Original Article

Malva Sylvestris Mucoadhesive Tablets in the Management of Recurrent Aphthous Stomatitis: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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KEY WORDS
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ABSTRACT

Background: Recurrent aphthous stomatitis (RAS) is an oral inflammatory lesion with unspecified etiology and no definite treatment. Mallow is an herbal medicine with anti-oxidant and anti-inflammatory properties.

Purpose: Considering the effectiveness of mallow (*Malva sylvestris* L.) in managing wounds and inflammation, this research was conducted to discover the efficacy of mallow mucoadhesive tablets on aphthous lesions.

Materials and Method: This randomized, double-blind clinical trial was conducted evaluating 42 patients. The participants were randomly allocated into two groups including the intervention (mallow) and the control (placebo) groups. The patients took tablets three times a day. The lesions' diameter was measured with caliper on days zero (base-line), three, five, and seven. The pain intensity was evaluated by the visual analogue scale. To examine homogeneity of the two groups, chi-square test and the independent t-test were used for qualitative and quantitative variables, respectively. Independent t-test and Mann-Whitney's non-parametric t-test were used to analyze pain intensity and lesion diameter, respectively. A significance level of 5% was considered. Data were analyzed by SPSS23.

Results: The mean lesion diameter on the third day did not show a significant difference between the two groups (p Value> 0.05), but on the base-line, fifth, and seventh days, the difference between the two groups was significant, and the size of lesions of the intervention group decreased in shorter healing time (p< 0.05). Pain intensity had a significant decrease over time (p< 0.05), and pain intensity in the intervention group was significantly lower than in the control group (p< 0.05).

Conclusion: It seems that mallow mucoadhesive tablets effectively reduce pain intensity and boost the healing process in patients with RAS.

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Introduction

Recurrent aphthous stomatitis (RAS) is idiopathic but recurrent, causing painful lesions in the non-keratinized mucosa. These lesions are prevalent in patients aged 10-

40 years [1]. The etiopathogenesis of this issue is unknown, but several factors have been found to impact the immune system and resulting in aphthous lesions formation [2-3]. These factors include infections, nutritional deficiencies, genetic, systemic complications, endocrine alterations, and physical and mental trauma [4-7]. These factors cause the imbalance in oxidants-antioxidants ratio in body and result in aphthous lesions formation [8].

RAS can be treated with various substances, such as topical corticosteroids, local anesthetics, antiseptics, anti-inflammatory medications, and toothpaste with unique enzyme components that decrease pain and the frequency of aphthous lesions recurrence [9]. Unfortunately, long-term use of some of these medications results in fungal infection and drug resistance which in severe cases endanger life [10]. Recently, herbal medicines have been widely studied in dentistry [11-14]. Besides, several studies have shown the remarkable effectiveness of herbal medicines in managing aphthous lesions [4, 15-16]. Combining herbal medicines with chemical medicines may reduce the side effects or increase the efficacy of chemical medicines. For this purpose, a study was designed by Chiu *et al.* [17] comparing the efficacy of prednisolone (a common corticosteroid in managing oral lichen planus) combined with herbal medicines, and herbal medicine and prednisolone separately in managing oral lichen planus. The topical use of this medicine causes secondary candidiasis. The possible toxicity of this medication dictates its administration only if necessary, with the lowest dose and the shortest treatment period. Their results demonstrated greater efficacy when administrating herbal medicines combined with prednisolone. Additionally, a reduced corticosteroid dosage minimizes adverse effects.

Malva sylvestris (*M. sylvestris)* is an herb with therapeutic effects such as antioxidant, anti-microbial, anticancer, and anti-inflammatory properties [18]. Furthermore, previous studies have shown the effectiveness of *M. sylvestris* flower-based preparations in improving wound-healing [19-21]. The Phenolic compounds found in this plant play an important role in its biological activities [22].

Literature review reveals that the infusion or decoction of *M. sylvestris* flowers and leaves has been traditionally used for treating inflammatory conditions affecting the mouth and throat. In a study evaluating the plants used in traditional medicine in southern Italy, the use of *M. sylvestris* flowers infusion as a mouthwash to manage aphthous ulcer was mentioned [23]. In another study conducted in Portugal *M. sylvestris* was chosen to be studied according to Portuguese folk pharmacopoeia and the anti-oxidant efficacy and chemical composition of its leaves, flowers, immature fruits, and leafy flowers stems were compared [24]. In an evidence-based study, Hasheminasab *et al.* [25] studied the effect of Persian traditional medicines, including *M. sylvestris*, on oral mucositis; this medicine is also mentioned as a Persian traditional medicine in the Qanon fi al-Teb book. The anti-inflammatory and anti-bacterial efficacy of *M. sylvestris* in human oral cells in an *in vitro* condition has been previously shown [26]. However, recently it has been demonstrated that this herbal medicine has significantly lower efficacy than chlorhexidine in reducing gum inflammation caused by gingivitis [27].

Considering the anti-inflammatory effects of *M. sylvestris*, its effectiveness in healing wounds, and the lack of proper studies regarding managing RAS, the current study was conducted to discover the efficacy of *M. sylvestris* mucoadhesive tablets in the management of RAS.

Materials and Method

Participants and inclusion criteria

The study population consisted of patients referring to the dental faculty of Mazandaran University of Medical Sciences in 2024. The study duration was six months.

The inclusion criteria included patients with minor RAS who had aphthous lesions in the lips and buccal mucosa. The exclusion criteria consisted of those wearing dentures, taking antibiotics or immunosuppressive drugs, smokers, pregnant women, cases with allergic reactions, and patients who had syndromes characterized by aphthous-like lesions, such as Crohn's disease or MAGIC (mouth and genital ulcers with inflamed cartilage) syndrome, and Behçet's syndrome [28-29].

The sample size was calculated to be 42 patients (21 in the control group and 21 in the intervention group), based on Babaee *et al.*'s [30] investigation with the mean lesion diameter of 1.29±0.66 mm in the intervention group and 0.60 ± 0.69 mm in the control group, and considering the following equation (confidence level of 95%, the test power of 90%):

$$n = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2 * ({\sigma_1}^2 + {\sigma_2}^2)}{(\mu_1 - \mu_2)^2}$$

A total number of 42 patients were selected using the conventional sampling method. The intervention group included patients with RAS who received *M. sylvestris* mucoadhesive tablets, and the control group received mucoadhesive tablets containing placebo. Initially, patients were examined by an oral medicine specialist who was not the researcher of the study and minor aphthous lesions were confirmed. This study was designed as a parallel-group randomized clinical trial with a 1:1 allocation ratio. Random sequence generation was performed using a blocked randomization method with a fixed block size of two to ensure balanced group sizes throughout the enrollment process. The unit of randomization was the individual participant. A total of 42 participants were sequentially assigned unique identification numbers based on the order of enrollment, prior to any clinical examination or intervention. Allocation to the study groups was carried out using random allocation software. The randomization sequence was generated independently and was used to assign participants to one of the two study groups. To create a random sequence, codes A and B were generated by the software, where code A signified the intervention group and code B signified the control group for each individual. Finally, the codes were placed in a sealed envelope and the number of each patient was written on the envelope. As each patient was admitted, the head nurse of the dental clinic, opened the envelope and administered the designated treatment. The nurse of the dental clinic who was not the researcher of the study and did not have any information about the details of the study, handed over the tablets to the patients.

Developing mucoadhesive tablets

M. sylvestris flowers were purchased from a traditional herbal shop (Attari) and after identification, the specimen was deposited at the Herbarium of the Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran (MAZUMS-A1023). The flowers were extracted by maceration with ethanol. The resulting extract was concentrated by a rotary evaporator. The Folin-Ciocalteu assay was used to determine the total phenol content in the extract [17]. The standard calibration curve was prepared using various concentrations of gallic acid (6.25-100 µg/mL). The total phenol was expressed as milligram gallic acid equivalents per gram of dried extract.

M. sylvestris mucoadhesive tablet was produced in the Faculty of Pharmacy of Mazandaran University of Medical Sciences. The *M. sylvestris* flower was grinded and extracted with ethanol solvent by using maceration method. The resulting extract was concentrated with a rotary machine. Ultimately, a freeze dryer was used to ensure total drying and avoid any possible ingredient contamination. Subsequently, due to the mucilaginous properties of the extract, Aerosil® 200, (Merk, USA), was used to prepare dry and fine powder. Carbopol 974P, (Dae-Jung, South Korean), as bio-adhesive and biodegradable polymers was used. Also, we used Avicel® PH102 as disintegrant and to enhance the mucoadhesive effect. D-mannitol, (Merk, USA), was used as a diluent, a tongue coolant, and a sweetener agent. Finally, magnesium stearate, (Merk, USA), as lubricant was added. After weighing and mixing the extract, polymer and other excipients, the flowability of the prepared powder was evaluated based on Hausner ratio. Then the tablets were pressed with single punch eccentric tablet machine press. The detail of the formulation is presented in Table 1. In the control group the formulation of the tablets was mostly similar to the intervention group, just higher percentage of mannitol was added and the *M. sylvestris* extract was removed from the formulation.

Study protocol

The patients were asked to visit the dental clinic within the first 24 hours after observing aphthous lesions, and this time was considered the baseline. During the first visit, an informed consent and a questionnaire about their demographic information was completed by them. The patients were randomly divided into two groups.

Patients in the intervention group received *M. sylvestris* mucoadhesive tablets daily, which they had to apply thrice daily on their lesions. The patients received the necessary instructions, along with the recommendation to abstain from food and liquids for half an hour

Table 1: The detail of formulation

Ingredients	Extract	Aerosil® 200	Carbopol 974 p	Avicel® PH102	D-mannitol	Magnesium stearate
Amount(%w/w)	10	2	10	15	62	1

following its application. The same process was carried out in the control group. In the present study, both participants and the examiner were blinded; in a way that the participants did not know whether they were receiving *M. sylvestris* tablets or placebo. Also, the examiner was not aware of the treatment that patients had received, because both placebo and *M. sylvestris* tablets had similar packaging, and were handed over to the participants in sealed envelopes. Also, the examiner was not informed about the treatment that each patient had received.

A metal caliper was used to measure the lesions and the surrounding inflammatory halo on days zero (baseline), three, five, and seven in order to assess the lesions' healing [4].

The visual analogue scale was used as a guide to help the patients determine their pain intensity. Visual analogue scale is a numerical scale and includes a 10 cm line, showing 10 points from zero to 10; zero indicates no pain and 10 demonstrates the maximum pain. Patients utilized this numerical scale (e.g., one to ten) to rate the degree of pain and indicated the point on the scale that best described their pain intensity. Following each meal, patients recorded their pain intensity thrice daily in the questionnaire. Individuals were considered healed if they had lesions smaller than 1 mm and a pain score of one [29, 31].

Data analysis

Mean, standard deviation, and frequency distribution indices were used to describe the research samples. To examine the homogeneity of the two groups in terms of the qualitative variable (gender), the chi-square test was used, and the independent t-test was used for the quantitative variable (age). The Shapiro-Wilk test was used to check the normality hypothesis. To compare the two groups, an independent t-test was used in terms of pain intensity, and Mann-Whitney's non-parametric test was used for lesion diameter. To control simultaneous effects of time and group on lesions diameter generalized estimating equations analysis was used and repeated measures analysis of variance was performed for pain intensity. In the conducted tests, a significance level of less than 5% was considered, and SPSS 23 software was used for analysis.

Ethical consideration

The present study obtained ethical approval from the Ethics Committee of Mazandaran University of Medical Sciences (IR.MAZUMS.REC. 1402.664) and the Iranian clinical trial registration was done prospectively (IRCT20170430033722N5).

The current double-blind randomized clinical trial was conducted based on the *declaration of Helsinki*, Consolidated Standards of Reporting Trials (CONSORT) (Figure 1) [32]. Informed consent was obtained from the participants before any intervention.

Results

The present double-blind clinical trial was conducted studying 42 patients (24 female, 18 male) and all patients completed the study (Figure 1). The mean age of patients was 38.50± 12.29 years old. The findings of the independent t-test showed no significant difference between the mean age of intervention (37.81±9.73) and control (39.19±14.62) groups (*p* Value=0.999). Moreover, no significant difference was observed between the gender distribution in the control and intervention groups, and the gender distribution was homogeneous (*p*= 0.999). In both groups, the percentage of women was higher than men. There were no side effects or complaints about the mucoadhesives.

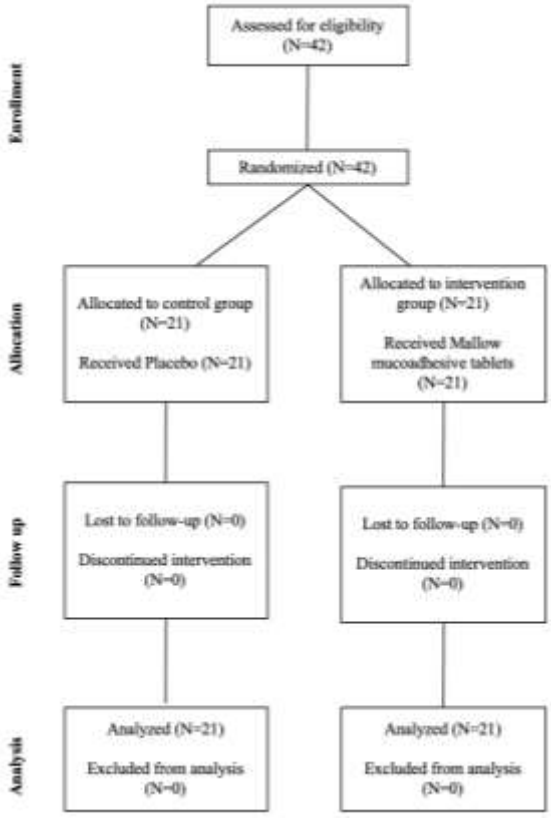

Figure 1: CONSORT flowchart

Table 2: Comparison of lesion diameter during study in both groups

Days	Main values (millimeter)		*p* Value	Difference to Baseline (millimeter)		*p* Value
	Intervention (Mean±SD)	Control (Mean±SD)	(Mann Whitney)	Intervention (Mean±SD)	Control (Mean±SD)	
0	6.29±1.52	4.43±1.43	0.001*	-	-	-
3	5.05±1.32	4.48±1.29	0.189	1.24±0.44	-0.05±1.20	<0.001*
5	3.71±1.23	2.81±1.44	0.048*	2.57±0.75	1.62±1.36	0.004*
7	2.07±1.05	1.29±1.19	0.034*	4.21±1.10	3.14±1.39	0.018*

The mean lesion diameter on days zero, three, five, and seven is reported in Table 2. The results showed that on all days, the lesion diameter in the intervention group was greater than the control group. The Mann-Whitney test suggested that this difference between the two groups was significant on all measurement days except day three (p= 0.189).

The diameter of the lesions on all measurement days was compared with the baseline. According to the test results in Table 2, the reduction of lesion diameter in the intervention group when comparing with the base-line, was significantly greater than the control group on all measurement days, p< 0.001, p= 0.004, and p= 0.018 on days 3, 5, and 7 of the study, respectively.

A T-test was used to analyze the pain intensity from day one to seven of the study and the results demonstrated lower pain intensity in the intervention group during the study. Considering the significance of the difference between the two groups at the baseline, the t-test was also used to analyze the difference in pain intensity to the baseline during all studied days. Until the fourth day of the study, higher pain reduction was observed in the intervention group, and on the second day this difference was significantly greater in the intervention group (p= 0.041) (Table 3).

Discussion

The present study evaluated the effectiveness of *M. sylvestris* mucoadhesive tablets in managing the inflammation and pain intensity of patients suffering from minor RAS. According to the results, the reduction of the lesion diameter was significantly greater in patients treated with *M. sylvestris* mucoadhesive tablets. In short-term the control group demonstrated better pain management but, in long-term the intervention showed greater efficacy. In overall, the intervention group experienced lower pain during the study.

A decoction or infusion of *M. sylvestris* flowers are traditionally used as mouthwash or gargle due to its anti-inflammatory properties against gingivitis, toothache and aphthous ulcers [33]. Rezaipour *et al.* [34] examined the effectiveness of an Iranian medicinal plant composition that included powdered Khatmi and *M. sylvestris* flowers in preventing radiation-induced acute mucositis in patients with head and neck cancer. The results demonstrated that the intervention group's average pain intensity and mucositis severity were not only significantly lower than those of the control group, but also these factors remained constant throughout the study and did not exhibit an upward trend.

Besides, Kovalik *et al.* [35] investigated the healing property of the stem and leaves of *M. sylvestris* with ethanol solvent on the palatal mucosal ulcer in rats and found that the extract of *M. sylvestris* did not show a significant reduction in ulcer size in comparison with the control group, and did not have a positive effect on the re-epithelialization of the palatal mucosa. The results of their study are contrary to the findings of the current study, which was conducted on the ethanol extract of the *M. sylvestris* flowers. The difference between the results of this study and our research may be attributed to different studied formulations, plant organ used, studied samples, moreover, the difference between the severity of the studied oral lesions.

Table 3: Comparison of pain intensity during study in both groups

Days	Main values (Score)		*p* Value	Difference to Baseline (Score)		*p* Value
	Intervention (Mean±SD)	Control (Mean±SD)	(t-test)	Intervention (Mean±SD)	Control (Mean±SD)	
1	7.46±1.30	6.43±0.97	0.006	-	-	-
2	7.13±1.55	5.54±1.28	0.001	0.33±0.97	0.89±0.72	0.041*
3	6.29±1.62	4.68±1.35	0.001	1.17±1.08	1.75±1.10	0.097
4	5.30±1.93	3.98±1.35	0.014	2.16±1.39	2.44±0.96	0.444
5	4.38±1.90	3.36±1.13	0.040	3.08±1.41	3.07±0.96	0.971
6	2.76±1.67	2.41±0.92	0.404	4.70±1.10	4.02±0.83	0.029*
7	1.32±1.33	1.33±0.91	0.969	6.14±1.09	5.10±0.81	0.001*

Ameri *et al*. [36] searched into how *M. sylvestris* -containing herbal compounds affected patients with head and neck cancer suffering from dry mouth. Radiation therapy, a treatment for head and neck cancer, causes several side effects such as erythema, edema, and pain of the oral mucosa. Additionally, it damages and irritates salivary glands, thus their function is reduced. This condition results in dry mouth. Dry mouth can also be the main factor causing inflammation by increasing the acidity of the saliva and higher growth of fungi and bacteria. In their study, 62 participants were investigated; one group consumed the composition, including *M. sylvestris*, while the other group used artificial saliva for four weeks. According to their research, the *M. sylvestris* -containing product was more effective than the control group in preventing dry mouth. According to this research, *M. sylvestris* is one of the mucilaginous plants that can improve dry mouth. The efficacy of this medicine may be related to its mucilaginous, anti-inflammatory, and analgesic properties.

In line with the current research, Pirbaluti *et al*. [37] investigated the wound-healing property of diethyl ether extract of *M. sylvestris* and pomegranate flowers in alloxan-induced diabetic rats. The study's findings demonstrated that the histological analysis of tissue taken from mice received *M. sylvestris* treatment on days 9 and 18 revealed a rise in collagen bands, an increase in fibroblasts, and a decrease in inflammatory cells. Comparing these results to the other groups indicated that *M. sylvestris* extract successfully induces wound contraction. Antioxidant properties of *M. sylvestris* provide evidence for improving wound healing.

Pharmacological effects of *M. sylvestris* can be justified from two perspectives; new research has revealed that it has antioxidant and immunomodulatory properties in addition to its ability to alleviate the irritation and inflammation of the mucous membrane covering oral cavity, throat, and stomach. Additionally, research has been done on antiseptic properties of *M. sylvestris*. Persian medical literature also suggests using this plant topically and systemically to relieve skin and mucosal inflammations and discomfort and mucous membrane swelling [34]. In a systematic review conducted by Mousavi *et al*. [18], anti-oxidant, anti-inflammatory, and wound healing activities of *M. sylvestris* was studied. They concluded that its anti-oxidant activity is attributed to the phenolic components and the anti-inflammatory properties is related to malvidin 3-glucoside. Additionally, they demonstrated that the ethanolic hydroalcoholic extract found in leaves of *M. sylvestris* enhances wound contraction and healing process in rats.

The oxidative and anti-oxidants components balance are essential factors for wound healing. High levels of reactive oxygen species (ROS) and oxidative stress disturb wound healing [4]. As anti-oxidant activity of *M. sylvestris* is shown in previous studies, we assume that the therapeutic effect of *M. sylvestris* may be attributed to analgesic, anti-inflammatory, anti-oxidant, and wound healing properties of this herbal medicine.

Phenols, flavonoids, and anthocyanins are the main bioactive compounds found in the flowers of this plant [38]. According to our results, the total phenol content of *M. sylvestris* flower ethanol extract was 11.95 ± 0.34 mg gallic acid equivalents/g dried extract. The anti-ulcer activities of *M. sylvestris* extracts have been reported in several studies which are partially attributed to its mucilage content [23, 37, 42]. Considering the sticky nature of the extract, it seems that part of the effect observed in the present study is related to the mucilage in the extract [39]. Rich in anthocyanins, the aqueous extract of *M. sylvestris L.* flower is frequently used to treat inflamed mucous membranes. There is little data on this species' overall chemical and phenolic contents. However, according to studies by Beghdad *et al.* [40] that examined the flower's antioxidant activity, phenolic content, and flavonoid content in a 96% ethanol solvent, *M. sylvestris* flowers are rich in phenolic and antioxidant compounds. Furthermore, Petkova *et al.* [41] showed that the *M. sylvestris* flower in a 70% ethanol solvent is rich in flavonoids and phenolic compounds, and the flower of this plant generally contains more soluble carbohydrates. Overall, the study's findings indicated that the *M. sylvestris* flower is a rich source of bioactive substances essential for a balanced diet for humans.

In a study conducted by Areesanan *et al.* [42] on the possible therapeutic effectiveness of *M. sylvestris* in managing dry-eye disease, findings demonstrated the efficacy of this plant by its anti-oxidant, wound healing, and anti-inflammatory properties. In this study, three tested preparations including polyphenol fraction, mucilage fraction, and flower extract inhibited ROS. Fur-

thermore, flower extract and polyphenol fraction were responsible for modulating immune cells signals thus, regulating inflammatory responses.

There are recommendations in the literature for using biological activity of *M. sylvestris* to treat and prevent inflammation due to its ability to control eicosanoid products, which include cytokines like interleukins (IL-1β, IL-6, IL-8), and granulocyte-macrophage colony-stimulating factor (GM-CSF) and prostaglandin, a pro-inflammatory mediator [43]. Phytochemistry evaluations suggest that quercetin, scopoletin, and malvidin 3-glucoside may be related to biological activity. Furthermore, research has indicated that multiple phenolic compounds in *M. sylvestris* may account for its potential antioxidant properties. Having such properties can make this plant a suitable candidate for managing chronic inflammatory diseases [43].

Mucoadhesive tablets are a good choice to treat oral lesions as they adhere to the lesions and provide medicines for more extended periods to the lesions. Furthermore, they cover lesions and prevent further traumas and infections. More studies with larger sample sizes and longer study periods are recommended. Furthermore, due to anti-inflammatory properties of *M. sylvestris* mucoadhesive tablets, studying the effectiveness of this substance on other oral inflammatory lesions may have favorable results. Our findings showed *M. sylvestris* mucoadhesive tablets have significant efficacy, however, due to the lack of similar studies studying this substance in the form of mucoadhesive tablets, comparing the results of the present study with other studies was impossible. Furthermore, the current study assessed one center, and its sample size was relatively small, which limits the generalizability of the findings. The study duration was short, and the long-term effects or the possibility of recurrence of aphthous lesions were not evaluated. The frequency of using the medicine was not directly controlled. However, we tried to remind participants to use the medicine through various means of communication. It seems that more studies are necessary to evaluate side effects and accurately assess the quality and stability of *M. sylvestris* mucoadhesive tablets formulation.

Conclusion

The results of the present study demonstrated that *M. sylvestris* mucoadhesive tablet reduces the pain and lesion diameter of aphthous lesions, thus results in faster healing of these oral mucosal lesions. It seems that antioxidant, anti-inflammatory, wound healing and analgesic properties of *M. sylvestris* are considerable on attaining the results. However, as this study was preliminary, more studies with larger sample size are required. Finally, by conducting more studies and obtaining favorable results, *M. sylvestris* mucoadhesive tablets are recommended to treat recurrent oral aphthous lesions.

Conflict of Interest

There is no conflict of interest among the authors.

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