.

4. Discussion

The results of the present study showed that the different herbal products used for the treatment of opioid addiction were adulterated with synthetic pharmaceutical agents mainly diphenoxylate, tramadol, and methadone.

During recent years, the popularity of traditional herbal medicines is increasing across the world because of the many side effects of synthetic pharmaceuticals [11-13]. Opioid abuse/addiction is a chronic and recurring disorder, whose recurrence is the most important problem in the treatment of this disease. Nowadays, maintenance pharmacotherapy using opioid agonist agents such as buprenorphine or methadone is considered the most effective intervention for opioid abuse/addiction treatment in many countries [23]. However, OAT is related

Table 4. The most common organic compounds detected in the herbal products

Herbal-derived Organic Compound	%
Capsaicin	29.4
Cinnamaldehyde	17.5
Vanillin	11.8
Rosmarinic acid	5.9
Harmine	5.9
Vanillin and capsaicin	5.9
Capsaicin and narceine	5.9
Capsaicin, narceine, and thebaine	5.9
None detected	11.8

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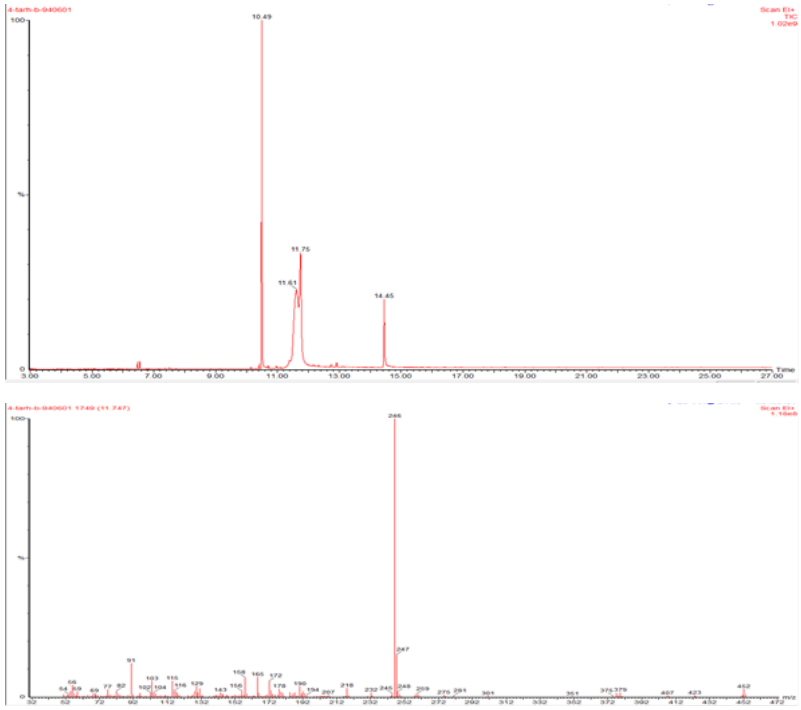

Figure 1. Mass spectrum of diphenoxylate

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Retention time =11.75 minutes

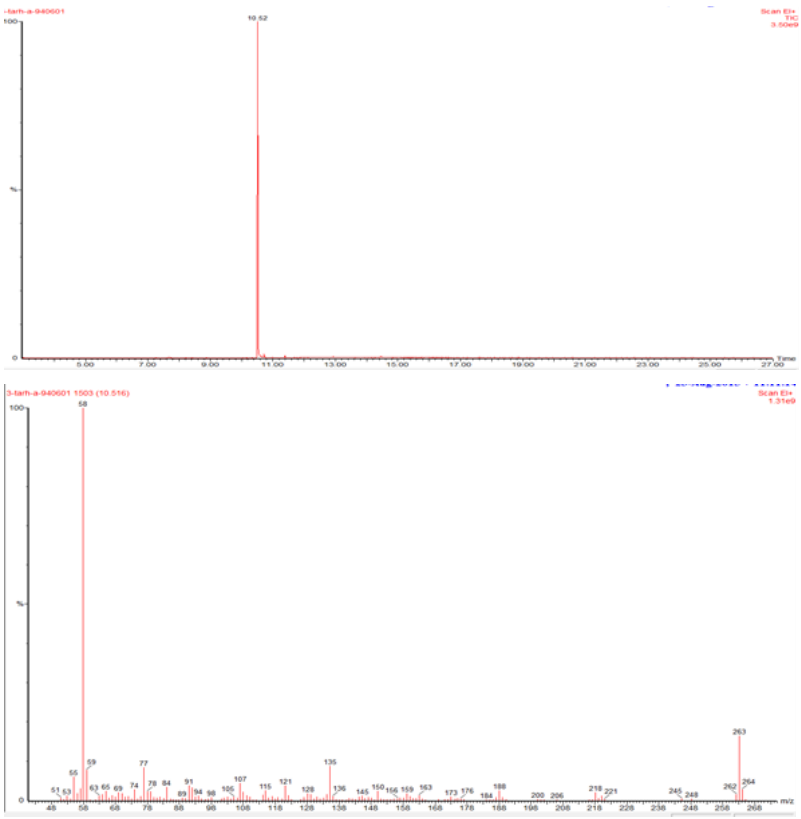

Figure 2. Mass spectrum of tramadol

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Retention time =10.52 minutes

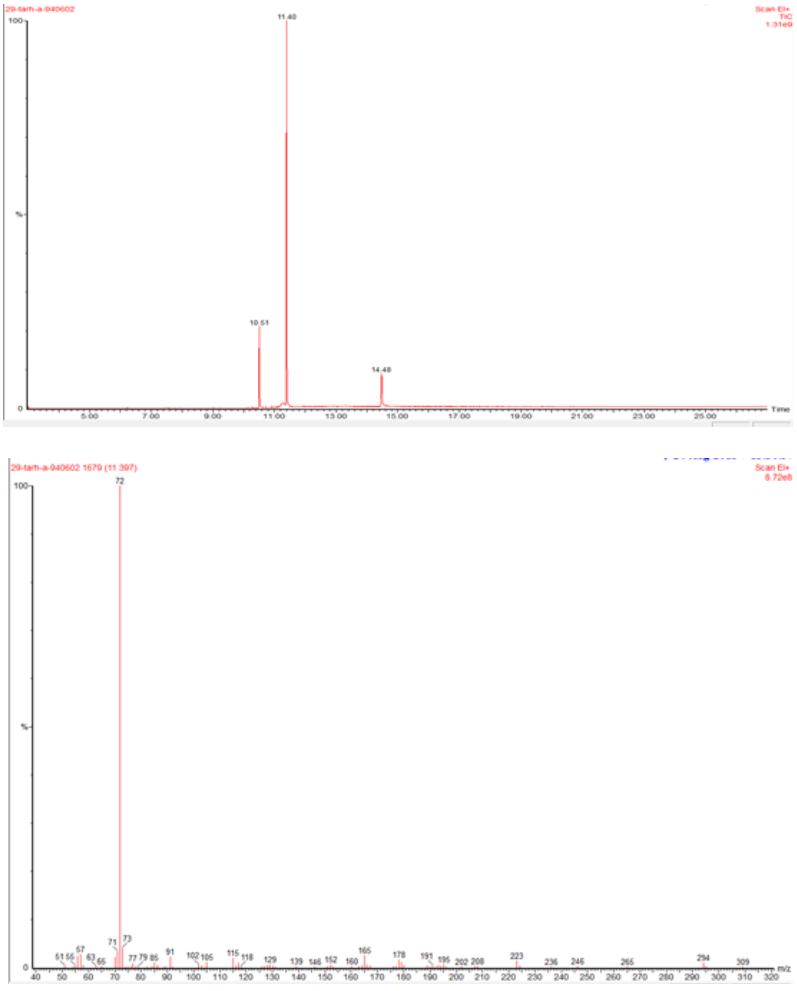

Figure 3. Mass spectrum of methadone

Retention time =11.40 minutes

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to drug overdose, misuse, and side effects, especially among high-risk individuals [6, 7]. Based on this view, an increased interest in the administration of herbal remedies is considered an alternative pharmacotherapy modality for opioid addiction.

Unfortunately, the adulteration of herbal medicines with undeclared active pharmaceuticals is a growing and global concern. The adulteration of herbal remedies used for the treatment of opioid addiction with synthetic drugs has been reported worldwide. For example, the analysis of krypton, an herbal mixture containing "Kratom" (leaves of Mitragyna speciosa), had shown a tramadol metabolite (O-desmethyltramadol), which could be added to this herbal mixture [24]. In a recent study in Tehran, Iran, the analysis of 80 traditional herbal medicinal products used as opioid substitution therapy has shown that more than 96% of the samples contained at least 1 pharmaceutically active ingredient and diphenoxylate and tramadol were detected in 90% and 67% of the products, respectively [25]. These findings are in concordance with the results of this study that stated diphenoxylate and tramadol are the most common adulterants of herbal medicines sold in herbal shops for opioid addiction treatment in Kermanshah, Iran.

Diphenoxylate is a centrally active opioid belonging to the phenylpiperidine class that is used in combination with atropine for the treatment of diarrhea. Diphenoxylate has a morphine-like effect at therapeutic doses and at high doses, it exhibits codeine-like effects [26]. In Iran like many countries, diphenoxylate is produced in tablet dosage form with a combination of 2.5 mg diphenoxylate and 0.025 mg atropine as an antidiarrheal agent. Diphenoxylate is an opioid receptor agonist and it has a potential for abuse [26]. Atropine is present to prevent drug abuse and overdose. Previous studies reported that diphenoxylate abuse has occurred among patients with medical illnesses and substance abusers. Although it has been administered during the detoxification stage of opi-

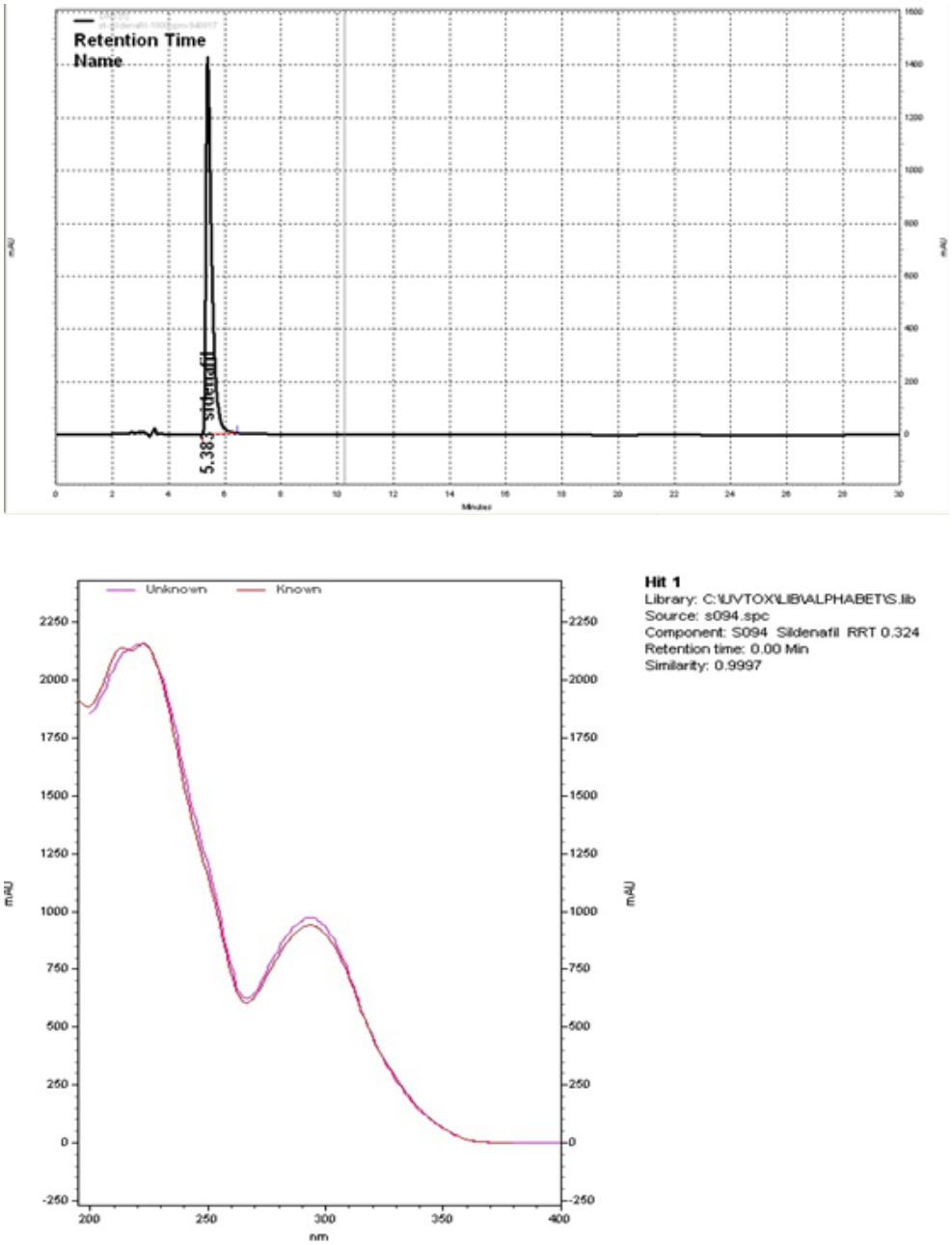

Figure 4. HPLC chromatogram and ultraviolet spectrum of sildenafil

Retention time =5.38 minutes

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oids addiction, there is not an official label used for the administration of the drug in this regard [26]. However, at high doses, it causes side effects like tachycardia, dry mouth, blurring of vision, the risk of respiratory depression, anticholinergic toxicity, and opioid overdose.

Other common adverse effects include euphoria, lethargy, confusion, drowsiness, dizziness, restlessness, headache, hallucinations, nausea, and vomiting [26, 27]. For these reasons, diphenoxylate added to the herbal remedies could suppress the opioid withdrawal symptoms (especially diarrhea) and induces central opioid-like effects. Because of these effects and low price, as well as its availability, diphenoxylate is a common pharmaceutical adulterant in herbal products used for opioid addiction treatment.

Tramadol is another synthetic pharmaceutical, which was detected in the herbal products in the present study and the previous ones. Tramadol is a unique centrally acting analgesic that is structurally related to codeine with a dual mechanism that acts as a monoamine reuptake

inhibitor and opioid receptor agonist. [28, 29]. It is increasingly prescribed worldwide as an opioid in the treatment of both acute and chronic pains [29]. Tramadol is a prodrug that is metabolized by cytochrome P450 (CYP) enzymes such as CYP2D6 and CYP3A4 to its more potent analgesic metabolites, particularly the O-desmethyltramadol. The opioid analgesic potency of tramadol is dependent on the individual's CYP genetics [29].

Although tramadol can be an alternative medication for harm reduction in patients with opioid dependence, there is not an official label used for this propose [30]. Some of the serious side effects of tramadol, including seizures, increased risk of serotonin syndrome, decreased alertness, and drug addiction have been reported. The sudden cessation of tramadol increases the risk of both opioid and serotonin-norepinephrine reuptake inhibitor withdrawal syndromes [29]. Tramadol is a common cause of acute pharmaceutical poisoning and drug-induced seizures in Iran.

The previous studies showed that a low dose of tramadol might lead to acute generalized seizures in the patients [31, 32]. Also, in the previous study, the quantitative analysis of herbal samples showed that tramadol has been detected at concentrations of 67 mg/capsule to 150 mg/capsule [25]. Thus, the seizures and serotonin syndrome could be considered a threat to consumers of these adulterated herbal products. Another reason for adding tramadol to herbal remedies might be related to the analgesic effect of the drug that mediated through mu opioid receptors. It could relieve pain and craving during the opioid withdrawal syndrome in the patients.

In the present study, methadone and buprenorphine, as mu opioid receptors agonists, were detected in the herbal products as pharmaceutical adulterants. Although the previous study has shown methadone as a chemical adulterant in herbal products, to the best of our knowledge, there has been no report regarding the presence of buprenorphine as an adulterant of herbal medicines used for the treatment of opioid addiction [33]. As a high-affinity and partial mu opioid receptor agonist, buprenorphine suppresses opioid withdrawal and craving. These drugs considered the most common medicines in OAT around the world [5]. Regarding the serious side effects such as respiratory depression and cardiac dysrhythmia as the result of methadone abuse, the consumption of adulterated herbal products is considered a health threat.

Benzodiazepines (diazepam and chlordiazepoxide) have been detected in our study. This finding is in line with other previous studies in Iran [25, 33]. Anxiolytic, hypnotic, and euphoric effects of benzodiazepines might be considered desirable in patients' increased potential usage of the drugs for the adulteration of herbal remedies. However, dependence and addiction are the most serious complications of benzodiazepines during usage. Thus, the dependency and addiction to these adulterated herbal products are probable.

Moreover, sildenafil in combination with diphenoxylate and tramadol has been detected in our samples. The finding is interesting and previous studies did not report sildenafil in herbal remedies used for the treatment of opioid addiction. Sildenafil, as a phosphodiesterase-5 inhibitor, is the most important drug used in the management of erectile dysfunction and it was detected as an adulterant in herbal remedies used as a sexual enhancer [34].

Previous studies showed that sexual dysfunction is a significant problem among men with opioid abuse/addiction. Also, premature ejaculation occurs predominantly in discontinuing opioids [35]. On the other hand, sexual dysfunctions like erectile dysfunction, the decrease of libido, and premature ejaculation are the main common sexual problems among the opioid abusers. Therefore, the adulteration of herbal remedies used for opioid addiction treatment with sildenafil and tramadol occurs.

The use of tramadol in the improvement of sexual dysfunction is controversial. The previous study showed that tramadol may be effective in premature ejaculation treatment [36]. However, the adulteration of the herbal products adulterated with sildenafil and tramadol may improve the sexual problems and enhance the sexual activity of the consumers. In addition, the adverse effects of sildenafil such as visual disturbances, muscle pain, and flushing have occurred in the consumers of herbal products. When herbal products are adulterated with undeclared pharmaceuticals, the consumer could be susceptible to drug-drug interactions. These adverse effects are especially important in patients with comorbid conditions such as cardiovascular and metabolic disorders. This point is very important, especially in products adulterated with more than 1 undeclared pharmaceutical. For example, the result of the present study simultaneously showed the presence of the combination of methadone and tramadol or methadone and diphenoxylate in 1 product.

There are major clinically important drug interactions. The concomitant use of tramadol with other central nervous system depressants including methadone or diphenoxylate may result in sedation, respiratory depression, coma, and death. The risk of hypotension and seizures may also be increased. In patients, who have been

previously dependent on or chronically using opioids, tramadol can reinitiate physical dependence or precipitate withdrawal symptoms. Also, methadone may cause dose-related prolongation of the QT interval. Tramadol may also prolong the QT interval, and theoretically, the co-administration of multiple agents that can prolong the QT interval may result in additive effects and increase risk of ventricular dysrhythmias including torsade de pointes and sudden death [37].

The pattern of undeclared pharmaceuticals in herbal products in the study was different from a similar study, in which some other pharmaceuticals like acetaminophen, codeine, sertraline, and fluoxetine were found [25]. These drugs were not detected in the present study and this may be related to economic factors and the availability of these drugs, as well as the total price of adulterated products.

In the current study, the presence of herbal-derived organic compounds in the majority of the products was related to the alteration of an herbal-based formulation with synthetic pharmaceuticals. None of the herbal samples in our study had standard labels, indicating their kind of herbal ingredients and active ingredients, patient package inserts, manufacturer identifications, and addresses. This finding is similar to previous studies [25, 33].

4. Conclusion

In the present study, diphenoxylate, tramadol, methadone, buprenorphine, diazepam, chlordiazepoxide, and sildenafil, alone or in combination with each other, were identified as synthetic adulterants in herbal medicinal products used for the treatment of opioid addiction. The components are not declared on the products and can have very serious consequences on the quality of life of the consumers. Therefore, more regulations should be needed for analyzing herbal remedies and evaluating their safety.

Ethical Considerations

All ethical principles were considered in this article.

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Author's contributions

Designing this study and writing the manuscript: Kambiz Soltaninejad, Vida Shiri-Ghaleh; Performing the experiments: Vida Shiri-Ghaleh, Mehrdad Moradi; Data and statistical analysis, Reading and approving the final manuscript: All authors.

Conflict of interest

The authors declared no conflict of interest.

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