Archives of Psychiatry and Psychotherapy, 2017; 3: 27–33

DOI: 10.12740/APP/74385

The role of alcoholic extract of *Zataria multiflora Boiss* in controlling opium withdrawal symptoms: a randomized, double-blind study

Mehdi Sayyah, Alireza Siahpoush. Fakher Rahim

Summary

Background: Opium addiction is a common and disabling disease. Despite patients' interest in herbal remedies, there is lack of valid evidence in the context of herbal treatment for opium withdrawal symptoms, which hinders treatment. Thyme leaves are used in traditional medicine to relieve pain and for seizure control.

Aims: To compare the effect of an alcoholic extract of *Zataria multiflora Boiss* [thyme extract] with methadone in controlling the symptoms of opium withdrawal.

Methodology: In a double-blind, randomized clinical trial, an alcoholic extract of thyme plus methadone were given to 40 patients and compared with a group receiving methadone with placebo. Withdrawal symptoms in days 0, 2, 7, 11 and 15 were evaluated with the Clinical Institute Narcotic Assessment (CINA) scale.

Results: Withdrawal symptoms were controlled in both study groups and were tolerated when reducing the methadone dose in the thyme group.

Conclusion: Alcoholic thyme extract can be used as an effective agent in controlling the symptoms of opium withdrawal and should be further investigated.

***Zataria multiflora Boiss*, alcoholic extract, drug addiction, methadone**

People in countries with a history of ancient civilization have a particular interest in the use of medicinal plants; they tend to demand these to treat diseases, especially those for which medicine has no treatment. But if the use of medicinal plants is not supported by medical studies and scienfitic evidence, they cannot be safely applied in treatment. In recent decades, the popularity of natural herbs and herbal products has grown [1], and general beliefs about their usefulness are strengthening [2].

Drug addiction is a major problem in society nowadays and a diverse range of solutions to cure or control it has been proposed. Patients' interest in herbal remedies and lack of valid evidence in this context is causing problems in treatment. Some patients are seeking treatment with medicinal plants, but as medicine lacks sufficient evidence on their effectiveness, the impact of this type of treatment could be equally attributed to the plant itself, the psychological effect of treatment and the placebo effect. The use and abuse of opium is a chronic and recurrent disorder that affects the person, disrupts their family life and causes harm in the community. Several reasons have been given for opium use and abuse, such as emotional and mental health problems, as well as

Mehdi Sayyah[1], Alireza Siahpoush[2], Fakher Rahim[3]: [1]Psychiatrist, Associate Professor, Faculty of Ahvaz Jundishapur, University of Medical Sciences, Ahvaz, Iran; [2]Associate Professor, Faculty of Medicinal Plant Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; [3]Apadana clinical research center.
Correspondence address: sayah_bargard@Aol.com

to manage and handle stress [3]. Millions of people around the world use and abuse opium. It has been habitually used in Asian countries such as Iran, Afghanistan, Pakistan, India, China, Myanmar, Laos, Thailand, Bangladesh, Nepal, Sri Lanka, Turkey, Iraq, Jordan, Egypt, Bahrain, Oman and Kuwait [4,5]. Clinical evidence shows that many people are turning to opium during post-detoxification phase due to the chronic and recurrent nature of substance dependence [6,7]. It was reported that, in the best of circumstances and with the best treatment, during a 6-month follow-up, 95% of addicts returned to the drug addiction cycle and the remaining 5% returned over the next 1 or 2 years [8]. It was reported that 16.5 million individuals globally use opiates, of whom 4 million use raw opium; moreover, epidemiologic evidence reported an association between opium use and cancer incidence and mortality [9]. Opium use was associated with an increased risk of major health problems such as cancers, though the associations are possibly causal [3].

Zataria multiflora Boiss (thyme extract) is a member of the mint (Labiatae) family with multiple, thin, radiating, thyme-like stems. The plant grows in Iran, Afghanistan and Pakistan, and is also known as thyme and oregano [2]. Its growth and distribution in Iran are limited to Khuzestan, Lorestan, Isfahan, Kerman, Fars and Khorasan provinces [2,10]. The effective substance of *Z. multiflora* is composed of thyme and carvacrol. Its other content includes Zatarioal, p-cymene and β-sitosterol [11]. In traditional medicine, various properties of thyme extract are mentioned, including digestion regulation and curing indigestion (syrup) [12,13]. Pre-clinical studies reported various beneficial effects of thyme extract, including antimicrobial [14-16], antifungal [17], antioxidant, anti-inflammatory [18], and analgesic potentials [10,18,19]. An animal study also revealed that this herb has protective effects against analgesic drug-induced hepatotoxicity [20]. The opioid agonist properties of thyme extract have been examined previously [10,21,22]. Historical physician documents show its positive effects in the treatment of seizures, spasms and pain, including menstrual pain.

The use of thyme in modern medicine dates back many years. For example, Briseid et al. studied the smooth muscle relaxing effect of thyme [*Thymus vulgaris L*] in 1966 [23]. It was found that naloxone prevents the analgesic effects of this plant; thus, thyme herb may affect opiate receptors [10]. It was reported that the alcoholic extract of thyme has about 90% of the analgesic effect on mice that is similar to the analgesic effect of morphine in a dose of 10 mg/kg [10]. Antispasmodic properties have also been reported for this plant, which is because of its phenolic structure whose major component is thymol [21].

Opium detoxification is a controlled and medically supervised withdrawal from the addictive drug, usually under the care of a physician, which is designed to treat the immediate effects of quitting opium use on the body, as well as to eliminate toxins and waste substances. Opium detoxification takes place in various locations, including the community, residential places, inpatient wards and prisons [24]. Tapering the opium slowly under careful monitoring is gradually performed based on the amount of opium consumed and symptoms.

Methadone is a safe drug effective in chronic pain management. In low dose, it is used safely in various types of patients, following the general rule of "start low, go slow" [25,26]. A dose of 1 mg of opium is equivalent to approximately 5–10 mg of oral methadone; but due to varying purity of street opium, empirical methadone dosing based on recent opium use is recommended instead of equivalent dosing [27].

Considering the equivalent dose of methadone and various purity of opium we used low dose (7.5 mg) of methadone to begin with. Considering the interest of patients and their families in using medicinal herbs as well as evidence of the impact of the plant on opiate receptors, the effect of an alcoholic extract of thyme along with gradually decreasing methadone in controlling the symptoms of opium withdrawal was compared with placebo in a double-blind study.

MATERIALS AND METHODS

Participants

In this double-blind clinical trial patients with opium addiction aged 25–35 years and referred to that participated in the study. Opium dependence was diagnosed based on DSM-IV-TR crite-

ria by two resident psychiatrists in the clinic. Patients who were taking 1 to 1.5 g of opium were included. If a patient was taking other forms of opium, such as heroin, or cannabis or alcohol (based on a urine drug test), glass they were excluded. Patients with neurological or psychiatric illnesses were also excluded. History of sensitivity to medicinal herbs, historical or current psychiatric drug consumption, IQ of less than 70, consumption of more than 1.5 g of opium daily, self-harm and a history of suicide attempts were other exclusion criteria.

Initially, 43 patients were enrolled, 3 of whom were excluded: 2 due to re-consumption of drugs and 1 for unknown reason. If patients scored more than 31 points on the Clinical Institute Narcotic Assessment (CINA) questionnaire [28], they were excluded to avoid symptoms of severe deprivation; they were later treated using standard treatments. Setting: the addiction treatment clinic in Imam Khomeini Hospital in Ahvaz, Iran.

Questionnaire

To evaluate the severity of withdrawal symptoms the CINA scale was used [28]. This is an 11-item questionnaire and each item scores from 0 to 2, 3 or 6. The questionnaire was translated and validated in the Center for Medicinal Herbs of Ahvaz Jundishapur University of Medical Sciences. Scoring higher than 31 on the questionnaire is considered as having severe withdrawal symptoms [28]. Scoring is based on clinical findings seen by the therapist.

Preparation and pharmaceutical dosage of the plant

Thyme was purchased from a grocery store in Ahvaz and validated by an expert at the Center of Medicinal Herbs. An alcoholic extract of plant leaves was used in this study. To prepare the extract, the leaves were washed, dried and powdered. 60 g of the powder was poured in a paper Kartvsh, and 200 ml of methanol was added. Then extraction and concentration were performed at 50°C, which resulted in 13g of extract. Afterwards, 500 mg of the extract was poured inside a prepared capsule. Previously, the LD-50 of this plant was estimated at 3.85 and 3.47 g/kg [21]; thus, to avoid possible side-effects, the dose of 1500 mg was considered [10]. For the preparation of a placebo in the form of similar capsules, starch was used.

Intervention

Patients were randomly divided into two groups using a table of random numbers. Considering the availability of methadone as a 5 mg tablet, to obtain a 7.5 mg preparation and to ensure masking, methadone was given in powder form. The first group received 1500 mg thyme extract and 7.5 mg methadone orally for 5 days, while

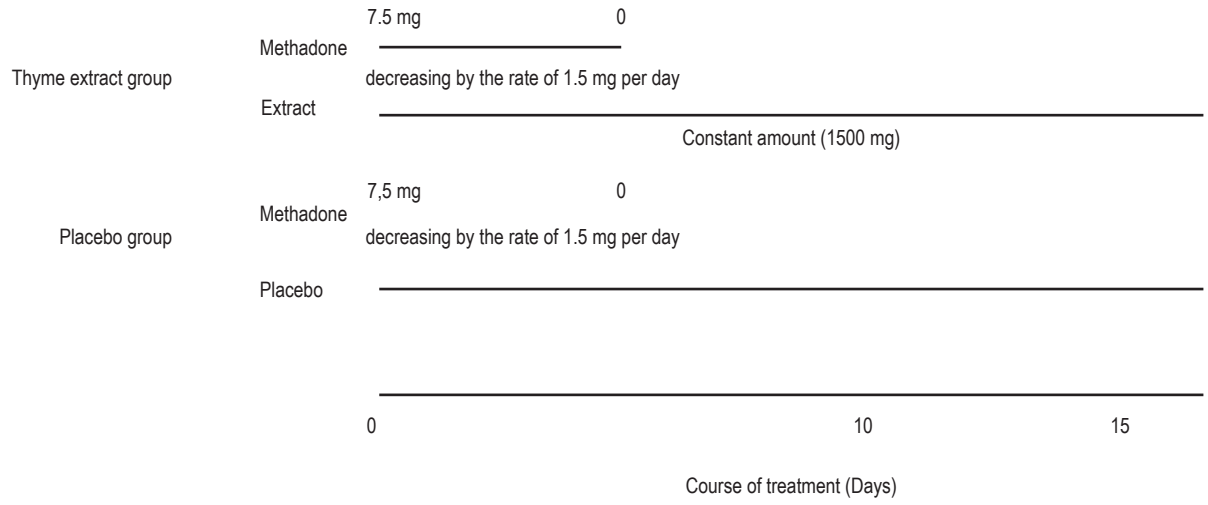

Figure 1. Administration regimen of methadone, plant extract and placebo

the second group received oral placebo (acetaminophen powder similar to methadone) with 7.5 mg methadone for 5 days (Figure 1). After 5 days, 1.5 mg of methadone was deducted daily so no patient received methadone after the ninth day. Thyme extract dose was unchanged. Patients were checked on the second, seventh, eleventh and fifteenth day using the CINA scale. The first dose of the drugs was administered 24 hours after opium was taken.

Outcome measures

The primary outcome was considered to be symptoms of opium withdrawal, which were measured using CINA. The secondary outcome was measured as side-effects of opium withdrawal. We used a block randomization design, in which the sample was divided into relatively homogeneous subgroups. The procedure was designed as a double-blind study in which neither the patients nor the persons administering the experiment knew the critical aspects of the experiment.

Ethical approval was granted by Ahvaz Jundishapur University of Medical Sciences Ethics Committee and all participants signed an informed consent form prior to enrollment.

Statistical analysis

To evaluate results, the Mixed Model Repeated Measure (ANOVA) was used, which includes the main effect of time, the main effect of group and time effect and group interaction. Then, for the analysis of continuous quantitative and categorical qualitative data, t-test and chi-square test were used, respectively; $p< 0.05$ was considered significant. Quantitative results are expressed as mean ± SD, hence qualitative findings were reported as a percentage.

RESULTS

Demographics

All patients were male. There were significant differences between the two groups in terms of age, amount of substance taken (grams per day) and addiction duration. The number of married people in the placebo group was significantly higher than in the thyme extract group (P = 0.021) (Table 1).

Table 1. Demographic characteristics of the study sample

Demographic characteristics	Thyme extract plus methadone group (n=19)	**Placebo plus** methadone group (n=21)	P-values
Age, years: mean ± SD	28 ± 2.8	29 ± 3.1	0.454
Marriage, n (%)			
Married	8 (42.1%)	14 (66.7%)	0.021
Single	11 (57.8%)	7 (33.3%)	0.689
Duration of drug dependence, years: mean ± SD	6 ± 1.3	6 ± 1.7	0.981
Opium consumption, g/day: mean ± SD	1 ± 0.2	1 ± 0.2	1.000

DRUG EFFECTS ON SYMPTOMS OF OPIUM WITHDRAWAL

Overall, 40 patients completed the study. They were randomly allocated into a thyme extract group (n=19) and a placebo group (n=21) (Figure 2). The two groups had no significant differences at the start of treatment in terms of symptoms of opium withdrawal based on CINA (P = 0.169). Analysis of variance indicated that the main effect of time (time effect) was significant (P < 0.000). Treatment efficacy, time effect and group interaction were significant (P < 0.000). The course of treatment and the average CINA scores on the seventh, eleventh and fifteenth day decreased more significantly in the thyme extract group (P = 0.018, P = 0.0023, P = 0.041, respectively) (Figure 3).

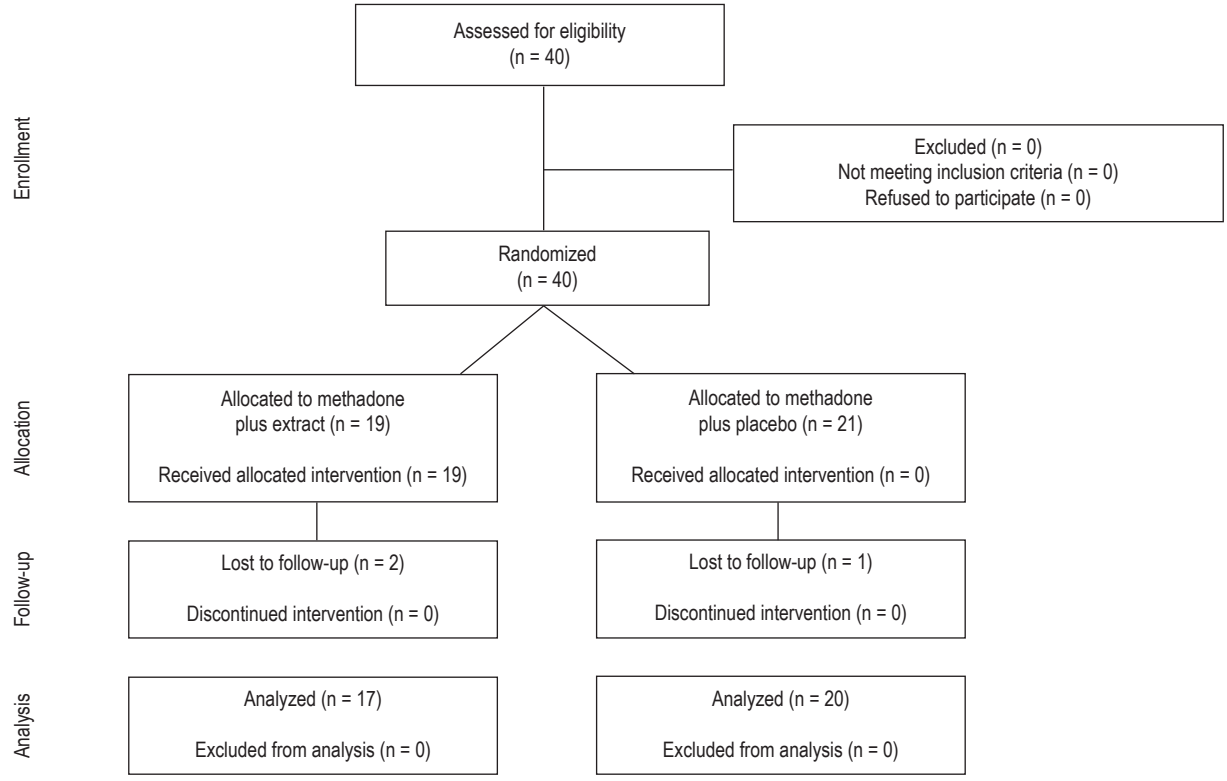

Figure 2. The flow of participants through each stage of the trial

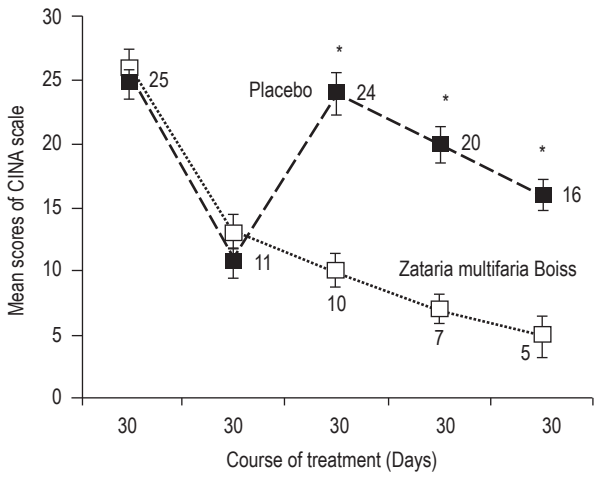

Figure 3. Mean CINA scores in both groups (values given as mean ± SD)

Repeated measure regression analysis revealed statistically significant effects on CINA for drug (thyme extract vs. placebo) ($F= 77.3$, $df =39$, $p<0.0001$), time ($F=13.03$, $df =495$, $p<0.0001$), and drug-by-time interaction ($F=13.82$, $df=476$, $p<0.0001$). Three patients discontinued the study, 2 from the medication group due to re-consumption of drugs and 1 from the placebo group because of cannabis consumption. There was no significant difference between the two study groups.

A summary of adverse events is given in Table 2. A total of 3/17 (17.64%) and 5/20 (25%) subjects in the thyme extract and placebo groups, respectively, experienced adverse events (Table 2).

Table 2. Summary of most frequent adverse events

Adverse events (AEs)	Extract plus methadone group (n=17)		Placebo plus methadone group n=20)	
	N	%	N	%
Headache	0	0	2	10
Dizziness	1	5.88	0	0
Nausea	1	5.88	0	0
Vomiting	0	0	2	10
Dyspepsia	0	0	0	0

Upper abdominal pain	1	5.88	1	5
Any AEs	3	17.64	5	25

DISCUSSION

Herbs have been used to treat various diseases, especially chronic and treatment-resistant diseases in countries with a long-established traditional culture. However, if this is done in an unsystematic and unstructured manner, it can be problematic both for patients and health services. One of the problems with using herbal remedies is that therapists do not realize what the reason for treatment effects is due to lack of sufficient evidence. Considering the results of this double-blind clinical trial, we can say that alcoholic thyme extract can be beneficial in controlling the symptoms of opium withdrawal compared to methadone. Thus, the use of this herb, similar to methadone, may be considered as a standard treatment for opium withdrawal [29].

One of the problems with gradual withdrawal using methadone is that patients are experiencing milder symptoms of withdrawal; evidently, this is one of the causes of recurrence of addiction in these patients. In this study, patients did not experience these symptoms during methadone withdrawal, and unlike in the placebo group, symptoms were easier to bear with.

Previous studies in animal models confirmed the effect of thyme on pain associated with opium withdrawal [10,23]. This study, in line with previous studies, showed the effect of the plant in human subjects. During the study, patients showed fewer symptoms of restlessness and tremors (based on CINA questionnaires); this points to the potential effect of the plant on benzodiazepine receptors. It could lead researchers to a new direction for research and future studies on the plant.

The results showed that hydro-alcoholic extracts of thyme are effective for withdrawal symptoms, and given that the extract acted similarly to methadone in reducing such symptoms we can say that this therapy is effective in controlling symptoms in patients with a low level of opium consumption. A combination of thyme extract with methadone was generally well tolerated. All adverse events were mild or moderate in severity and complied with the known safety profile of thyme extract [30, 31].

LIMITATIONS

The results of this study should be interpreted alongside its limitations. The researchers selected only patients with small levels of opium consumption (1 to 1.5 g) for ethical reasons. The number of patients in this study also constitutes a limitation. Since human samples were used in this study, relatively low doses were used to avoid serious complications; no serious side-effects at this dosage were observed. To determine the effectiveness of the drug, the dose of thyme remained constant, but it could be tapered in subsequent studies. No patient developed thyme dependency.

In summary, this study showed that an alcoholic extract of thyme can help control withdrawal symptoms of opium, as an effective, safe and relatively inexpensive drug. The need for further studies in this area is strongly felt.

Acknowledgments

Authors want to express their thanks to the addiction treatment clinic in Imam Khomeini Hospital, Ahwaz, Iran for help in the care and treatment of patients, as well as to all patients who participated in this study.

Funding

This study was supported by the deputy of research affairs, Ahvaz Jundishapur University of Medical Sciences (AJUMS).

REFERENCES

1. GM. C. A molecular approach. In: Associates SMS, editor. The Development and Causes of Cancer. 2nd edition ed2000.
2. Saki K, Bahmani M, Rafieianb-Kopaei MD, Asadollahi K, Emaneini M, Taherikalani M. An ethnobotanical study of medicinal plants with narcotic, sedative and analgesic effects in west of Iran. J Biol Reg Homeostatic Agents. 2016; 30(3): 807–810.
3. Kamangar F, Shakeri R, Malekzadeh R, Islami F. Opium use: an emerging risk factor for cancer? Lancet Oncol. 2014; 15(2): e69–77.
4. Suwanwela C, Poshyachinda V. Drug abuse in Asia. Bull Narc. 1986; 38(1-2): 41–53.

5. Rahimi-Movaghar A, Amin-Esmaeili M, Hefazi M, Yousefi-Nooraie R. Pharmacological therapies for maintenance treatments of opium dependence. Cochrane Database Syst Rev. 2013; 1: CD007775.
6. Fareed A, Stout S, Casarella J, Vayalapalli S, Cox J, Drexler K. Illicit opioid intoxication: diagnosis and treatment. Subst Abuse. 2011; 5: 17–25.
7. Kleber HD. Pharmacologic treatments for opioid dependence: detoxification and maintenance options. Dialogues Clin Neurosci. 2007; 9(4): 455–470.
8. Ardame A, Bassaknejad S, Zargard Y, Rokni P, Sayyah M. Examine the relationship between mindfulness and drug craving in addicts undergoing methadone maintenance treatment. Iran J Public Health. 2014; 43(3): 349–354.
9. Naghibzadeh Tahami A, Khanjani N, Yazdi Feyzabadi V, Varzandeh M, Haghdoost AA. Opium as a risk factor for upper gastrointestinal cancers: a population-based case-control study in Iran. Arch Iran Med. 2014; 17(1): 2–6.
10. Hosseinzadeh H, Ramezani M, Salmani G. Antinociceptive, anti-inflammatory and acute toxicity effects of Zataria multiflora Boiss extracts in mice and rats. J Ethnopharmacology. 2000; 73(3): 379–385.
11. Ali MS, Saleem M, Ali Z, Ahmad VU. Chemistry of Zataria multiflora (Lamiaceae). Phytochemistry. 2000; 55(8): 933–936.
12. Heydari M, Hashempur MH, Zargaran A. Medicinal aspects of opium as described in Avicenna's Canon of Medicine. Acta Med Histor Adriatica: AMHA. 2013; 11(1): 101–112.
13. Naseri M, Babaeian M, Ghaffari F, Kamalinejad M, Feizi A, Mazaheri M, et al. Bloating: Avicenna's perspective and modern medicine. Evid Based Complement Alternat Med. 2016; 21(2): 154–159.
14. Dadashi M, Hashemi A, Eslami G, Fallah F, Goudarzi H, Erfanimanesh S, et al. Evaluation of antibacterial effects of Zataria multiflora Boiss extracts against ESBL-producing Klebsiella pneumoniae strains. Avicenna J Phytomed. 2016; 6(3): 336–343.
15. Khosravi AR, Shokri H, Fahimirad S. Efficacy of medicinal essential oils against pathogenic Malassezia sp. isolates. J Mycol Med. 2016; 26(1): 28–34.
16. Saeidi S, Hassanpour K, Ghamgosha M, Heiat M, Taheri RA, Mirhosseini A, et al. Antibacterial activity of ethyl acetate and aqueous extracts of Mentha longifolia L. and hydroalcoholic extract of Zataria multiflora Boiss. plants against important human pathogens. Asian Pac J Trop Med. 2014; 7S1: S186–189.
17. Panjehkeh N, Jahani Hossein-Abadi Z. Inhibitory effects of essential oils of medicinal plants from growth of plant pathogenic fungi. Commun Agric Appl Biol Sci. 2011; 76(4): 705–714.
18. Nakhai LA, Mohammadirad A, Yasa N, Minaie B, Nikfar S, Ghazanfari G, et al. Benefits of Zataria multiflora Boiss in experimental model of mouse inflammatory bowel disease. Evid Based Complement Alternat Med. 2007; 4(1): 43–50.
19. Amanlou M, Beitollahi JM, Abdollahzadeh S, Tohidast-Ekrad Z. Miconazole gel compared with Zataria multiflora Boiss. gel in the treatment of denture stomatitis. Phytother Res. 2006; 20(11): 966–969.
20. Ahmadipour A, Sharififar F, Najafi A, Atashbar J, Karami-Mohajeri S. Preventive effect of methanolic extract of Zataria Multiflora Boiss on liver toxicity of paracetamol in rats. J Med Life. 2015; 8(Spec Iss 4): 270–274.
21. Sajed H, Sahebkar A, Iranshahi M. Zataria multiflora Boiss. (Shirazi thyme)—an ancient condiment with modern pharmaceutical uses. J Ethnopharmacology. 2013; 145(3): 686–698.
22. Gharib Naseri MH, Goshaiesh M, Vakilzadeh G, Heidari A. Antispasmodic effect of Zataria multiflora Boiss. leaf extract on the rat uterus. Ir J Pharm Res. 2006; 2: 131–136.
23. Briseid Jensen K, Dyrud OK. The smooth muscle relaxing effect of thyme (Thymus vulgaris L). Acta Pharmacol Toxicologica. 1962; 19: 345–355.
24. National Institute for Health and Clinical Excellence. Drug Misuse: Opioid Detoxification. Leicester (UK): NICE; 2008.
25. Anghelescu DL, Patel RM, Mahoney DP, Trujillo L, Faughnan LG, Steen BD, et al. Methadone prolongs cardiac conduction in young patients with cancer-related pain. J Opioid Manag. 2016; 12(2): 131–138.
26. Santiago-Palma J, Khojainova N, Kornick C, Fischberg DJ, Primavera LH, Payne R, et al. Intravenous methadone in the management of chronic cancer pain: safe and effective starting doses when substituting methadone for fentanyl. Cancer. 2001; 92(7): 1919–1925.
27. Anderson IB, Kearney TE. Use of methadone. West J Med. 2000; 172(1): 43–46.
28. Peachey JE, Lei H. Assessment of opioid dependence with naloxone. Br J Addict. 1988; 83(2): 193–201.
29. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev. 2009; 3: CD002209.
30. Grant A, Parveen S. All natural and clean-label preservatives and antimicrobial agents used during poultry processing and packaging. J Food Prot. 2017; 80(4): 540–544.
31. Ludwig S, Stier H, Weykam S. Evaluation of blood alcohol concentrations after oral administration of a fixed combination of thyme herb and primrose root fluid extract to children with acute bronchitis. Drug Res (Stuttg). 2016; 66(2): 69–73.