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RESEARCH ARTICLE

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Efficacy and safety of *Sophora alopecuroides* var. *alopecuroides* seed extract for opioid detoxification: A randomized, double-blind, and placebo-controlled clinical trial

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The seeds of *Sophora alopecuroides* L. var. *alopecuroides* (*S. alopecuroides*) have alleviated morphine withdrawal in mice. Therefore, in this study, the alkaloid composition of *S. alopecuroides* extract was determined by gas chromatography (GC) and gas chromatography–mass spectrometry (GC–MS) analysis. Moreover, 50 abstinent opium addicts consumed three 400 mg extract capsules once daily and 50 other patients took placebo for 8 days. At the baseline and days 3 and 8, the clinical opiate withdrawal scale (COWS) was used to assess withdrawal symptoms. At the baseline and Day 8, the patients' blood levels of serum glutamate oxaloacetate transferase; serum glutamate pyruvate transferase; alkaline phosphatase; total, direct, and indirect bilirubins; creatinine and blood urea nitrogen; complete blood count; and prothrombine time were measured. The groups' parameter values were also compared. Sophocarpine, matrine, and sophoramine were the major alkaloids constituting, respectively, 32.85, 26.55, and 6.91% of the extract. The extract decreased the COWS score at Days 3 and 8 significantly compared with the placebo ($p < .001$). The extract did not significantly affect the blood parameters' values compared with the placebo ($p > .05$). There was no adverse drug effect. In conclusion, the extract reduces the acute opioid withdrawal symptoms and seems to have good safety and tolerability.

KEYWORDS
detoxification, opioid, *Sophora alopecuroides*, withdrawal

1 | INTRODUCTION

Opioid addiction is a significant cause of morbidity and mortality and has great social costs (Diaper, Law, & Melichar, 2014). Opioid withdrawal symptoms include dysphoria, nausea, vomiting, muscle aches, lacrimation, rhinorrhea, pupillary dilatation, piloerection, diarrhea, yawning, fever, and insomnia. The withdrawal symptoms can be terrifying to the opioid addicts. The main reason that causes the opioid addicts to continue opioid use is to avoid withdrawal symptoms (Kosten & Baxter, 2019). Detoxification, defined as pharmacological management of withdrawal symptoms, assists the addicts to achieve abstinence and remain in treatment programs. Therefore, detoxification is a key component of opioid addiction treatment (Ayanga, Shorter, & Kosten, 2016). Despite the high prevalence of opioid addiction, there are few licensed pharmacotherapies for opioid addiction (Bailey & Husbands, 2014). The standard pharmacological agents for opioid withdrawal are methadone, buprenorphine, clonidine, and lofexidine. These drugs are limited by efficacy and adverse effect profiles, accessibility, and cost. Thus, new therapeutic agents for opioid withdrawal symptoms are needed (Kosten & Baxter, 2019).

Medicinal plants can be a suitable source for the development of new therapies for opioid detoxification (Tabatabai, Dashti, Doosti, & Hosseinzadeh, 2014). The seeds of *Sophora alopecuroides* L. var.

alopecuroides (Leguminosae) are administered orally in the Iranian folk medicine for detoxification and maintenance treatment of opium and heroin addicts. Moreover, *S. alopecuroides* 90% ethanol seed extract alleviated morphine withdrawal and had moderate toxicity in the oral LD_{50} test in mice (Kianbakht, Hajiaghaee, & Ramezani Salehabad, 2017). However, there has been no clinical trial investigating the efficacy and safety of *S. alopecuroides* in the treatment of opioid addiction. Therefore, this study was conducted to examine the efficacy and safety of *S. alopecuroides* in the detoxification of opium addicts.

2 | MATERIALS AND METHODS

2.1 | Plant material

The seeds of *S. alopecuroides* were collected from the Kerman Province of Iran at the fruiting stage in November 2017. A voucher specimen of the plant (number 512) was deposited in the Herbarium of Institute of Medicinal Plants, ACECR, Karaj, Iran.

2.2 | Extraction

The plant seeds were dried, powdered (5 kg), and macerated with 90% ethanol solution for 3 days with three changes of the solution. The resulting extract was filtered and evaporated under vacuum into a dry powder (400 g). The yield of extraction was 8%.

2.3 | Preparation of the extract and placebo capsules

The extract powder as the active drug and toast powder as the placebo were separately filled into oral gelatin capsules by a hand-operated capsule-filling machine (Scientific Instruments and Technology Corporation). The *S. alopecuroides* capsules contained 400 mg of the extract powder. The *S. alopecuroides* and placebo capsules were identical in every respect.

2.4 | Determination of some alkaloids by GC and GC–MS analyses

Analysis of 90% ethanol extract was carried out as described previously (Kamada, Okamura, Satake, Harada, & Shimomura, 1986). A total amount of 200 ml of $CHCl_3$—CH_3 OH—NH_4OH (15:5: 1) was added to 600 mg of 90% ethanol extract for 10 min. After filtration, the residue was washed with 200 ml of solution twice. The pooled filtrate was evaporated to dryness. Then 5 ml of $CHCl_3$ and 2 ml of 1 N H_2SO_4 were added to the residue and the solution was mixed. The $CHCl_3$ phase was removed and the H_2SO_4 phase was adjusted to pH 10 with 28% NH_4OH. Alkaloids were extracted once with 2 ml and twice with 1 ml of $CHCl_3$ from the solution. The combined extracts were filtered after adding anhydrous Na_2SO_4 and were evaporated to dryness at 40°C (265 mg).

The extraction of alkaloids was analyzed on a Younglin Acm 600 instrument with an flame ionization detector (FID) detector operated with a split/splitless injector (Younglin, Korea) and a DB-5 capillary column, 30 m × 0.25 mm i.d., 0.25 μm film thickness (Agilent, USA). Carrier gas is helium; linear velocity is 30 cm/s; flow is 0.8 ml/min; injection temperature is 290°C; injection volume is 1.0 μl; injection mode is split (1:50); temperature program is 50°C for 5 min increasing at 3°C/min to 240°C, then increasing at 15°C/min to 300°C, held at 300°C for 3 min; FID (290°C); H_2 flow is 50 ml/min; and air flow is 400 ml/min. GC–MS analysis was performed using an Agilent 6890/5973N instrument and a DB-5 capillary column (30 m × 0.25 mm i.d., 0.25 μm film thickness); carrier gas: helium; linear velocity: 32.4 cm/s; flow: 0.8 ml/min; injection temperature: 290°C; injection volume: 1.0 μl; injection mode: split (1:10); temperature program: 50°C for 5 min increasing at 3°C/min to 240°C, and then increasing at 15°C/min to 300°C, held at 300°C for 3 min; MS interface temperature: 290°C; MS mode: EI; ionization voltage: 70 eV; mass range: 40–500 u; scan speed: 3.18 scans/s; interval: 0.50 s (2 Hz). Data handling was conducted using a Chem. Station (Agilent, USA).

2.5 | Identification of the alkaloids

The compounds of the extraction of alkaloids were identified by comparison of their retention indices calculated by using the retention times of injected n-alkanes (C8–C28) (obtained from Fluka) under the same chromatographic conditions, along with the fragmentation patterns of the mass spectra with those reported in the literature studies and the published mass spectra or WILEY library (Kite & Pennington, 2003; Lee et al., 2013; Wu, Chen, & Cheng, 2005). The percentages of the identified alkaloids were calculated based on GC peak areas without any correction factors.

2.6 | The trial protocol

A randomized, double-blind, placebo-controlled, parallel-group trial was conducted in a residential addiction treatment center named Izad Mehr Setayesh (Karaj city, Iran) from April 21, 2018 to June 21, 2019. The extract was compared with placebo instead of a standard drug because this study aimed at detecting any nonspecific (placebo-related) effects of the extract. Urinalysis was performed to detect 6-acetylmorphine by GC–MS (Smith et al., 2001), and morphine, amphetamine, methamphetamine, methadone, buprenorphine, benzodiazepine, tramadol, cocaine, tetrahydrocannabinol, and tricyclic antidepressants by kit (Farafan Diagnostics Company, Tehran, Iran). Inclusion criteria are as follows: Iranian males aged 18 to 70 years with a history of opium addiction for at least 1 year and positive urine test for only morphine; patients addicted to opium according to the Diagnostic and Statistical Manual of Mental Disorders (*DSM–5*) criteria; patients whose dose of opium has been constant for at least

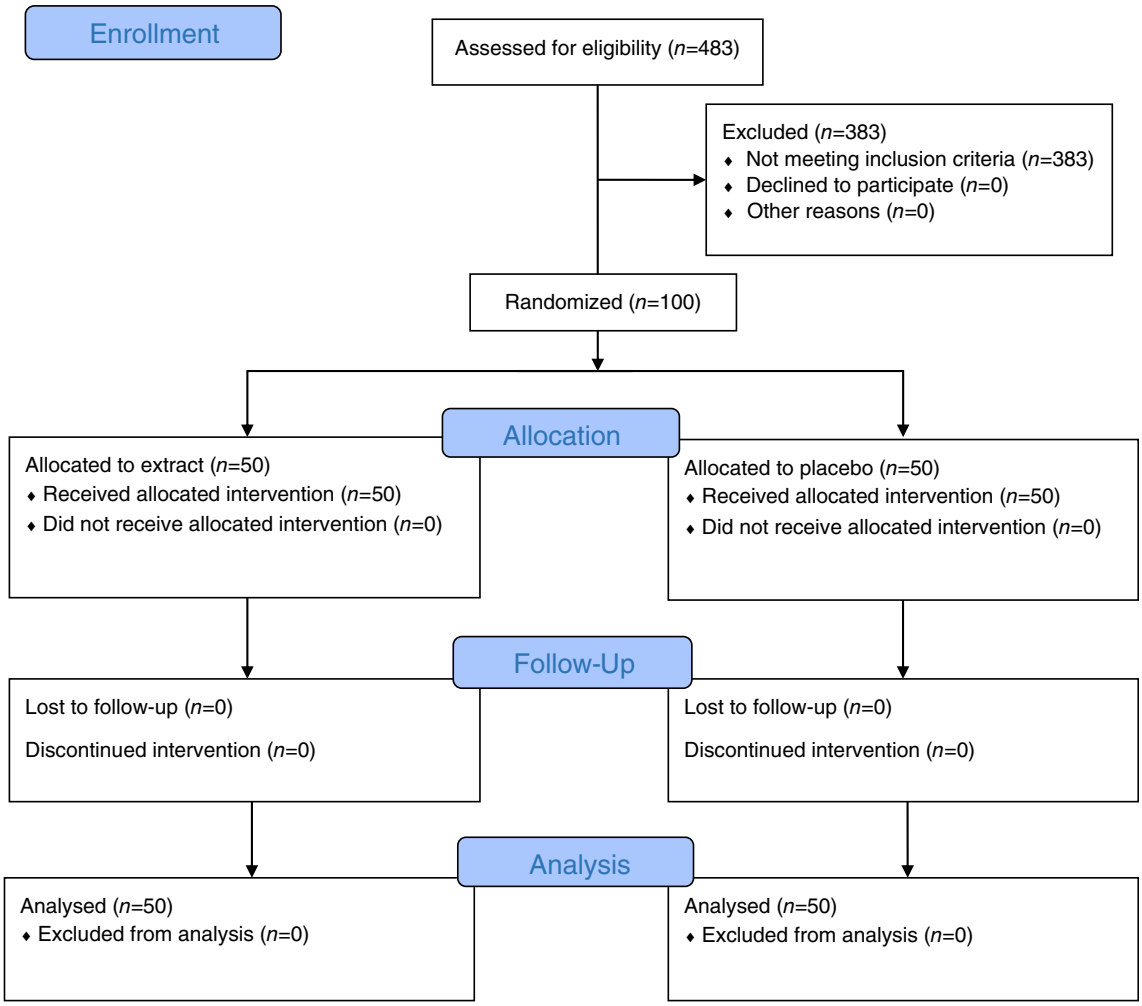

FIGURE 1 CONSORT flow diagram of the clinical trial [Colour figure can be viewed at wileyonlinelibrary.com]

1 month before the trial; abstinent opium addicts residing in an addiction treatment center; patients who have not used opium for at least 5 h before arrival at the center. Exclusion criteria are as follows: patients who besides opium abuse other substances except for tobacco; patients with other psychiatric diseases, organic brain disease, mental retardation, and important diseases such as cardiac, renal, and hepatic disease. No normal inclusion/exclusion criteria were employed for clinical chemistries, vital signs, and so on. A total of 483 patients were screened. The excluded patients did not meet one or more of the inclusion criteria or met one or more of the exclusion criteria. The recruited patients were randomized to the *S. alopecuroides* extract and placebo groups (Figure 1). Block randomization using computer-generated random numbers and sequentially numbered containers each representing a block of 10 patients was used for treatment assignment. The patients took three extract or placebo capsules once daily after breakfast under direct observation from 7 a.m. to 8 a.m. for 8 days. The extract dosage was found empirically. The treatments were given for 8 days because the duration of acute withdrawal of short-acting opioids is 7–10 days (Blanco & Volkow, 2019). No concomitant medication was allowed, and the patients did not use any other drug except for the extract and placebo capsules during the trial. The opium withdrawal symptoms were rated using the clinical opiate withdrawal scale (COWS) (Wesson & Ling, 2003) from 12 p.m. to 1 p.m. at Days 1 (baseline), 3, and 8 of intervention. Withdrawal severity was not assessed on other days of the trial. A minimal level of COWS score was not required to be demonstrated as proof of withdrawal. No other assessment was performed to confirm the COWS findings. A physician asked the patients nonspecific questions about any adverse drug effects and medical complaints from 12 p.m. to 1 p.m. every day during the intervention. The patients' satisfaction of the treatments was also rated by a physician using an 11-point visual analog scale (VAS) from 12 p.m. to 1 p.m. at the day 8. The patient's satisfaction increased from 0 to 10 in the VAS. Moreover, from 12 p.m. to 1 p.m. at Days 1 and 8, the patients' blood levels of serum glutamate oxaloacetate transferase; serum glutamate pyruvate transferase; alkaline phosphatase; total, direct and indirect bilirubins; creatinine and blood urea nitrogen; complete blood count and prothrombin time were determined by an autoanalyzer (Hitachi, Japan). No other medical examinations such as vital signs, electrocardiograms, and so on were performed on the patients. The patients

were not further treated and followed up after completion of the trial. Primary outcome variable is the COWS score. Secondary outcome variables are the VAS score and blood parameters. Three different persons generated the random assignment sequence, recruited the patients, and allocated them to interventions. These persons, care-providers, patients, and data analyzer were blinded to interventions. This study's principal author was not blinded. A total of 50 patients in each group completed the trial, which shows the effect size of 3.3 for COWS score, type I error of 0.05, and 80% power. The independent samples *t* test and repeated measurements analysis of variance followed by the Tukey's post hoc test were used for data analyses. $p < .05$ was considered as statistically significant. The data were analyzed as per the protocol approach. The protocol was approved by the Ethics Committee of the Tehran University of Medical Sciences (approval number: IR.TUMS.VCR.REC.1395.350). The trial was conducted in compliance with the revised Declaration of Helsinki 2013. The participants signed written informed consent before recruitment. This study is registered with the Iranian Registry of Clinical Trials (www.irct.ir) as IRCT20090804002288N15.

3 | RESULTS

3.1 | The extract alkaloids

The major alkaloids of the extract were sophocarpine (32.85%), matrine (26.55%), and sophoramine (6.91%).

3.2 | The trial

The patients' demographics are presented in Table 1-. The extract and placebo groups did not differ significantly in demographics, COWS scores, and blood parameters values at the beginning of the study ($p > .05$). The COWS scores of the extract group decreased significantly compared with that of the placebo group at Days 3 and 8 (both $p < .001$). In the extract group, the COWS score at Day 3 was not significantly different from the COWS score at Day 8 ($p > .05$). The VAS score of the extract group was significantly higher than that of the placebo group ($p < .001$) (Table 2). In the extract group, 1 patient reported pain of the upper and lower extremities, another patient reported insomnia, and 1 other patient reported abdominal cramps and fever. The extract did not change the values of the blood parameters significantly compared with the placebo ($p > .05$). No adverse drug effect was observed in the patients.

TABLE 1- The patients' demographics. The values are given as mean ± *SD*

Parameter	Extract group	Placebo group
Age (years)	40 ± 8.2	36 ± 7.9
Duration of opium addiction (years)	11.7 ± 5.6	11.6 ± 4.7
Body mass index (kg/m^2)	26.5 ± 4.4	27.2 ± 6.1

4 | DISCUSSION

The results indicate that sophocarpine, matrine, and sophoramine are the major alkaloids of the *S. alopecuroides* extract. Also, both groups developed typically mild opium withdrawal, which decreased at Days 3 and 8 relative to baseline. However, the COWS scores of the extract group at Days 3 and 8 exhibit significant and drastic reduction versus placebo, suggesting considerable efficacy of the extract in reducing the withdrawal symptoms. Moreover, suppression of withdrawal by the extract can be observed after 3 days of use, and the effect of the extract on withdrawal at the day 3 is not significantly different from that at Day 8. Report of arms and legs pain, insomnia, abdominal cramps, and fever by some patients suggests that the extract has insufficient effects on these withdrawal symptoms in some patients. The VAS score of the extract group is very higher than that of the placebo group, indicating high patients' satisfaction of treatment with the extract. Ineffectiveness of the extract versus placebo on the blood parameters demonstrates that the extract has no renal, hepatic, and hematological toxicities. Lack of patient dropout in this trial may be due to residence of the patients in a center where any drug use was not allowed, short trial duration, and high patients' satisfaction of the treatment. Overall, this study suggests that intake of three 400 mg *S. alopecuroides* extract capsules once daily has efficacy, safety, and tolerability in controlling the opioid withdrawal symptoms. These trial results are consistent with the report of efficacy of the *S. alopecuroides* extract in reducing morphine withdrawal in mice (Kianbakht, Hajiaghaee, & Ramezani Salehabad, 2017) and intake of the plant for treatment of opium/heroin addiction in the Iranian folk medicine (Kianbakht, Hajiaghaee, & Ramezani Salehabad, 2017).

TABLE 2 Effects of the extract (E) and placebo (P) on the patients' COWS (clinical opiate withdrawal scale) and VAS (visual analog scale) scores. The values represent mean ± *SD*

Parameter	Day 1 (baseline)	Day 3	Day 8	*P* value (extract vs. placebo at Days 3 and 8)
COWS score	10.8 ± 5.8 (E)	2.7 ± 3.0 (E)	1.6 ± 2.2 (E)	<.001
	9.4 ± 5.9 (P)	6.4 ± 4.1 (P)	4.7 ± 3.7 (P)	
VAS score	—	—	8.6 ± 3.5 (E)	<.001
			1.2 ± 3.4 (P)	

The alkaloid fraction and matrine have been implicated in the suppression of morphine withdrawal by the *S. alopecuroides* extract in mice (Kianbakht & Hashem Dabaghian, 2016). Therefore, the alkaloid fraction, matrine, and the other major alkaloids sophocarpine and sophoramine may be involved in the efficacy of extract for opioid detoxification. To date, there has been no report showing that sophoramine could reduce one or more symptoms of the opioid withdrawal. However, the analgesic effect of sophocarpine has been demonstrated in mice (Gao et al., 2009). Thus, sophocarpine may to some extent reduce the pain of opioid withdrawal. Matrine has had analgesic and antidiarrheal effects in animal models (Huang & Xu, 2016) and antianxiety and antidepressant effects in mice (Khan et al., 2019). Therefore, matrine may reduce pain, diarrhea, anxiety, and dysphoria of opioid withdrawal. Three studies have reported involvement of the μ and κ opioid receptors in the analgesic effects of matrine in mice (Higashiyama et al., 2005; Kamei et al., 1997; Xiao et al., 1999). However, another study demonstrated that matrine had no affinity for the μ, κ, and δ opioid receptors in vitro. Furthermore, naloxone did not antagonize the analgesic effects of matrine in mice, suggesting that the opioid system may not be involved in the matrine analgesic effect. This study concluded that the analgesic effect of matrine was due to activation of the cholinergic system (Yin & Zhu, 2005). Agonists of nicotinic receptors can suppress opioid withdrawal (Rahman, Engleman, & Bell, 2015; Zarrindast & Farzin, 1996). Therefore, matrine may reduce the opioid withdrawal through activation of the nicotinic receptors. In another study, *S. alopecuroides* 90% ethanol seed extract had analgesic effect not reversed by naloxone in the rat formalin test. Moreover, the extract did not cause Straub tail effect in mice, showing inactivity on the μ_2 opioid receptors (Kianbakht & Hajiaghaee, 2014). This study concluded that the extract was nonopioid and may not produce side effects caused by μ_2 opioid receptor activation (physical dependence, respiratory depression, and constipation) (Kianbakht & Hajiaghaee, 2014). Notably, despite the traditional use of *S. alopecuroides* in Western and Central Asia for millennia, addictive potential of the plant has not been reported (Kianbakht & Hashem Dabaghian, 2016).

In the present trial, extract was used instead of the extract's alkaloid fraction because there were no data regarding toxicity and safety of the alkaloid fraction. Limitations of this study are lack of a positive control including one of the standard drugs methadone, buprenorphine, lofexidine, and clonidine and short duration of the extract administration.

The implication of this study is that *S. alopecuroides* extract may have clinical efficacy, safety, and tolerability in the opioid detoxification. Given the limited number of pharmacological options particularly nonopioid agents for treatment of opioid addiction, *S. alopecuroides* extract may have a place in the pharmacotherapy of opioid addicts. Finally, the alkaloids and mechanisms mediating opioid withdrawal inhibitory effect of *S. alopecuroides* should be further investigated. Moreover, evaluation of the efficacy and safety of *S. alopecuroides* versus methadone, buprenorphine, lofexidine, and clonidine in the detoxification and maintenance treatment of opioid addicts are warranted.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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