Avicenna Journal of Phytomedicine (AJP)

Original Research Article

The effect of Azaraghi herbal compound on craving, sexual function, mental health, and sleep quality in opioid-dependent patients under methadone maintenance therapy: a clinical trial

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Article history:
Received: Aug 26, 2025
Received in revised form: Oct 29, 2025
Accepted: Nov 02, 2025
AJP, Vol. 16, No. 6, Nov-Dec 2026, 1093-1104.
https://dx.doi.org/10.22038/ajp.2026.27576

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Keywords:
Opioid use disorder
Herbal medicine
Azaraghi
Mental disorder

Abstract

Objective: Substance use disorders are chronic disorders that cause an imbalance of neurotransmitters. Conventional treatments often have limited efficacy and potential adverse effects, highlighting the need for adjunctive therapies. Herbal formulations such as Azaraghi Majoon (AM), rich in antioxidant and anti-inflammatory compounds, may offer therapeutic benefits. To evaluate the efficacy and safety of AM in reducing drug craving and improving psychological status, sexual function, and sleep quality in individuals with opioid dependence.

Materials and Methods: In this randomized, double-blind, placebo-controlled trial, 81 opioid-dependent patients on methadone maintenance therapy were randomly assigned to two groups: AM (n=40) or placebo (n=41). The herbal formulation was administered orally at 1–2 teaspoons/day, titrated to 4 teaspoons within one week, for four weeks. Methadone was continued at baseline doses, with up to 50% reduction allowed under supervision in improved patients. Primary outcomes were drug craving, depression, anxiety, and stress; secondary outcomes were sexual function and sleep quality. All outcomes were assessed at baseline, and week 2 and 4.

Results: AM significantly reduced drug craving compared to placebo ($p<0.01$), but improved depression, anxiety, stress, sexual function, and sleep quality (all $p<0.01$). No serious adverse effects or worsening of withdrawal symptoms were observed.

Conclusion: AM is a promising adjunctive therapy for opioid dependence, reducing craving, enhancing mood and sleep, improving sexual function, and demonstrating a favorable safety profile.

Please cite this paper as:
Ghaderi A, Razzaghi- Firozjaei F, Zahiry- Pour A.S, Memarzadeh M.R, Mohammad-Taghizadeh- Kashani L, Sadeghi A, Bekhradi R, Akbari H. The effect of Azaraghi herbal compound on craving, sexual function, mental health, and sleep quality in opioid-dependent patients under methadone maintenance therapy: a clinical trial. Avicenna J Phytomed, 2026; 16(6): 1093-1104.

Introduction

Drug addiction is recognized as a major social issue worldwide, leading to significant disability and impairing individual functioning (Sadock and Sadock 2010). In the United States, about 40% of the population has used an illegal substance at least once (Gelenberg et al. 2010; Sadock and Sadock 2010). In Iran, substance use is increasing; a 2016 national survey reported a lifetime prevalence of 3.02% and a 12-month dependency rate of 1.56%. The likelihood of using illegal substances or opioids more than five times was 12 and 10 times higher in men (6.4% and 2.8%) than in women (0.54% and 0.29%) (Amin-Esmaeili et al. 2016). Addiction has serious consequences for health, family life, economic security, social stability, and cultural development. Official estimates suggest that Iran has around 200,000 habitual and 800,000 recreational drug users (Bagheri et al. 2024; Chavan et al. 2007; Panahi et al. 2012; Parham et al. 2020; Sharif et al. 2024; Tahvilian et al. 2024).

Opium is the most commonly abused substance in Iran (82%), followed by opium ashes, methadone, heroin, and morphine in varying proportions (Amin-Esmaeili et al. 2016; Eskandarieh et al. 2014). Methadone, due to its affordability and effectiveness in controlling withdrawal symptoms and cravings, is widely applied for detoxification and maintenance therapy, making it a practical treatment option in Iran (Khodabandeh et al. 2008). Since the establishment of outpatient substance use treatment clinics in Iran around 2003–2004, the country has reached approximately 7,000 clinics, currently delivering opioid substitution therapy—mostly methadone maintenance—to nearly 700,000 individuals (Radfar et al. 2023).

A major challenge in methadone maintenance therapy is ensuring long-term adherence and preventing relapse, which occurs in 20–90% of treated individuals (Friedmann et al. 1998; Wallace 2012). Craving is a key predictor of treatment failure (Vafaie and Kober 2022). Methadone is also associated with multiple side effects including dizziness, fatigue, sleep disturbances, depression, anxiety, sexual dysfunction, gastrointestinal issues, and respiratory problems (Gholami et al. 2015). Psychological complications such as anxiety, depression, and insomnia are common among patients on methadone maintenance therapy (Callaly et al. 2001; Stein et al. 2004).

Some herbal medicines can alleviate addiction symptoms by modulating GABAergic and dopaminergic pathways, offering sedative and mood-stabilizing effects with high physiological compatibility and low side-effect risk (Karami et al. 2019). In traditional Persian medicine, one of the most well-known and widely used formulations for managing addiction-related symptoms is the Azaraghi Majoon (AM). This polyherbal mixture contains medicinal plants such as *Strychnos nux-vomica*, *Echium amoenum*, *Zingiber zerumbet*, *Astragalus gossypinus*, *Cocos nucifera*, *Lavandula angustifolia*, *Pinus gerardiana*, *Polygonatum orientale*, *Elettaria cardamomum*, *Santalum album*, *Aquilaria agallocha*, *Eugenia caryophyllata*, *Terminalia chebula*, and *Phyllanthus emblica* (Tavakoli et al. 2024). These herbs have traditionally been recognized for their neurostimulant, analgesic, and tonic properties, and their combination may help reduce psychological dependence on opioids while alleviating withdrawal symptoms. Given the complex nature of addiction, integrating traditional medicine as an adjunct therapy could mitigate treatment complications, lower healthcare costs, and minimize the side effects associated with conventional medications.

This study therefore aims to evaluate the effects of this herbal formulation in individuals with opioid dependence.

Materials and Methods

Study design

This randomized, double-blind, placebo-controlled clinical trial was conducted on opioid-dependent patients receiving methadone maintenance therapy (MMT) at a public addiction treatment center in Kashan, Iran, from February to September 2024. Eligible participants were recruited through convenience sampling.

Sample size

Based on prior studies reporting higher treatment success with homeopathy containing *Strychnos nux-vomica* (61.7% vs. 33% in controls) (Butehorn et al. 2015), and assuming a 95% confidence level and 90% power, the minimum required sample size was calculated as 47 participants per group.

Procedure

The study protocol was approved by the Ethics Committee of Kashan University of Medical Sciences. Patients receiving regular MMT were screened against inclusion and exclusion criteria, and informed about the study, and they provided written consent. After a one-week observation period to confirm adherence, participants were randomized by block allocation into two groups: the intervention group receiving the herbal formulation AM (Rahayesh®) and the placebo group. Both products were manufactured and identically packaged by Barij Essence Pharmaceutical Company.

The herbal formulation was administered orally at1–2 teaspoons per day , titrated up to 4 teaspoons within one week. Methadone treatment was continued at the baseline dose; however, in patients showing clinical improvement (reduced craving, improved mood, or better sleep), the methadone dose could be reduced by up to 50% under medical supervision, with the date of dose reduction documented. Outcomes were assessed at baseline, week 2, and week 4.

Herbal intervention

AM (Rahayesh®) consists of 14 medicinal plants combined with honey: *Strychnos nux-vomica*, *Echium amoenum*, *Zingiber zerumbet*, *Astragalus gossypinus*, *Cocos nucifera*, *Lavandula angustifolia*, *Pinus gerardiana*, *Polygonatum orientale*, *Elettaria cardamomum*, *Santalum album*, *Aquilaria agallocha*, *Eugenia caryophyllata*, *Terminalia chebula*, and *Phyllanthus emblica*.

Preparation follows Persian medicine texts, including detoxification of *S. nux-vomica* seeds by soaking in milk for seven days before grinding (Kashani et al. 2016). Ingredients are milled, sieved, and blended with honey. The formulation is standardized to contain ≤0.4 mg strychnine and ≤0.2 mg brucine per gram of the final product.

Blinding and randomization

Placebo syrup was designed to mimic the color, taste, and viscosity of the active formulation. Both were packaged and labeled identically. Randomization codes were generated using the Clinical Trial Randomization Tool and kept by an independent statistician, ensuring concealment from participants, researchers, and clinicians.

Eligibility criteria

Inclusion criteria: diagnosis of opioid dependence (DSM-IV), age 18–65 years, methadone dose ≤50 mL/day of a 5 mg/mL methadone oral solution (≤250 mg/day), as specified by the clinic protocol, treatment duration >6 months, and no prior methadone dose reduction.

Exclusion criteria: positive urine test for morphine, methamphetamine, or cannabis; significant medical illness; psychiatric medication use; pregnancy or lactation; allergy to herbal ingredients; or recent use of antioxidants/anti-inflammatories.

Outcome measures

Drug craving: assessed using the 14-item Drug Desire Questionnaire (DDQ).

Withdrawal/relapse: monitored with urine morphine test.

Psychological state: measured using the depression anxiety stress scale-21 (DASS-21).

Sexual function: assessed with the international index of erectile function (IIEF).

Sleep quality: evaluated using the Pittsburgh sleep quality index (PSQI).

Statistical analysis

Quantitative data are expressed as mean±SD and qualitative variables as frequencies. Normality of data distribution was tested using the Shapiro–Wilk test. Between-group comparisons were performed with independent t-tests or Mann–Whitney U tests. Within-group analyses used paired t-tests or Wilcoxon signed-rank tests. Categorical variables were analyzed using the Chi-square or McNemar's test. Repeated-measures ANOVA was applied for longitudinal comparisons. A p-value <0.05 was considered statistically significant.

Ethical considerations

The study was approved by the Ethics Committee of Kashan University of Medical Sciences (IR.KAUMS.MEDNT.REC.1402.152) and registered in the Iranian Registry of Clinical Trials (IRCT20231014059714N1).

Results

A total of 90 participants were randomized. Of these, 81 completed the trial and were included in the final analysis (AM: n = 40; placebo: n = 41). During the treatment phase, 4 participants in the AM herbal group and 5 participants in the placebo group discontinued the study, mainly due to the unpleasant taste of the preparations and difficulty in adherence (Figure 1). No significant differences were observed between the groups regarding demographic characteristics, marital status, education level, place of residence, underlying illnesses, type or duration of addiction, prior abstinence attempts, or baseline measures of craving, depression, anxiety, stress, sexual function, or sleep quality (p>0.05) (Figure 1, Tables 1–2).

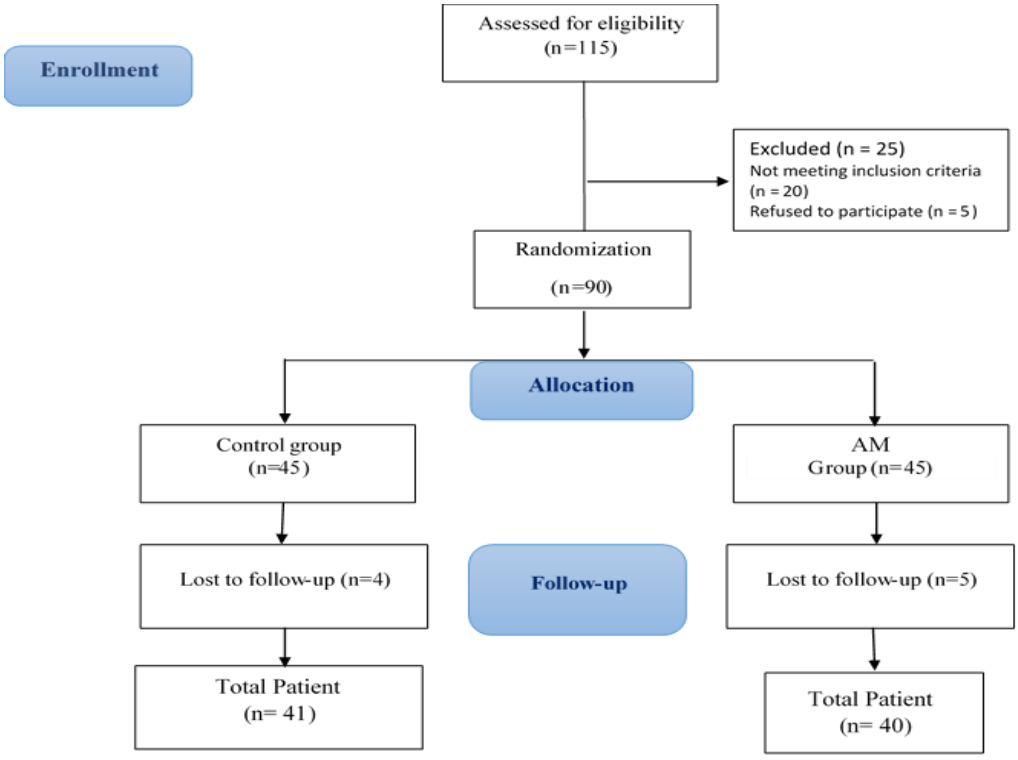

Figure 1. Consort flow diagram

Table 1. Distribution of demographic and clinical characteristics of patients in the two study groups

Variable		Treatment groups		p value
		AM	Placebo	
Sex (Male)		40 (100)	40 (97.6)	0.32
Marital status: Married		26 (65)	30 (73.2)	0.42
Education	Illiterate	2 (5.1)	1 (2.4)	0.43
	Primary school	15 (38.5)	18 (43.9)	
	Middle school	9 (23.1)	15 (36.6)	
	High school	13 (33.3)	7 (17.1)	
City of residence		39 (97.5)	40 (97.6)	0.98
Presence of underlying disease		10 (25)	12 (29.3)	0.66
Type of substance use disorder	Opium	39 (97.5)	38 (92.7)	0.32
	Heroin	18 (45)	16 (39)	0.586
	Methamphetamine	12 (30)	12(29.3)	0.943
	Crack	8 (25)	6 (14.6)	0.452
	Cannabis	15 (37.5)	12 (29.3)	0.562
Age (years) (mean ± SD)		51.8± 11.3	53.2± 10.08	0.539
Duration of substance use (years) (mean ± SD)		21.15±10.4	21.29±10.5	0.951
Number of quit attempts (mean ± SD)		1.60±2.24	1.98±2.4	0.469
Duration of abstinence (months) (mean ± SD)		8.45±22.05	6.59±24.89	0.722

Table 2. Mean and standard deviation of craving, DASS, IIEF, and sleep scores at baseline

Tools	Domains	Treatment Groups		p value
		Placebo	AM	
Craving		23.4±24.1	24.7±25.7	0.814
DASS	Depression	7.85±6.32	8.38±5.42	0.692
	Anxiety	6.32±5.70	6.98±5.65	0.604
	Stress	9.46±6.25	10.85±6.22	0.320
IIEF	Erectile function	10.27±8.63	12.65±8.67	0.308
	Pleasure function	8.8±3.41	8.81±2.9	0.993
	Libido	9.56±2.35	9.92±2.22	0.565
	Contact satisfaction	9.57±3.95	10.08±3.90	0.631
	Overall satisfaction	10.17±2.77	10.15±2.36	0.985
	Overall sexual function score	48.37±20.41	51.62±19.42	0.546
sleep	Subjective sleep quality	1.73±1.07	1.55±1.01	0.435
	Sleep latency	1.29±1.07	1.38±1.10	0.735
	Sleep duration	1.24±1.15	1.10±1.08	0.565
	Sleep efficiency	0.61±0.94	0.43±0.81	0.349
	Sleep disorders	1.02±0.61	1.20±0.51	0.167
	Use of sleeping pills	1.32±1.45	1.02±1.42	0.364
	Daily functioning disorders	1.17±1.22	0.75±0.98	0.92
	Pittsburgh total score	8.39±4.65	7.42±4.95	0.369

DASS: Depression Anxiety Stress Scales; IIEF:International Index of Erectile Function

After two weeks, craving scores decreased significantly in both groups (placebo: 23.3→20.9; and AM: 24.7→16.7; p<0.01), with a notably greater reduction in the AM group (mean difference 7.95 vs 2.41; p=0.024). Depression decreased significantly in both groups (p<0.02), while anxiety significantly declined only in the AM group (6.98→5.6; p=0.002). Stress scores decreased in both groups compared to baseline (p<0.01). Regarding sexual function, significant improvements were observed in the AM group in terms of intercourse satisfaction and total IIEF score (p<0.02), whereas no meaningful changes occurred in the placebo group. Sleepquality, measured by the PSQI, improved in both groups after two weeks (p<0.05), indicating early benefits of treatment on restorative sleep (Table 3).

By the fourth week, craving further decreased in both groups (placebo: 20.2; AM: 14.6; p<0.01), with AM participants demonstrating significantly larger reductions than placebo (10.10 vs 3.21; p=0.01). Depression, anxiety, and stress continued to decline, with significantly greater improvements in the AM group compared to placebo (p<0.05). In sexual function, only sexual desire improved in the placebo group (p=0.026), whereas AM participants experienced significant enhancements in intercourse satisfaction and erectile function (p<0.05). Sleep parameters showed improvements in both groups, with AM participants benefiting across all PSQI subscales and the total score, reflecting more comprehensive improvements in sleep quality (Tables 4–5).

Table 3. Mean and standard deviation of craving, DASS, sexual function, and sleep scores at baseline and week 2

study outcome		Treatment Groups					
		Placebo			AM		
		study onset	Two weeks later	p value	study onset	Two weeks later	p value
Craving		23.3±24.1	20.9±21.8	0.01	24.7±25.7	16.7±23.4	<0.001
DASS	Depression	7.9±6.3	6.4±5.7	0.015	8.4±5.4	6.4±5.4	<0.001
	Anxiety	6.32±5.7	5.8±5.5	0.449	6.98±5.6	5.6±4.8	0.002
	Stress	9.5±6.3	7.2±5.4	<0.001	10.9±6.2	7.6±5.3	<0.001
sexual function	Erectile function	10.3±8.6	10.1±8.6	0.815	12.7±8.7	13.4±9.1	0.152
	Pleasure function	8.8±3.4	8.8±3.4	1.000	8.8±2.9	8.9±2.9	0.161
	Libido	9.6±2.4	9.8±2.4	0.070	9.9±2.2	9.7±2.1	0.134
	Contact satisfaction	9.6±3.9	9.8±4.1	0.133	10.1±3.9	10.4±4.0	0.018
	Overall satisfaction	10.2±2.8	10.1±2.7	0.448	10.2±2.4	10.4±2.4	0.203
	Total	48.4±20.4	48.6±20.1	0.737	51.6±19.4	52.8±19.8	0.120
sleep quality	Subjective sleep quality	1.73±1.07	1.44±1.07	0.003	1.55±1.01	1.3±1.06	0.006
	Sleep latency	1.29±1.07	1.1±1.06	0.118	1.38± 1.10	1.15±0.97	0.011
	Sleep duration	1.24±1.15	1.20±1.20	0.48	1.10±1.08	0.80±1.04	0.003
	Sleep efficiency	0.61±0.94	0.39±0.80	0.018	0.43±0.81	0.28±0.59	0.11
	Sleep disorders	1.02±0.61	0.9±0.58	0.133	1.20±0.51	0.9±0.44	<0.001
	Use of sleeping pills	1.32±1.45	1.34±1.42	0.76	1.02±1.42	0.75±1.21	0.02
	Daily functioning disorders	1.17±1.22	1.10±1.13	0.18	0.75±0.98	043±0.74	<0.001
	Pittsburgh total score	8.39±4.65	6.31±3.69	<0.001	7.42±4.95	4.55±3.26	<0.001

Table 4. Mean and standard deviation of craving, DASS, sexual function, and sleep scores at baseline and week 4

study outcome		Treatment Groups					
		Placebo			AM		
		study onset	Four weeks later	p value	study onset	Four weeks later	p value
Craving		23.3±24.1	20.2±21.1	0.005	24.7±25.7	14.6±22.3	<0.001
DASS	Depression	7.9±6.3	5.7±5.5	0.002	8.4±5.4	4.9±3.8	<0.001
	Anxiety	6.3±5.7	5.2±5.3	0.042	6.98±5.6	4.18±4.2	<0.001
	Stress	9.5±6.3	6.5±5.6	<0.001	10.9±6.2	5.9±4.9	<0.001
sexual function	Erectile function	10.3±8.6	10.2±8.8	0.912	12.7±8.7	14.1±9.0	0.032
	Pleasure function	8.8±3.4	8.9±3.4	0.423	8.8±2.9	9.4±2.9	0.070
	Libido	9.6±2.4	9.9±2.4	0.026	9.9±2.2	9.9±2.1	0.857
	Contact satisfaction	9.6±3.9	9.9±4.1	0.110	10.1±3.9	10.9±4.3	0.003
	Overall satisfaction	1. 2±2.8	10.0±2.6	0.362	10.2±2.4	10.4±2.3	0.148
	Total	10.3±8.6	1. 1±8.6	0.815	12.7±8.7	13.4±9.1	0.152
sleep quality	Subjective sleep quality	1.73±1.073	1.22±1.10	<0.001	1.55±1.01	1.08±0.97	<0.001
	Sleep latency	1.29±1.07	1.07±0.93	0.04	1.38±1.10	0.98±0.86	<0.001
	Sleep duration	1.24±1.15	1.17±1.20	0.53	1.10±1.08	0.78±1	0.002
	Sleep efficiency	0.61±0.94	0.48±0.92	0.27	0.43±0.81	0.23±0.42	0.05
	Sleep disorders	1.02±0.612	0.90±0.583	0.096	1.2±0.51	0.73±0.5	<0.001
	Use of sleeping pills	1.32±1.45	1.34±1.38	0.81	1.02±1.42	0.55±0.95	0.002
	Daily functioning disorders	1.17±1.22	1.10±1.11	0.37	0.75±0.98	0.43±0.74	<0.001
	Pittsburgh total score	8.39±4.65	7.26±4.40	0.004	7.42±4.95	4.75±3.55	<0.001

Table 5. Mean and standard deviation of changes in craving, psychological, sexual, and sleep scores over 2 and 4 weeks

study outcome		Two-week treatment			Four-week treatment		
		Treatment Groups		p value	Treatment Groups		p value
		Placebo	AM		Placebo	AM	
Craving		2.41±5.75	7.95±13.95	0.024	3.21±7.01	10.10±14.72	0.010
DASS	Depression	1.46±3.67	2.02±2.81	0.44	2.19±4.22	4.1±3.81	0.036
	Anxiety	0.43±3.67	1.37±2.68	0.195	1.12±3.42	2.80±3.48	0.032
	Stress	2.26±3.22	3.25±3.30	0.180	2.92±3.68	4.87±4.71	0.041
sexual function	Erectile function	0.13±3.09	-0.73±2.52	0.262	0.07±3.26	-1.46±3.28	0.088
	Pleasure function	0±0.91	-0.15±0.54	0.455	-0.13±0.9	-0.54±1.44	0.224
	Libido	-0.23±0.67	0.19±0.63	0.019	-0.30±0.7	-0.04±1.07	0.280
	Contact satisfaction	-0.27±0.94	-0.38±0.69	0.602	-0.37±1.2	-0.77±1.17	0.214
	Overall satisfaction	0.10±0.71	0.19±0.74	0.141	0.17±.098	-0.27±0.91	0.094
	Total	-0.26±4.31	-1.19±3.77	0.40	-0.56±4.7	-3.1±6.1	0.088
sleep quality	Subjective sleep quality	0.29±0.60	0.25±0.54	0.738	0.51±0.7	0.47±0.6	0.800
	Sleep latency	0.19±0.78	0.22±0.53	0.841	0.21±0.7	0.37±0.7	0.319
	Sleep duration	0.04±0.44	0.30±0.60	0.038	0.07±0.75	0.32±0.61	0.104
	Sleep efficiency	0.21±0.57	0.15±0.57	0.588	0.14±0.85	0.20±0.64	0.751
	Sleep disorders	0.12±0.50	0.30±0.46	0.104	0.12±0.45	0.47±0.55	0.003
	Use of sleeping pills	-0.02±0.52	0.27±0.75	0.035	-0.02±0.65	0.47±0.90	0.006
	Daily functioning disorders	0.07±0.34	0.32±0.57	0.020	0.07±0.51	0.32±0.57	0.042
	Pittsburgh total score	2.07±0.73	2.87±2.6	0.106	1.12±2.4	2.67±2.8	0.008

At two weeks, significant between-group differences favored AM in craving reduction, sexual desire, sleep duration, use of sleep medications, and daytime dysfunction ($p<0.05$), while reductions in depression, anxiety, or stress were not significantly different ($p>0.05$). By four weeks, AM demonstrated significantly greater reductions in craving, depression, anxiety, and stress compared to placebo ($p<0.05$). No significant differences were found in IIEF domains, but AM participants showed significantly greater improvements in sleep disturbances, use of sleep medications, daytime dysfunction, and total PSQI score ($p<0.05$).

Adverse events were generally mild and self-limited. At two weeks, anxiety-related side effects were reported in 2.5% of AM participants, while none occurred in the placebo group. The most common side effect was rhinorrhea (AM: 12.5% and placebo: 7.3%). At four weeks, the most frequent adverse events in the AM group were rhinorrhea and nausea (12.5%), whereas in the placebo group, nausea was most common (12.2%). No statistically significant differences in the incidence of adverse effects were observed between groups ($p>0.05$).

Overall, these results indicate that AM supplementation produced earlier, more pronounced, and sustained improvements in craving, psychological symptoms, sexual function, and sleep quality compared to placebo, with a favorable safety profile, supporting its potential as an adjunctive treatment for opioid dependence.

Discussion

The present clinical study investigated the therapeutic effects of the AM polyherbal formulation in individuals with Substance Use Disorder (SUD), and the findings support its beneficial role in reducing drug craving, improving psychological well-being, enhancing sexual function, and promoting sleep quality. These outcomes are particularly important given the complex neurobiological mechanisms of addiction which include oxidative stress, neuroinflammation, mitochondrial dysfunction, dopaminergic dysregulation, and NMDA receptor alterations. Together, these processes contribute to drug-induced euphoria and vulnerability to relapse (Ma et al. 2015; Nechifor 2018; Su et al. 2021).

These clinical findings are consistent with preclinical evidence. Tavakoli et al. showed that AM reduced naloxone-induced withdrawal signs and conditioned place preference in opium-dependent rats, suggesting benefits for both physical and psychological aspects of opioid use disorder. Its main component, *S. nux-vomica*, provides strychnine and brucine with GABAergic and antioxidant activity, while *A. gossypinus* contributes triterpenoid saponins with immunomodulatory and neuroprotective effects (Tavakoli et al. 2024).

Given these multifaceted pathological processes, therapeutic strategies targeting multiple pathways may provide greater efficacy. Polyherbal formulations like AM, containing bioactive compounds with antioxidant, anti-inflammatory, neuroprotective, and neurotransmitter-modulating effects, represent a promising integrative approach for addiction treatment (Heidari et al. 2006; Zakaria et al. 2010).

The beneficial effects observed with the AM polyherbal formulation align with previous reports on multi-component herbal preparations from traditional Chinese and Indian medicine which have been shown to reduce opioid withdrawal symptoms while producing relatively mild adverse effects (Doosti et al. 2013).

A major finding was the significant reduction in drug craving among participants receiving AM compared with placebo. Craving scores declined significantly at both two and four weeks in the treatment group ($p<0.01$), whereas only modest changes were observed in the placebo group. These results are consistent

with preclinical work by Tavakoli et al. which showed that AM reduced craving and withdrawal in morphine-dependent animals. This anti-craving effect may be attributed to the synergistic actions of *E. amoenum* (borage) and *Ferula gummosa* (galbanum), whose antioxidant and anti-inflammatory properties mitigate oxidative stress in reward-related brain regions and suppress drug-seeking behavior (Tavakoli et al. 2024).

Additional ingredients such as *C. nucifera* (coconut) and *T. chebula* (black myrobalan) have also been implicated in the mitigation of addiction-related symptoms. Emerging evidence suggests that coconut oil may modulate oxidative biomarkers, improve hippocampal antioxidant status, and influence glutamatergic and GABAergic receptor activity—mechanisms that can counteract neurochemical imbalances induced by substance abuse (Edem et al. 2022; Mansouri et al. 2024). *Terminalia chebula*, with its documented anti-inflammatory and metabolic effects, may also contribute to the reduction of craving and mood dysregulation observed in individuals with SUD (Naik et al. 2004). Psychological assessments further revealed that participants in the AM group experienced significant improvements in anxiety, depression, and stress levels as early as the second week of treatment ($p<0.001$). In contrast, the placebo group showed improvement only in depression and stress domains. The anxiolytic and antidepressant effects observed may be attributed to key ingredients such as *L. angustifolia* (lavender) and *E. cardamomum* (cardamom), both of which have been shown in multiple studies to modulate central nervous system function, particularly through GABAergic and serotonergic pathways (Prusinowska and Smigielski 2014; Saeed et al. 2014; Yoshida et al. 2017). Lavender, in particular, has demonstrated the capacity to modulate limbic activity and promote neurochemical balance, while cardamom's stress-reducing and sedative properties contribute to enhanced mood stability (López et al. 2017; Shetty and Rani 2023). These neuropsychological benefits align with the broader literature on herbal therapeutics, which emphasizes the role of antioxidant-rich botanicals in supporting neurotransmitter homeostasis and neurogenesis—factors often disrupted in chronic substance users. *Echium amoenum* and *L. angustifolia* are believed to exert their neuropsychiatric benefits partly through the modulation of GABA and serotonin receptors, both of which are crucial to emotional regulation and impulse control (Azizi et al. 2018; Prusinowska and Smigielski 2014). The serotonergic activity of *E. amoenum*, a key component of the AM formulation, has been shown in previous studies (on conditions such as Premenstrual syndrome) to modulate mood and anxiety, which may help explain the observed improvements in psychological well-being and reduction of craving in opioid-dependent patients (Haghi et al. 2024).

Another noteworthy finding was the significant improvement in sexual function observed in the AM group ($p<0.01$), an aspect often impaired in individuals with opioid dependence due to hormonal disruption and vascular dysfunction. Compounds such as *S. aromaticum* (clove) and *P. emblica* (amla) have been shown to enhance reproductive function through increased testosterone levels, improved blood flow, and regulation of sexual hormones, which may account for the observed benefits (Kadiri et al. 2024; Moghimian et al. 2018). Clove, in particular, is recognized for its aphrodisiac properties and positive influence on male reproductive parameters, especially in contexts involving opioid-induced sexual dysfunction (Moghimian et al. 2018).

Finally, the improved sleep quality reported by participants in the AM group highlights the formulation sedative and anxiolytic potential. This effect is likely mediated by plants such as *L.angustifolia* and *S. album* (sandalwood), both of which

have been widely studied for their sleep-promoting effects. Clinical and experimental studies have demonstrated that inhalation or ingestion of lavender and sandalwood essential oils can improve sleep architecture, reduce latency, and enhance sleep efficiency, particularly in individuals experiencing anxiety-related insomnia (Samadi et al. 2021; Yang et al. 2023).

Taken together, the therapeutic efficacy of AM may stem from its multi-targeted pharmacological profile. Its bioactive constituents exert complementary effects on oxidative stress, neuroinflammation, neurotransmitter systems (including GABA, serotonin, and dopamine), and hormonal regulation, thereby addressing several core dysfunctions present in substance use disorders.

This study demonstrated that the Azaraghi herbal formulation significantly reduced craving, improved psychological well-being, enhanced sexual function, and improved sleep quality in patients with SUD compared with placebo. These therapeutic benefits are likely attributable to the synergistic antioxidant, anti-inflammatory, sedative, and neuromodulatory properties of its botanical components, and the formulation was generally well tolerated, showing a favorable safety profile. Importantly, the use of such a multi-component herbal strategy offers the advantage of synergistic efficacy with potentially fewer side effects than synthetic polypharmacy.

Nonetheless, the relatively small sample size, short follow-up duration, and absence of biochemical assessments limit the generalizability of the findings and the ability to confirm the underlying mechanisms. Future investigations with larger cohorts, extended follow-up periods, precise molecular evaluations, and mechanistic studies are warranted to validate these results, elucidate pharmacological pathways, explore optimal dosing strategies, and assess the potential integration of AM with conventional pharmacotherapies in addiction management. Given its broad spectrum of action and low risk of side effects, AM may serve as a promising adjunctive herbal remedy in the management of substance withdrawal and recovery.

Acknowledgment

The authors sincerely thank the administrative staff at Barij Essence Pharmaceutical Company for their valuable assistance in providing Azaraghi Majoon (Rahayesh®). Also, the study teams wish to express their gratitude to the Clinical Research Development Unit at Kashan Shahid Beheshti Hospital, Kashan University of Medical Sciences, Kashan, Iran.

Conflicts of interest

Dr. Leila Mohammad Taghizadeh Kashani and Dr. Mohammad Reza Memarzadeh work as employees of Barij Essence Pharmaceutical Company. However, they had no involvement in the process of data collection and analysis and writing the results section of the article, and were involved in the design, formulation, blinding and writing of the materials and methods section of the article. The other authors declare that they have no conflicts of interest or potential conflicts of interest in this study.

Funding

This study was financially supported by Barij Essence Pharmaceutical Company and was approved by kashan university of medical sciences (Grant No.: IR.KAUMS.402046).

Ethical considerations

The study was approved by the Ethics Committee of Kashan University of Medical Sciences (IR.KAUMS.MEDNT.REC.1402.152) and registered in the Iranian Registry of Clinical Trials (IRCT20231014059714N1).

Code of ethics

IRCT20231014059714N1)

Authors' contributions

Amir Ghaderi: Investigation, Data curation, Writing – Original draft.
Farkhondeh Razzaghi-Firozjaei: Investigation, Data curation, Formal analysis, Writing – review & editing.
Amineh Sadat Zahiri-Pour: Investigation, Data curation, Visualization, Writing – review & editing.
Mohammad Reza Memarzadeh: Conceptualization, Methodology, Resources, Writing – Original draft.
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Abbreviations

AM: Azaraghi Majoon
DASS-21: Depression Anxiety Stress Scales-21
DDQ: Drug Desire Questionnaire
IIEF: International Index of Erectile Function
MMT: Methadone Maintenance Therapy
PSQI: Pittsburgh Sleep Quality Index
SUD: Substance Use Disorder

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