Complementary Therapies in Clinical Practice 51 (2023) 101740

Contents lists available at ScienceDirect

Complementary Therapies in Clinical Practice

journal homepage: www.elsevier.com/locate/ctcp

A randomized controlled trial on the seeds of *Sophora alopecuroides* var. *alopecuroides* for the treatment of acute heroin withdrawal syndrome

Fataneh Hashem-Dabaghian [a], Saeed Kianbakht [b,*]

[a] Department of Traditional Medicine, Institute for Studies in Medical History, Persian and Complementary Medicine, School of Persian Medicine, Iran University of Medical Sciences, Tehran, Iran
[b] Medicinal Plants Research Center, Institute of Medicinal Plants, ACECR, Karaj, Iran

ARTICLE INFO

Keywords:
Detoxification
Heroin
Opioid
Sophora alopecuroides
Withdrawal

ABSTRACT

Background: and purpose: The seeds of *Sophora alopecuroides* var. *alopecuroides* have attenuated the acute opium withdrawal syndrome in humans. Therefore, the efficacy and safety of a standardized extract of the plant for the treatment of acute heroin withdrawal syndrome was evaluated in abstinent heroin addicts.
Materials and methods: The patients were randomized to take three 400 mg extract capsules (N = 50) or placebo (N = 50) once per day orally for eight days. The severity of withdrawal syndrome was assessed by the clinical opiate withdrawal scale (COWS) as the primary outcome measure at the baseline and on the days 3 and 8. The hepatic and renal functions and complete blood count were the secondary outcome measures tested at the baseline and end of the study.
Results: The COWS score decreased in both groups after eight days, but the decrease was significantly higher in the experimental group ($p < 0.001$); the effect size of the decrease was 2.64. The groups had significant differences in the COWS scores on the days 3 and 8 ($p < 0.001$ for both). The extract had no significant effect on the other parameters. No side effect was noted.
Conclusion: The extract seems to alleviate acute heroin withdrawal syndrome safely.

1. Introduction

Addiction to heroin and opium is common and associated with morbidities and mortalities which cause huge costs [1,2]. Heroin and opium have differences in chemistry, pharmacokinetics and pharmacodynamics [3,4]. Heroin (3, 6-diacetylmorphine) is a semisynthetic derivative of morphine and a prodrug [4], and morphine is the main constituent of opium [2]. The effects of opium are primarily due to morphine [2]. As heroin is more lipid-soluble than morphine, its entry into brain is faster than morphine. Heroin is rapidly metabolized to the active metabolites 6-acetylmorphine and morphine in the brain. Heroin has faster onset of action and more severe effects than morphine. The nature and duration of acute heroin and opium withdrawal syndromes are comparable [4]. The acute heroin withdrawal syndrome begins after 4–6 h, peaks on day 3 and lasts for 6–10 days [5]. The acute heroin withdrawal syndrome is more intense than acute opium withdrawal. Thus, data about treatment of opium withdrawal may not apply to heroin [6]. Treatment of opioid addiction has 2 goals: first, treatment of acute withdrawal syndrome or detoxification and second, maintenance treatment [7]. Treatment of acute withdrawal syndrome facilitates abstinence from opioid and retention of patients in treatment programs [7]. Maintenance treatment maintains abstinence and prevents relapse to addiction [7]. Mu-opioid receptor agonists (e.g., methadone), μ-opioid receptor partial agonists (e.g., buprenorphine), and α_2-adrenergic receptor agonists (e.g., lofexidine) are the standard drugs used for the treatment of acute heroin withdrawal syndrome [7].

Medicinal plants are one of the modalities of treatment of the opioid withdrawal syndrome [8]. Decoction of the seeds of *Sophora alopecuroides* var. *alopecuroides* (*S. alopecuroides*) is used for the treatment of heroin, opium, methamphetamine and nicotine addiction, and pain and diarrhea in the Iranian folk medicine [9,10]. Also, *S. alopecuroides* 400 mg extract capsules are manufactured for the treatment of acute opium withdrawal syndrome in Iran. The *S. alopecuroides* extract was as effective as methadone in suppressing the morphine withdrawal in mice [9]. Also, three 400 mg extract capsules once daily for 8 days safely mitigated the acute opium withdrawal in a randomized controlled trial

* Corresponding author. Institute of Medicinal Plants, Research Complex of the Iranian Academic Center for Education, Culture and Research (ACECR), Poleh Kordan, Karaj, P.O. Box (Mehr Villa): 31375-369, Iran.
E-mail addresses: kianbakht@imp.ac.ir, skianbakht@yahoo.com (S. Kianbakht).

https://doi.org/10.1016/j.ctcp.2023.101740
Received 10 April 2022; Received in revised form 12 February 2023; Accepted 16 February 2023
Available online 18 February 2023

[10]. However, there has been no research into the effects of *S. alopecuroides* on the acute heroin withdrawal. Moreover, the efficacy and safety of *S. alopecuroides* for the treatment of opioid withdrawal needs further research. Therefore, this study was conducted to assess the efficacy and safety of the *S. alopecuroides* extract in the treatment of the acute heroin withdrawal.

2. Materials and methods

2.1. Plant

The seeds of the plant were collected from the Kerman Province (Iran) in November 2019 and a voucher specimen of the plant (number 1012-IMPH) was deposited in the Herbarium of Institute of Medicinal Plants (Karaj, Iran).

2.2. Extraction

Five kilograms of the seed powder were macerated in 90% ethanol for 3 days during which ethanol was changed 3 times. The extract was filtered, the solvent was evaporated under vacuum, and after mixing the extract with toast powder, 427 g of dry powder of the extract was produced. The yield of extraction was 11%.

2.3. Extract and placebo capsules

Oral gelatin capsules were filled with 400 mg of the extract powder as drug or toast powder as placebo using a hand-operated capsule-filling machine. The extract and placebo capsules were produced according to the good manufacturing practices guidelines in the Institute of Medicinal Plants (Karaj, Iran) under supervision of the Ministry of Health of Iran. The extract and placebo capsules were indistinguishable in every respect.

2.4. Extraction and quantification of the alkaloids

The extract was standardized by quantification of the main alkaloids by gas chromatography and gas chromatography-mass spectrometry according to a previous study [10]. First, the alkaloids were extracted as follows. Two hundred 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. Five 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 pH of 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). Then, the extraction of alkaloids was analyzed on a Younglin Acm 600 instrument with a flow ionization detector (FID) operated with a split/splitless injector (Younglin, Korea) and DB-5 capillary column (30 m × 0.25 mm i.d., 0.25 μm film thickness) (Agilent, USA). Carrier gas was helium. Linear velocity was 30 cm/s. Flow was 0.8 mL/min. Injection temperature was 290 °C. Injection volume was 1.0 μL. Injection mode was split (1:50).Temperature program was 50 °C for 5 min rising at 3 °C/min to 240 °C, then rising at 15 °C/min to 300 °C, and held at 300 °C for 3 min. Temperature of FID was 290 °C. H_2 flow was 50 mL/min. Air flow was 400 mL/min. GC-MS analysis was performed by an Agilent 6890/5973 N instrument and DB-5 capillary column (30 m × 0.25 mm i.d., 0.25 μm film thickness). Carrier gas was helium. Linear velocity was 32.4 cm/s. Flow was 0.8 mL/min. Injection temperature was 290 °C. Injection volume was 1.0 μL. Injection mode was split (1:10). Temperature program was 50 °C for 5 min rising at 3 °C/min to 240 °C, then rising at 15 °C/min to 300 °C, and held at 300 °C for 3 min. MS interface temperature was 290 °C. MS mode was EI. Ionization voltage was 70 eV. Mass range was 40–500 u. Scan speed was 3.18 scans/sec. Interval was 0.50 s (2 Hz). Data handling was conducted using a Chem. Station (Agilent, USA).

The retention indices of the compounds of the extraction of alkaloids were calculated using the retention times of injected n-alkanes (C8–C28) (obtained from Fluka) under the same chromatographic conditions. Afterward, the compounds were identified by comparison of their retention indices and fragmentation patterns of mass spectra with those in the literature or WILEY library. Also, the percentages of the identified alkaloids were calculated based on GC peak areas without any correction factors.

2.5. Clinical trial

2.5.1. Design, location and duration of the trial

This trial was randomized, placebo-controlled and triple-blind, conducted in a residential addiction treatment center named Izad Mehr Setayesh (Karaj city, Iran) between February 2020 and June 2021.

2.5.2. Ethics and trial registration

The Ethics Committee of Iran University of Medical Sciences approved the study protocol (code of ethical approval: IR.IUMS.REC.1398.1128; date: 8 February 2020). Also, the study was registered in the Iranian Registry for Clinical Trials (code: IRCT20090804002288N16).

2.5.3. Sample size

Given the score of COWS (clinical opiate withdrawal scale) as the primary outcome, study power of 80%, effect size of 0.6 between experimental and control groups, type 1 error of 0.5, and attrition rate of 10%, the sample size of each of the experimental and control groups was calculated at 50 patients. The effect size was calculated empirically. Calculation of sample size was prospective.

2.5.4. Patients

Urine was analyzed on arrival of the patients at the treatment center. Urine was analyzed for detection of 6-acetylmorphine (a metabolite of heroin) by GC-MS [11]. Also, urine was analyzed for detection of amphetamine, buprenorphine, benzodiazepine, cocaine, methadone, methamphetamine, morphine, tetrahydrocannabinol, tramadol and tricyclic antidepressants using the kits of the Farafan Diagnostics Company (Tehran, Iran).

The inclusion criteria were as follows. Male volunteer patients aged 18–70 years; addiction to heroin according to the DSM-5 criteria for at least 1 year; detection of 6-acetylmorphine in the urine; residence in the addiction treatment center; using a fixed dose of heroin for at least 1 month before the study; and lack of heroin use for at least 5 h before arriving at the treatment center.

The excluded patients were those abusing substances other than heroin (except for cigarette), and patients with psychiatric, heart, kidney, liver and organic brain diseases and mental retardation.

The attrition criteria were occurrence of any intolerable side effect attributable to the extract or placebo during the study, and personal desire of patients to withdraw from the study.

After taking the informed written consent forms, demographic, disease-related and patient-related data were recorded, and blood samples were taken for biochemical analyses. In addition, COWS questionnaire was completed for each patient, and the patients' satisfaction with the extract and placebo was rated.

2.5.5. Randomization

The patients were allocated to experimental and control groups through the block randomization method with an allocation ratio of 1:1. This allocation ratio increases the power of study and is usually used. For block randomization, all possible forms of blocks for drug and placebo with block sizes of 4 were created and then selected randomly using the table of randomized numbers. Finally, a randomization list consisting of

the patients' numbers and their allocated treatments was created. For concealment of allocation, the number of each patient was written on the external part of an envelope, and the treatment of each patient was written on a paper inside the envelope.

2.5.6. Blinding

Similar capsules with the same amount of the extract and placebo, and similar containers, and packages were used in both groups. The patients, physician who assessed the signs and symptoms of patients, and data analyzer did not know anything about the allocated treatments. The randomization list was decoded at the end of the study.

2.5.7. Interventions

The patients took 3 extract or placebo capsules once per day after meal for 8 days under direct supervision. The dose regimen was according to a previous study [10]. Given that the average duration of the acute heroin withdrawal syndrome is 8 days [5], the treatment period was 8 days. Also, the times of assessment of the patients (days 1, 3, and 8) were according to the previous study [10]. In the previous study [10], we found empirically that the average duration of acute withdrawal syndrome of short-acting opioids like opium and heroin was 8 days and the severity of the withdrawal syndrome reached a maximum on the day 3, declined thereafter, and reached a minimum on the day 8. The patients did not go out of the treatment center or receive any adjunctive therapy or drug except the extract or placebo capsules during the trial. Notably, the patients are not treated with any therapy in the residential addiction treatment centers of Iran. Also, there was no follow-up after this study.

2.5.8. Outcomes

COWS is a questionnaire that scores 11 common signs and symptoms of acute opioid (like heroin) withdrawal, i.e. gooseflesh, tearing or runny nose, bone and joint pain, pinpoint pupils, irritability or anxiety, tremor, yawning, restlessness, perspiration, tachycardia and gastrointestinal discomfort. Each score indicates the symptom severity and total score of COWS shows the severity of acute opioid withdrawal syndrome as "mild" (scores 5–12), "moderate" (scores 13–24), "moderately severe" (scores 25–36) and " severe " (scores >36) [12]. Clinical use of COWS is common and COWS validity as a tool for measuring the severity of acute opioid withdrawal syndrome has been demonstrated [13]. COWS was assessed at the baseline and on the days 1, 3, and 8. The patients' satisfaction with the extract and placebo was evaluated by an 11-point visual analogue scale (VAS). At the baseline and on day 8, CBC (complete blood count); blood urea nitrogen (BUN); and the blood levels of creatinin (Cr); prothrombin time (PT); total, direct and indirect bilirubins (TB, DB and IB); alkaline phosphatase (ALP); alanine aminotransferase (ALT); and aspartate aminotransferase (AST) were determined by an autoanalyzer (Hitachi 917, Japan). The patients were asked to report any abnormal health issue and side effect to the physician of the treatment center. The physician was a psychiatrist who completed the COWS questionnaire, evaluated the patients' satisfaction, and asked open-ended questions about side effects. The total score of COWS was the primary outcome measure and VAS, CBC, BUN, Cr, PT, TB, DB, IB, ALP, ALT, AST and side effects were secondary outcome measures.

2.5.9. Statistical analyses

Data were analyzed using the version 17 of the SPSS software. Mean ± standard deviation or median (inter-quartile range) was used for description of the quantitative parameters. Frequency was used for description of the qualitative parameters. The qualitative parameters of the groups were compared by the Chi-squared test. The normality of distribution of quantitative parameters was evaluated by the Kolmogorov-Smirnov test. The quantitative parameters of the two groups were compared by the Student's t or Mann-Whitney *U* test. In addition, Friedman test was used to analyze the changes of COWS scores during the study. The standardized mean difference between the decrease of COWS scores of the experimental and control groups was calculated for determination of the effect size. *P*-values <0.05 were statistically significant. The method of data analysis was intention-to-treat.

3. Results

3.1. Quantification of the alkaloids

Sophocarpine (35.92%), matrine (28.12%) and sophoramine (8.57%) were the major alkaloids of the extract.

3.2. Clinical trial

The eligibility of 524 patients was assessed. One hundred patients were included in the study and randomly allocated to the experimental and control groups. Fifty patients in each group completed the trial. Fig. 1 shows the CONSORT flow diagram. The results of Kolmogorov-Smirnov test and patients' demographics are set forth in Tables 1 and 2, respectively. The COWS score decreased in both groups after 8 days, but the decrease was significantly more in the experimental group compared to the control group ($p < 0.001$) (Table 3, Fig. 2); the effect size of the decrease as compared between the experimental and control groups was 2.64. The COWS scores of the experimental and control groups were significantly different on the days 3 and 8 ($p < 0.001$ for both) (Table 3, Fig. 2). The withdrawal severity decreased in the experimental group sooner than the control group (Table 3, Fig. 2). The VAS score of the experimental group was significantly higher than that of the control group (7.18 ± 2.13 vs 0.62 ± 1.79, $p < 0.001$). There was no significant difference between the values of blood parameters of the experimental and control groups. Residual withdrawal syndrome was observed in the patients, but no side effect was detected.

4. Discussion

The aim of this study was examination of the efficacy and safety of *S. alopecuroides* for the treatment of acute heroin withdrawal in the abstinent heroin addicts residing in a treatment center. The results show that sophocarpine, matrine and sophoramine were the main alkaloids of the extract. The severity of withdrawal syndrome surged on the day 3 in the control group, but it declined on the days 3 and 8 in the experimental group. Also, the severity of withdrawal syndrome reduced significantly in the experimental versus the control group on the days 3 and 8. Despite the blood tests and inquiry about side effects, no side effect was noted. More satisfaction of the patients with the extract versus placebo is also notable. Body mass index was added to the demographics only for giving an impression of the heights and weights of the patients. The results seem to be generalizable to the population with the characteristics mentioned in the inclusion and exclusion criteria of this study.

The results are consistent with the study indicating blockade of the morphine withdrawal syndrome by the extract of *S. alopecuroides* in mice [9]. Matrine, cytisine, sophoridine, n-methyl cytisine, sophocarpine and sophoramine were the major alkaloids of the extract in the aforementioned study [9]. The present study indicates that in spite of the fact that cytisine, sophoridine and n-methyl cytisine were not the major alkaloids in the extract of this study, the extract mitigated acute heroin withdrawal syndrome. The alkaloid composition, withdrawal suppressing effects, and safety of the extract used in this study are similar to those of the extract used in the trial evaluating the effects of the extract on the acute opium withdrawal [10]. Importantly, the baseline COWS scores in this study were in the moderate to severe range, while those of the just-mentioned trial [10] were in the mild range. Notably, the severity of acute heroin withdrawal syndrome is typically moderate to severe, whereas the severity of acute opium withdrawal syndrome is usually mild [6].

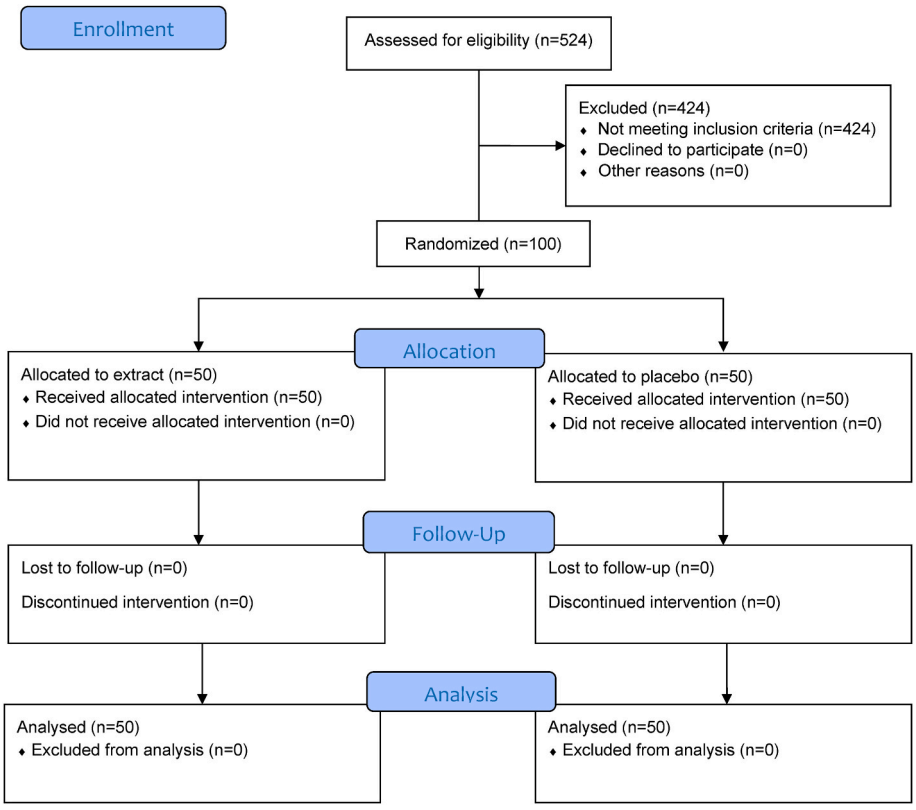

Fig. 1. CONSORT flow diagram.

Table 1
Results of the Kolmogorov-Smirnov test.

Variable	Statistic	Degree of freedom	*P*-value
COWS1	0.136	100	0.000
COWS3	0.237	100	0.000
COWS8	0.190	100	0.000
VAS	0.295	100	0.000
Age (years)	0.102	100	0.012
Duration of addiction (years)	0.090	100	0.045
Body mass index (Kg/m^2)	0.101	100	0.014

COWS1, COWS3 and COWS8: The scores of clinical opiate withdrawal scale on the days 1, 3, and 8. VAS: the score of visual analog scale for the patients' satisfaction with the treatments.

Table 2
Demographics of the patients. All patients were male.

	Experimental group (Mean ± SD)	Control group (Mean ± SD)	*P*-value
Age (years)	51.412 ± 13.273	46.522 ± 15.991	0.120[t]
BMI (Kg/m^2)	29.983 ± 3.735	28.585 ± 4.424	0.091[t]
Duration of the addiction (years)	9.561 ± 6.072	10.651 ± 5.163	0.259[m]

BMI: body mass index, m: Mann-Whitney *U* test, SD: standard deviation, t: Student's t-test.

Table 3
The score of clinical opiate withdrawal scale in each group during the study.

	Baseline (Mean ± SD)	Day 3 (Mean ± SD)	Day 8 (Mean ± SD)	*P*-value for comparison within groups[f]	Percent change (day 8 vs day 1) (Mean ± SD)
Experimental group	30.476 ± 3.745	10.103 ± 3.276	5.925 ± 1.248	<0.001	80.546 ± 3.431
Control group	29.780 ± 3.361	38.957 ± 3.724	15.920 ± 2.853	<0.001	56.808 ± 7.215
P-value for comparison between groups[m]	0.344	<0.001	<0.001		<0.001

f: Friedman test, m: Mann-Whitney *U* test, SD: standard deviation.

According to pharmacological studies discussed below, the alkaloids of the extract including sophocarpine, matrine and sophoramine may play a role in the effects observed in this trial. The alkaloid fraction and matrine were responsible for the blockade of morphine withdrawal by the extract in mice [9]. Also, the extract, its alkaloid fraction and matrine blocked naloxone-induced diarrhea in morphine-dependent mice [9]. A study suggested that sophocarpine had peripheral and central analgesic properties in the hot plate and acetic acid-induced writhing tests in mice [14]. However, according to another study, (−)-sophocarpine and (−)-sophoramine did not show analgesic action in the acetic acid-induced writhing and tail flick tests in mice [15]. Various studies have reported analgesic effect of matrine. In a study, (+)-matrine exerted analgesic effect via μ and κ opioid receptors in the acetic acid-induced writhing, tail flick and hot plate tests in mice [16,17]. In another study, (+)-matrine had no in vitro binding for the μ, κ and δ opioid receptors and exerted anti-nociceptive effect in the writhing, tail-pressure and hot plate models in mice through several mechanism(s) such as cholinergic stimulation in the central nervous system rather than direct action on the opioid receptors [18]. It is noteworthy that agonists of nicotinic receptor may reduce severity of opioid withdrawal syndrome [19]. Thus, theoretically, matrine might attenuate opioid withdrawal via stimulation of the nicotinic receptors. Further, matrine alleviated the neuropathic pain due to chronic nerve constriction in mice [20]. Matrine decreased the pain produced by mechanical stimulus and

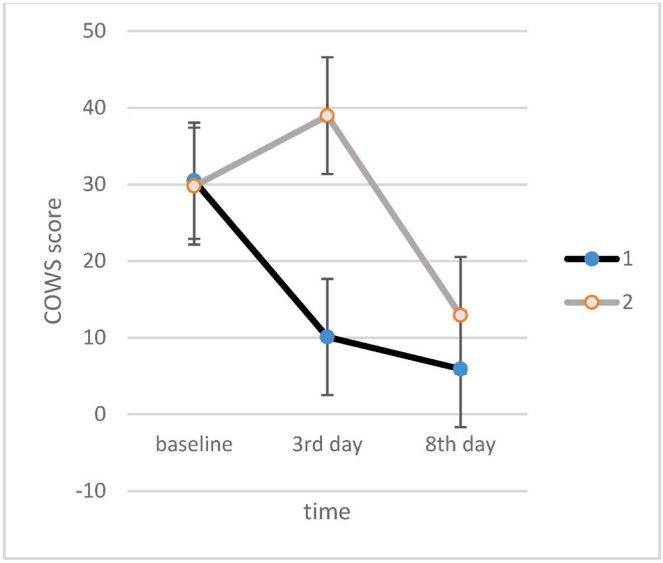

Fig. 2. Changes of the COWS (clinical opiate withdrawal scale) scores of the experimental (1) and control (2) groups during the study. The points represent mean ± standard deviation.

cold in a mouse model of vincristine-induced neuropathic pain [21]. Synergism of the analgesic activity of matrine and paracetamol has been reported in the mouse acetic acid-induced writhing test [22]. Also, it is noteworthy that several studies have suggested that matrine may have anti-depressant and anti-anxiety effects. Matrine exhibited anti-depressant effect in the forced swimming and tail suspension tests in mice via stimulation of the hippocampus phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin signaling [23]. Matrine had anxiolytic and anti-depressant activity in the plus-maze, light-dark, open-field, forced swimming and tail suspension models following an acute burn injury in mice through modulation of the c-Jun N-terminal kinase and brain-derived neurotrophic factor/vascular endothelial growth factor pathways [24]. Matrine demonstrated anxiolytic and anti-depressant effects in the open field, plus maze, light-dark, forced swimming and tail suspension models in mice with carbon tetrachloride-induced liver injury through anti-inflammatory, anti--oxidative, nerve-growing and anti-apoptotic actions [25]. Moreover, the extract had analgesic effect in the rat formalin model of pain which was not antagonized by naloxone, and did not produce Straub reaction in mice, indicating the extract is a non-opioid and may not produce the opioid side effects (physical dependence, constipation and respiratory depression) [26]. Of note, despite the millennia-long use of *S. alopecuroides* in the Central and Western Asia, the plant is not considered as addictive [9,27]. As regards the extract mechanism of action, standard drugs for the treatment of opioid withdrawal including acute heroin withdrawal act through μ receptor agonism (methadone and buprenorphine) or α_2 adrenoceptor agonism (lofexidine) [28]. Mechanism of the opioid withdrawal reducing effect of the extract is unclear. It can be concluded from the above data that non-opioid mechanisms like α_2 adrenoceptor agonism might mediate the opioid withdrawal suppressing effect of the extract. It should also be noted that diarrhea, pain, anxiety and dysphoria are among the signs and symptoms of opioid withdrawal syndrome [7, 1213], and stimulation of nicotinic receptors alleviates the syndrome [19]. Therefore, the antidiarrheal effects of the extract and matrine [9]; analgesic effects of sophocarpine [14], matrine [16–18,20–22] and extract [26]; antianxiety and antidepressant effects of matrine [23–25); and nicotinic receptor stimulating effect of matrine [18] could be involved in the acute heroin withdrawal reducing effect of the extract. One of the limitations of this study is lack of comparison of the extract effects with the standard pharmacotherapies of opioid withdrawal syndrome. Further, some of the standard drugs used in the treatment of opioid withdrawal syndrome may produce cardiac arrhythmias or hypotension [7,29]. Thus, other limitations of this study are lack of examination of the extract effects on the patients' electrocardiogram and vital signs like blood pressure. To sum up, the extract alone seems to safely mitigate the moderate to severe acute heroin withdrawal.

5. Conclusion

Oral intake of three 400 mg extract capsules once daily after meal for 8 days may safely alleviate moderate to severe acute heroin withdrawal. Also, the patients seem to be more satisfied with the extract than placebo. The extract main alkaloids were sophocarpine, matrine and sophoramine. The compounds and mechanisms involved in the opioid withdrawal suppressing effect of the extract, and efficacy and safety of the extract for maintenance treatment of opioid addiction should be ascertained.

CRediT authorship contribution statement

Fataneh Hashem-Dabaghian: Formal analysis, Funding acquisition, Resources, Methodology, Writing – review & editing. **Saeed Kianbakht:** Conceptualization, Methodology, Project administration, Investigation, Writing – review & editing.

Declaration of competing interest

None.

Acknowledgement

This study was funded by the Institute for Studies in Medical History, Persian and Complementary Medicine (Iran University of Medical Sciences, Tehran, Iran).

References

[1] J. Mielau, M. Vogel, S. Gutwinski, New approaches in drug dependence: opioids, Curr. Addict. Rep. 8 (2021) 298–305, https://doi.org/10.1007/s40429-021-00373-9.
[2] C.C. Presley, C.W. Lindsley, DARK classics in chemical neuroscience: opium, a historical perspective, ACS Chem. Neurosci. 9 (2018) 2503–2518, https://doi.org/10.1021/acschemneuro.8b00459.
[3] M.A. Emery, S. Eitan, Members of the same pharmacological family are not alike: different opioids, different consequences, hope for the opioid crisis? Prog. Neuro-Psychopharmacol. Biol. Psychiatry 92 (2019) 428–449, https://doi.org/10.1016/j.pnpbp.2019.02.010.
[4] J. Mella-Raipán, J. Romero-Parra, G. Recabarren-Gajardo, DARK classics in chemical neuroscience: heroin and desomorphine, ASC Chem. Neurosci. (2020), https://doi.org/10.1021/acschemneuro.0c00262.
[5] M. Herscher, M. Fine, R. Navalurkar, L. Hirt, L. Wang, Diagnosis and management of opioid use disorder in hospitalized patients, Med. Clin. N. Am. 104 (2021) 695–708, https://doi.org/10.1016/j.mcna.2020.03.003.
[6] A. Rahimi-Movaghar, J. Gholami, L. Amato, L. Hoseinie, R. Yousefi-Nouraie, M. Amin-Esmaeili, Pharmacological therapies for management of opium withdrawal, Cochrane Database Syst. Rev. 6 (2018), CD007522, https://doi.org/10.1002/14651858.CD007522.pub2.
[7] A.B. Srivastava, J.J. Mariani, F.R. Levin, New directions in the treatment of opioid withdrawal, Lancet 395 (2020) 1938–1948, https://doi.org/10.1016/S0140-6736(20)30852-7.
[8] C. Kruszecki, C.R. Cameron, A.L. Hume, K.E. Ward, A systematic review of integrative medicine for opioid withdrawal, J. Subst. Abuse Treat. 125 (2021), 108279, https://doi.org/10.1016/j.jsat.2021.108279.
[9] S. Kianbakht, F. Hashem Dabaghian, *Sophora alopecuroides* L. Var. *alopecuroides* alleviates morphine withdrawal syndrome in mice: involvement of alkaloid fraction and matrine, Iran, J. Basic Med. Sci. 19 (2016) 1090–1095. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5110657/.
[10] S. Kianbakht, R. Hajiaghaee, S. Akhondzadeh, Efficacy and safety of *Sophora alopecuroides* Var. *alopecuroides* seed extract for opioid detoxification: a randomized, double-blind, and placebo-controlled clinical trial, Phytother Res. 34 (2020) 1108–1113, https://doi.org/10.1002/ptr.6578.
[11] M.L. Smith, E.T. Shimomura, J. Summers, B.D. Paul, A.J. Jenkins, W.D. Darwin, et al., Urinary excretion profiles for total morphine, free morphine, and 6-acetylmorphine following smoked and intravenous heroin, J. Anal. Toxicol. 25 (2001) 504–514, https://doi.org/10.1093/jat/25.7.504.

[12] D.R. Wesson, W. Ling, The clinical opiate withdrawal scale (COWS), J. Psychoact. Drugs 35 (2003) 253–259, https://doi.org/10.1080/02791072.2003.10400007.
[13] D.A. Tompkins, G.E. Bigelow, J.A. Harrison, R.E. Johnson, P.J. Fudala, E.C. Strain, Concurrent validation of the clinical opiate withdrawal scale (COWS) and single-item indices against the clinical Institute narcotic assessment (CINA) opioid withdrawal instrument, Drug Alcohol Depend. 105 (2009) 154–159, https://doi.org/10.1016/j.drugalcdep.2009.07.001.
[14] Y. Gao, G. Li, C. Li, X. Zhu, M. Li, C. Fu, et al., Antinociceptive and anti-inflammatory activity of sophocarpine, J. Ethnopharmacol. 125 (2009) 324–329, https://doi.org/10.1016/j.jep.2009.06.036.
[15] P. Xiao, H. Kubo, M. Ohsawa, K. Higashiyama, H. Nagase, Y.N. Yan, et al., Kappa-opioid receptor-mediated antinociceptive effects of stereoisomers and derivatives of (+)-matrine in mice, Planta Med. 65 (1999) 230–233, https://doi.org/10.1055/s-1999-14080.
[16] J. Kamei, P. Xiao, M. Ohsawa, H. Kubo, K. Higashiyama, H. Takahashi, et al., Antinociceptive effects of (+)-matrine in mice, Eur. J. Pharmacol. 337 (1997) 223–226, https://doi.org/10.1016/s0014-2999(97)01273-9.
[17] K. Higashiyama, Y. Takeuchi, T. Yamauchi, S. Imai, J. Kamei, Y. Yajima, et al., Implication of the descending dynorphinergic neuron projecting to the spinal cord in the (+)-matrine- and (+)-allomatrine-induced antinociceptive effects, Biol. Pharm. Bull. 28 (2005) 845–848, https://doi.org/10.1248/bpb.28.845.
[18] L.L. Yin, Z.Z. Zhu, The involvement of central cholinergic system in (+)-matrine-induced antinociception in mice, Pharmacol., Biochem. Behav. 80 (2005) 419–425, https://doi.org/10.1016/j.pbb.2004.12.008.
[19] L. Custodio, S. Malone, M.T. Bardo, J.R. Turner, Nicotine and opioid co-dependence: findings from bench research to clinical trials, Neurosci. Biobehav. Rev. 134 (2022), 104507, https://doi.org/10.1016/j.neubiorev.2021.12.030.
[20] W. Haiyan, L. Yuxiang, D. Linglu, X. Tingting, H. Yinju, L. Hongyan, et al., Antinociceptive effects of matrine on neuropathic pain induced by chronic constriction injury, Pharm. Biol. 51 (2013) 844–850, https://doi.org/10.3109/13880209.2013.767363.
[21] D. Linglu, L. Yuxiang, X. Yaqiong, X. Tingting, H. Yinju, L. Hongyan, et al., Antinociceptive effect of matrine on vincristine-induced neuropathic pain model in mice, Neurol. Sci. 35 (2014) 815–821, https://doi.org/10.1007/s10072-013-1603-6.
[22] G. Dai, B. Li, Y. Xu, Z. Li, F. Mo, C. Wei, Synergistic interaction between matrine and paracetamol in the acetic acid writing test in mice, Eur. J. Pharmacol. 895 (2021), 173869, https://doi.org/10.1016/j.ejphar.2021.173869.
[23] Z. Wu, Z. You, P. Chen, C. Chen, F. Chen, J. Shen, et al., Matrine exerts antidepressant-like effects on mice: role of the hippocampal PI3K/AKt/mTORsignaling, Int. Neuropsychopharmacol. 21 (2018) 764–776, https://doi.org/10.1093/ijnp/pyy028.
[24] A. Khan, B. Shal, M. Naveed, B. Nasir, N. Irshad, H. Ali, et al., Matrine alleviates neurobehavioral alterations via modulation of JNK-mediated caspase-3 and BDNF/VEGF signaling in a mouse model of burn injury, Psychopharmacology (Berl) 237 (2020) 2327–2343, https://doi.org/10.1007/s00213-020-05537-5.
[25] A. Khan, B. Shal, M. Naveed, F.A. Shah, A. Atiq, N.U. Khan, et al., Matrine ameliorates anxiety and depression-like behavior by targeting hyperammonemia-induced neuroinflammation and oxidative stress in CCl4 model of liver injury, Neurotoxicology (Little Rock) 72 (2019) 38–50, https://doi.org/10.1016/j.neuro.2019.02.002.
[26] S. Kianbakht, R. Hajiaghaee R, Effects of *Sophora alopecuroides* L., *Zingiber officinale* Rosc. And *Melissa officinalis* L. in formalin and Straub tail tests, J. Medicinal Plants 13 (2014) 33–40, file:///C:/Users/kianbakht.IMPNET/Downloads/jmpir-v13n51p33-en-1.pdf.
[27] R. Wang, X. Deng, Q. Gao, X. Wu, L. Han, X. Gao, et al., *Sophora alopecuroides* L.: an ethnopharmacological, phytochemical, and pharmacological review, J. Ethnopharmacol. 248 (2020), 112172, https://doi.org/10.1016/j.jep.2019.112172.
[28] A.B. Srivastava, J.J. Mariani, F.R. Levin, New directions in the treatment of opioid withdrawal, Lancet 395 (2020) 1938–1948, https://doi.org/10.1016/S0140-6736(20)30852-7.
[29] M.A. Raji, S. Priyadarshni, X. Yu, B. Digbeu, Y.F. Kuo, Association of medication-assisted therapy with new onset of cardiac arrhythmia in patients diagnosed with opioid use disorders, Am. J. Med. 135 (2022) 864–870, https://doi.org/10.1016/j.amjmed.2022.01.032.