



Effect of Zataria multiflora, Satureja, Oak Fruit Husk, and Jaftex Mouthwash on Treatment of Recurrent Minor Oral Aphthous Stomatitis

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Abstract

Context: The use of herbal medications can improve the quality of life and prevent the side effects of chemical drugs. The present narrative review study aimed to assess the efficacy and safety of Zataria multiflora, Satureja, oak fruit husk, and Jaftex herbal mouthwash for the treatment of minor oral aphthous stomatitis.

Evidence Acquisition: A literature review was conducted in electronic databases such as PubMed, Web of Science, Scopus, and Google Scholar, as well as Persian databases such as SID, Magiran, and IranMedex from 2000 to 2019, particularly in the last 10 years. The appropriate keywords were searched including "recurrent aphthous stomatitis", "oak tree", "Satureja", "Zataria multiflora", and "Jaftex mouthwash".

Results: Six clinical trials were analyzed in the present study. The results showed that Zataria multiflora, Satureja, oak fruit husk, and Jaftex mouthwash have beneficial effects on the treatment of recurrent aphthous stomatitis. The main outcome measures assessed in this study were the duration of the complete healing process, ulcer size, and the level of pain. No side effects were reported in Zataria multiflora, oak fruit husk, and Jaftex mouthwash, but Satureja khuzestanica essential oil revealed a trivial burning at the initial time of application.

Conclusions: Reviewing these studies indicated that Zataria multiflora, Satureja, oak fruit husk, and Jaftex mouthwash greatly improved the patients' symptoms by shortening the duration of the complete healing process, reducing ulcer size, and relieving pain. Therefore, these herbal medicines can be used as alternative treatment agents for recurrent aphthous stomatitis. More investigations are required to elucidate the probable mechanism(s) and mode(s) of action of these plants and standardization.

Keywords: Multiflorol, Satureja, Oak Tree, Mouthwash, Recurrent Aphthous Stomatitis, Review Article, Herbal Medicine

1. Context

Recurrent aphthous stomatitis (RAS) is a very common oral painful ulcerative lesion (1). It involves approximately 20% of the population, with the highest frequency in higher socioeconomic classes (2, 3). The exact etiology of RAS has been remained unclear (4). Various causative agents are involved in RAS including genetics, immune conditions, allergies, blood disorders, upper respiratory tract infections, hormonal conditions, and some drugs such as barbiturates (3, 5, 6). Many systemic disorders including Behcet's syndrome, vitamin deficiency, and Sweet's syndrome are correlated with RAS (7).

Histologically, RAS contains a mononuclear infiltrate with a fibrin coating (8). Based on clinical characteristics, RAS is categorized into minor ulcers, major ulcers, herpeti-

form ulcers, and severe aphthous ulcers. Minor aphthous ulcers are the most common type of RAS. The size of minor ulcers is usually less than 1 cm (< 1 cm diameter) and they heal within 1-14 days without scarring (9).

The commonly accepted treatment strategy for targeting RAS is to lessen the pain and duration of lesions. Topical corticosteroids and analgesics are highly recommended for patients with RAS. However, longer treatment with these medications may cause fungal infection and drug resistance (10).

Nowadays, patients tend to use natural medicine to avoid the side effects of synthetic drugs (11). In many countries, natural herbal medicines have been widely used as alternatives for the treatment of RAS (12). Clinical studies have suggested that herbal medications can relieve discomfort and shorten the duration of ulcers (13-16). Oak is

one of the natural herbal medicines used for its therapeutic properties (9). Jaft is known as the inner layer of the oak fruit with medical and industrial uses (17, 18). Many medicinal properties have also been reported for the husk of oak fruit. Various studies have been examined the effect of oak fruit husk (Jaft) in managing minor oral mucosal ulcers and healing cutaneous wounds (18).

Zataria multiflora, Avishan Shirazi (Persian name), is a thyme-like essential oil-bearing herbal plant that belongs to the *Lamiaceae* family. Zataria multiflora (ZM) grows broadly wild in the central and southern parts of Iran. Zataria multiflora is mostly used in folk and traditional medicine systems for its antiseptic, analgesics, and carminative nature (19).

Satureja (Marzeh in Persian) is native to the western and southern parts of Iran and has been used as an analgesic and antiseptic in traditional medicine (20, 21). Extract and essential oil of this plant, as well as carvacrol (the main constituent), have shown antimicrobial, analgesic, and antioxidant activity (22). Moreover, Satureja has traditionally been used in Iran for relieving toothache (23-25).

Jaftex is a new herbal mouthwash with the combination of oak fruit husk (Jaft) aquatic extract as a base, aquatic extract of Zataria multiflora and Satureja bachtiarica. Jaftex is the product of the Pharmaceutical Plant Growth Center of Ahvaz Jundishapur University of Medical Sciences (AJUMS). The main ingredient of Jaftex oral mouthwash is Jaft (9).

Iran has a wide variety of medicinal plants and Iranians are interested in using them, so herbal medicine has become increasingly popular among the Iranian population (26). Consequently, Iranian researchers have investigated the effects of various native herbal medicines on RAS treatment (27). However, there is no evidence indicating the safety or adverse reactions of herbal plants. Thus, a review study is required to access a reliable source and evidence-based information (26).

The present review study aimed to assess the efficacy and safety of Zataria multiflora (ZM), Satureja, oak fruit husk (Jaft), and Jaftex herbal mouthwash for the treatment of recurrent minor aphthous stomatitis. The results of the study would provide guidelines and evidence for clinical and public health specialists.

2. Evidence Acquisition

The present review article was conducted in electronic databases such as PubMed, Web of Science, Scopus, and Google Scholar, as well as Persian databases such as SID, Magiran, IranMedex from 2000 to 2019, particularly in the last 10 years. The appropriate keywords were searched including "recurrent aphthous stomatitis", "oak tree", "Sat-

ureja", "Zataria multiflora", "herbal medicines", and "Jaftex mouthwash" in the "title", "abstract", or "keywords", until December 2019. All databases were searched for published Iranian Randomized Controlled Trials (RCTs).

The inclusion criteria for the selection of articles were as follows: Human studies, RCTs, patients with RAS diagnostic criteria without any restriction on age, gender, or race, being performed by Iranian authors using Iranian native plants, and interventions consisting of any formulation of Zataria multiflora, Satureja, and oak fruit husk including mouthwash, paste, oral mucoadhesive gels, and tablets. The exclusion criteria were as follows: Clinical observations without control groups, animal studies, research reports without adequate information on participants, duplicate articles, and studies related to aphthous-like ulcers.

For each study, the following data were extracted according to a predefined checklist: First author, year, design, study period, age, intervention, control, number of participants in intervention and control groups, adverse effects, and outcome measures.

3. Results

The abstracts and full texts of the articles were studied. Finally, six RCTs were selected. The results are presented in Table 1. In terms of design, all the selected studies were double-blind or triple-blind studies. The sample sizes of studies ranged from 28 to 115 patients. The following herbal medicines were used as mouthwash and solutions for RAS treatment: leaves of ZM and flowers of Satureja and Jaft.

3.1. The Effect of Zataria multiflora (ZM) on RAS

Three clinical trials investigated the effect of ZM on RAS (28-30). Mansoori et al. examined the therapeutic effects of ZM essential oil on RAS treatment. In this study, 60 patients with RAS received ZM essential oil or placebo mouthwash (essential oil-free). The participants were instructed to use the mouthwash three times a day for four weeks. In the end, 83% of the patients showed positive responses to ZM essential oil. Favorable and immediate responses to the treatment were noted in 33% of the ZM group and 7% of the placebo group patients. The improvement of the ulcers after 2 - 7 days of treatment was achieved in 50% and 7% of ZM and placebo groups' patients, respectively. The duration of the healing process was different between the two groups. The results of this study indicated that the aqueous-alcoholic essential oil of ZM could be effectively used in the treatment of RAS. No adverse effect was reported (28).

Table 1. Characteristics of the Enrolled Studies

Author	Herb	Control	Outcome Measures	Dosage
Amanlou et al. (22)	Satureja khuzestanica + essential oil of Satureja khuzestanica	Hydroalcoholic solution in the absence of any active material	Time of pain elimination, duration of complete healing	Five drops, each time for one minute; four times daily, for seven days
Mansoori et al. (28)	Essential oil of Zataria multiflora	A liquid placebo of essential oil-free aquatic alcohol	Relief of pain, healing time	Three times daily, for four weeks
Jafari et al. (29)	Zataria multiflora + Anthemisnobilis	Myrtle mouthwash (positive control)	Date of elimination of pain, duration of healing	10 drops, each time for one minute; five times daily, for seven days
Babae et al. (30)	Essential oil of Zataria multiflora	Distilled water with a cap scented with essential oil of Zataria multiflora	Ulcer size, pain intensity, complete healing	15 drops, each time for two minutes; three times daily, for seven days
Jahanshahi et al. (31)	Oak fruit husk + Darcocephalum	Purslane plant	Duration of complete healing, pain level, ulcer size	Each time for one minute, four times daily, for 10 days
Babadi and Nabhani (9)	Jaftex (oak fruit husk + Zataria multiflora + Satureja)	(NaCl + water)	Pain level (VAS), ulcer size	Each time for two minutes, two times daily, for two weeks

Babae et al. showed that the average complete healing time and duration of burning sensation were significantly lower in the ZM group than in the control group. A significant difference was observed between the two groups concerning the diameter of lesions. The result of the study showed that ZM could reduce the RAS symptoms and other clinical features of aphthous lesions compared to the placebo group. No side effects of the ZM plant were noted (30).

In another study, Jafari et al. compared the efficacy of three herbal extracts for the management of RAS. Patients with aphthous stomatitis were divided into four groups. The participants of study groups received 20 mL topical preparation of Zataria multiflora, Anthemis nobilis, or 50% (v/v) mixture of Zataria multiflora and Anthemis nobilis. The positive control group received Myrtus communis (Myrtle, mouth rinse). The patients were instructed to apply the medications five times daily by putting a small sterile cotton pad impregnated with 10 drops of each preparation on the lesions for one minute. The result revealed that Zataria multiflora extract showed better effects than Myrtus communis. The authors concluded that the ZM extract was an effective product for the treatment of RAS. No adverse effect was addressed (29).

3.2. The Effect of Satureja khuzistanica (SK) on RAS

Amanlou et al. investigated the effect of Satureja khuzistanica (SK) extract and its essential oil preparations on the treatment of RAS. In this study, 60 patients with RAS were selected and divided randomly into three groups. Intervention groups A and B received topical preparations of SK extract and SK essential oil, respectively. Group C received a placebo. The participants of each group received 20 mL of anonymous herbal preparations and were

instructed to apply the medication four times daily by putting a small sterile cotton pad saturated with five drops of each preparation on the lesions for one minute and lasted at least 30 minutes. The results showed a significant difference in the mean duration of pain elimination between the intervention groups and the placebo group. The results obtained for group A were similar to those of group B. It was concluded that SK was an effective herbal medicine for the management of minor aphthous, but SK essential oil caused a slight burning sensation at the beginning of the application (22).

3.3. The Effect of Jaftex Mouthwash on RAS

In a study, Babadi et al. investigated the effect of Jaftex mouthwash on the treatment of RAS. In this study, 40 patients with RAS were selected and randomly divided into two groups. Group A received Jaftex mouthwash and group B received sodium chloride mouthwash as a placebo. The size of the lesions and the amount of pain before the treatment were recorded. Patients received the mouthwash for two weeks, twice a day, 15 cc for two minutes each time. The amount of pain and the size of ulcers were recorded at an interval time of two and six days after using the mouthwash. The mean pain level was significantly lower in group A than in group B. There was no significant difference in the mean size of lesions at the start of treatment and two days after treatment. However, on the sixth day, the mean size of lesions was significantly lower in group A than in group B. It was concluded that the Jaftex mouthwash was effective as an herbal mouthwash for the treatment of RAS. No side effects related to Jaftex mouthwash were noted in this study (9).

3.4. The Effect of Oak Fruit on RAS

Jahanshahi et al. in a study compared a combination extract prepared from the Oak fruit and the Darcocephalum plant as a medicine for the control and treatment of RAS. In this study, 86.6% of the cases showed ulcer improvement on the first day compared to the control group. Overall, improvement occurred in 1.2 ± 0.584 days in the case group and 3.8 ± 1.437 days in the control group. Complete resolution was obtained after 3.53 ± 1.664 days of treatment in the case group. No statistically significant difference was observed between the case and control groups concerning the recurrence rate after three months' follow-up. No adverse effect was reported (31).

3.5. Primary Outcome Measure

The duration of complete healing, ulcer size, and level of pain were the most important outcomes measured in the present study.

3.5.1. Complete Healing (No Ulcer and No Burning Sensation)

Babae et al. reported that the mean complete healing was significantly shorter in the Zataria multiflora group (6.53 ± 1.30 days) than in the placebo group (8.43 ± 1.29 days) (30). Mansoori et al. found that the healing time of the placebo group (9.1 days) was 4.6 days longer than that of the Zataria multiflora group (4.5 days) (28). In another study, Jafari et al. showed that after the application of Zataria multiflora extract, the average time for the complete healing of lesions was 6.00 ± 2.80 days, which was shorter than that of the placebo group (7.60 ± 3.10 days) (29). In the study by Amanlou et al., the average time for the complete healing of lesions in patients was 5.90 ± 1.24 days and 6.85 ± 1.3 days using Satureja khuzestanica extract and its essential oil, respectively, and it was 10.40 ± 1.66 days in the placebo group (22). In the study by Jahanshahi et al., the complete healing time was 3.53 ± 1.664 days in the case group (a combination of oak fruit husk and Darcocephalum plant) and 6.84 ± 0.688 days in the control group (31).

3.5.2. Ulcer Size

The ulcer size was described in two clinical trial studies. In the study by Babae et al., the lesion diameters were measured using a ruler (accuracy of 1 mm). A significant difference was observed in the mean halo diameters (mm) between the placebo (3.5 ± 1.45) and ZM (1.50 ± 1.55) groups (30). In the study by Babadi et al., the mean ulcer size was 0.80 ± 0.52 mm in patients using Jaftex mouthwash and 1.85 ± 1.23 mm in the placebo group (9).

3.5.3. Side Effects

Five clinical trial studies (Table 2) did not report side effects. In the study by Amanlou et al., two participants reported a slight burning sensation after using Satureja khuzestanica essential oil at the initial application (22).

Table 2. Follow-Up and Adverse Reactions of the Herbs

Herb	Follow-Up	Adverse Reactions
Essential oil of Satureja khuzestanica	Not mentioned	Slight burning
Essential oil of Zataria multiflora	Not mentioned	None
Zataria Multiflora + Anthemisnobilis,	Two weeks	None
Essential oil of Zataria multiflora	Not mentioned	None
Oak fruit husk + Darcocephalum	Three months	None
Jaftex (Zataria multiflora + Saturejabachtiarica + oak fruit husk)	Two weeks	None

4. Conclusions

Currently, people tend to change their lifestyles and use herbal medicines due to the safety of medicinal plants (32). In this study, researchers focused on the efficacy and safety of ZM, Satureja, Jaft, and Jaftex herbal mouthwash for the treatment of recurrent minor aphthous stomatitis. Six clinical trials were analyzed in the present study.

Reviewing these studies indicated that ZM, Satureja, Jaft, and Jaftex mouthwash greatly improved the treatment outcome by shortening the healing time, reducing the index ulcer size, and alleviating the pain symptoms. The active ingredients of ZM are carvacrol and flavonoids, which induce antimicrobial effects (29). The essential oil (EO) of ZM has been reported to have antibacterial, antiviral, antioxidant, and anti-inflammatory properties (19, 33-38). It also has been reported that the EO and ZM extracts can stimulate innate immunity (34). This property may be attributed to either the antimicrobial effect of ZM or the alteration of the microbial flora of the mouth, which results in less immunologic damage as reported in some antibacterial mouth rinses against RAS (39, 40). Satureja khuzestanica is an effective herbal medicine for the management of minor RAS. The positive curative property of SK in the management of minor types of RAS could be explained due to the presence of sitosterol or flavonoids in the extract of Satureja khuzestanica, which may act as an antioxidant and anti-inflammatory agent (25, 41, 42). Babadi and Nabhani reported that Jaftex mouthwash reduced the pain

level and the size of minor aphthous ulcers (9). The application of Jaftex herbal mouthwash is recommended as an antibacterial mouthwash. The ingredients of Jaftex are Jaft, ZM, and Satureja khuzestanica. The main basis for this oral mouthwash is Jaft. Furthermore, Jaft contains tannin that has potential therapeutic effects (43, 44). The anticoagulant property of Jaft extract can be attributed to the presence of flavonoids in the extract of Jaft, which accelerates the epithelial wound healing (31). Zataria multiflora and Satureja are the other compounds in the Jaftex mouthwash that have shown to be effective for the treatment of RAS. The combination of these three different herbal medicines in the Jaftex mouthwash increases the success of RAS treatment. This review study showed that placebos had a slight effect on reducing RAS symptoms. Several factors may be involved in the placebo response including doctor-patient relationship, patients' beliefs (positive/negative) and attitudes toward treatment, and cultural diversity (45). Likewise, the current review showed that SK essential oil causes slight burning at the first time of application. Herbal medicines have limited complications, allergic reactions, and adverse side effects, so medicinal plants can be used as complementary and alternative chemical/pharmaceutical medicines for the RAS treatment (46). However, to avoid herbal interactions with prescribed medications or other chemical drugs, medicinal plants should be prescribed by physicians (47). Further studies are required to elucidate the mechanism of action of herbal plants and the standardization of herbal medicinal products (9). A literature review survey showed that the main problems corresponding to the use of herbal medicines in the treatment of RAS included insufficient documentation or evidence about standardization of herbal medicines and lack of enough public health community acceptance (29). Some studies have reported limitations such as the small sample size. Additionally, the researchers were not absolutely sure of the herbal medicine consumption by patients in the follow-up period (28, 31). Well designed and high-quality RCTs are required for further exploration.

In summary, the current data showed favorable benefits of Zataria multiflora, Satureja, Jaft and, Jaftex mouthwash for the treatment of RAS. The main outcome measures assessed in this study were the duration of the complete healing process, ulcer size, and the level of pain. Therefore, these herbal medicines can be used as alternative therapeutic agents for reducing the symptoms of RAS.

Footnotes

Conflict of Interests: The author declare that there is no conflict of interests.

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