BJOS
Brazilian Journal of Oral Sciences

Original Article

Volume 22
2023
e237560

Effects of honey-lemon spray on recurrent aphthous stomatitis comparing to Triamcinolone ointment; a randomized controlled clinical trial

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Editor: Dr. Altair A. Del Bel Cury

Received: November 20, 2021
Accepted: September 16, 2023

Aim: Recurrent aphthous stomatitis (RAS) is recurrent and painful diseases of the oral mucosa that can be very painful and annoying despite their small size. There is no definitive cure for this disease and the usual treatments are mainly based on pain control. The aim of this study was to investigate the effect of honey-lemon spray (mucotin) in the treatment of recurrent aphthous stomatitis. **Methods:** This study is a randomized controlled clinical trial conducted in 2020 at Zahedan University of Medical Sciences on 46 RAS patients. The participants were randomly assigned to the intervention (mucotin) or control groups (Triamcinolone ointment) equally (23 patients in each group). Patients were evaluated for the severity of pain and ulcer size. Evaluations were performed on days 0, 2, 7 of the treatment using VAS. Data were analyzed using ANOVA statistical test. **Results:** The inner aspect of the lower lip was the most common site of RAS in the participants (48.8%) and the lowest site went for hard palate (2.4%). Four items including pain, burning sensation, necrosis area, and erythematous area were evaluated in both groups. There was no significant difference in all parameters before the treatment period (day 0). The mean pain score, burning sensation, necrosis, erythematous areas were not different in days 0, 2 and 7 between groups respectively (p=0.849, p=0.105, p=0.917, p=0.442). **Conclusion:** Honey-lemon spray (Mucotin) and topical corticosteroid have similar effects in RAS treating, So Mucotin can be used as the first line of treatment for RAS lesions. This herbal medicine has no side effects.

Keywords: Oral ulcer. Therapeutics. Honey.

Introduction

Recurrent aphthous stomatitis (RAS) is the most common recurrent acute oral ulcerative condition. The incidence rate of this disease varies 5 to 25% of the population and it is usually more common in women[1,2]. RAS is known by recurrent, multiple, small, round ulcers with circumscribed margins, erythematous haloes, and yellow or grey floors[3]. The RAS lesions influence on the soft oral mucosal surfaces of the lips, cheeks, lateral and ventral tongue, upper and lower nonattached gingivae and sometimes the soft palate and throat. The lesions of RAS are painful, relating symptoms of oral function like chewing, swallowing and speech, so, affect quality of life significantly and interferes with daily activities[2,4]. They usually take 2–6 weeks to heal[5]. Although RAS is a common oral problem, and there are many investigations about clinical, immunologic, hematologic and microbiological aspects of it, but the etiology of RAS is not clear exactly and it is known as a multi-factor disorder[2,4,6].

The best management for RAS is to control the oral ulcers for the longest period with the least adverse side effects[5]. There is no approved curative therapy for RAS, accordingly, treatments are usually nonspecific and limited efficacy, such as topical agents like anti-microbial mouth rinses, analgesics, corticosteroids, systemic therapy, and laser therapy[7]. So, trying to investigate an effective medication which has no side effects is continued. It seems the best treatment for RAS is topical medication, because not only the medication can directly affect the surface of the aphthous, also reduces systemic side effects.

Honey as a food and a natural medicine has been used since ancient times. In Persian medicine (PM), as an old traditional and complementary medicine, honey has been recommended to treat ulcers particularly in mouth[6,8-10]. Also, studies have shown the beneficial effects of honey such as anti-cancer[11], anti-microbial[12], anti-oxidant, anti-inflammatory[13], anti-ulcer, cytoprotective[14], as well as decreasing and the prevention of mucositis and mouth sores[15]. Halim et al.[16] study suggests to use of topical honey as an alternative medication to patients with RAS. Nevertheless, some studies have mentioned that eating sweet food like honey can worse the dryness of the mouth and they recommend patients to avoid it[17]. In PM, it has been recommended to use lemon (*Citrus lemon*) juice with honey. Lemon has anti-microbial, anti-radical, anti-oxidant and anti-inflammatory effects[18,19]. Lemon juice also has a sour taste, which causes sweetness of honey be less and does not make dry mouth.

Considering there is a lack of reports that assess the effect of the honey-lemon on the healing of RAS, this study was undertaken to assess the effects of honey-lemon spray (called Mucotin as the name of the intervention drug in this study) on RAS compared to triamcinolone ointment.

Materials and Methods:

Trial Design

This study was a randomized, open-label, parallel, active-controlled trial which was done between November 2019 to September 2020 on the patients who had RAS and

attended at Zahedan University of Medical Sciences (ZUMS) dental clinic. In this trial, we evaluated the safety and efficacy of honey-lemon spray in management of RAS. The methodology of the study did not change after the study was started.

Drug preparation

For making the drug honey and lemon juice were bought from Mahyar Company, Tehran, Iran. Honey and lemon juice were mixed with the ratio of 2 to 1 (the amount of honey was twice as much as lemon juice) in the room temperature. It was then filtered to become smooth and even. The liquid was then poured in 30ml spray bottles and similar labels were stuck on all the spray bottles. The prepared sprays went through control check, they became standard based on one of its indexes. For the group control, Triamcinolone acetonide ointment 0.1% was bought from Behvazan Company and used for the control group.

Participants

Patients who suffered of RAS entered into the study if fulfilled the inclusion criteria. According to the study inclusion criteria, patients who were healthy, without systemic diseases (Diabetes mellitus, hyperthyroidism, hypothyroidism, etc.), older than 18 years that had 1-5 aphthous ulcers less than 24 hours with a size of less than 10 mm (if there were more than one aphthous ulcers, the average diameter of all ulcers were the criterion), were conducted to the study. If aphthous ulcers were adjacent to trauma due to sharp edge of tooth, broken restoration, orthodontic appliance or partial prosthesis, didn't enter to the study. All participants signed the informed consent form to enroll in the study. Patients who had a history of receiving nonsteroidal anti-inflammatory drugs (NSAIDs), oral antihistamines, antibiotics, systemic corticosteroids, immunosuppressive or any medication related to treatment of ulcer, pregnant women, as well as patients who did not follow up were excluded from the study.

Intervention

Eligible patients were divided into two parallel groups. Participants were randomly assigned to receive honey-lemon spray either five days as the experimental group, or triamcinolone ointment, as the control group. In experimental group, patients were asked to use honey-lemon spray four times daily (one hour before meals and twenty minutes before bedtime), in each time, used 2-3 puffs of honey-lemon spray on the surface of ulcers, for five days. In control group, patients were asked to use triamcinolone ointment four times daily (one hour before meals and twenty minutes before bedtime), in each time, used a thin layer of triamcinolone ointment on the surface of ulcers, for five days. In both groups, patients were asked to dry the ulcer site, then use medication. Moreover, patients were asked to avoid eating and drinking for half an hour after using the medication.

Outcomes

Patients were evaluated for the severity of pain and ulcer size. Participants seated on a dental unit and were exposed to light, and ulcer dimensions were evaluated by using

a periodontal probe. Evaluations were performed on days 0, 2, 7 of the treatment. Visual Analogue Scale (VAS) score was used in this study as the primary outcome measure. The subjective pain and burning sensation measurement tool was scored between 0 and 10 in terms of intensity (zero = no pain/burning sensation and 10 the most severe pain/burning sensation state). The secondary outcomes were total painless time, the duration of treatment period in days, and the safety profile.

Safety

All the participants were requested to inform any side effects of the medication. Also, the phone number of the researcher was available for all participates.

Sample size

Considering the study power as 80%, with 0.05 of type I error, an expected difference of 40% and 25% possibility of patients' exclusion from the study, the sample size was defined 23 in each group.

Efficacy index (EI)

Efficacy index (EI) was obtained based on the improvement in ulcer size and pain severity through the formula:

*100% [V2 or V7_V0)/V0)] EI=

V0 is related to the baseline data, and V2-V7 are related to the date of second and seventh days of intervention.

The following defined criteria were used to evaluate EI.

Complete recovery: EI = 100

Significant improvement: 100 ≥ EI > 70

Moderate recovery: 70 > EI ≥30

No improvement: EI < 30

Randomization

Convenience sampling was done from all patients with RAS referring to dental clinic of ZUMS. Forty-six eligible patients were randomized in two parallel groups. A statistician generated a randomized list by using a statistical software, via simple block randomization method. Then, the eligible patients were assigned into two groups by a researcher according to the randomized list.

Ethical issues

The trial was in compliance with the Declaration of Helsinki and also reviewed, approved, and monitored by the ethics committee of Zahedan University of Medical Sciences (License number: IR.ZAUMS.REC.1398.295). It was also submitted to the Iranian Registry of Clinical Trial (IRCT20191012045067N2). All the participants signed an informed consent form prior to their enrollment in the study.

Statistical methods

For comparing the amount of pain based on VAS, the ANOVA was used. P-values less than 0.05 were considered significant. All the data was analyzed using Statistical Package for the Social Sciences software, version 21 (SPSS Inc., Chicago, IL, USA).

Results

Sixty-one patients with RAS were assessed for eligibility in the study period. Of them, 46 participants meet the inclusion criteria as shown in figure 1 (CONSORT flowchart). The participants were randomly assigned to the intervention or control groups equally (23 patients in each group). The mean of age in the intervention and control groups were 27.86±11.59 years and 28.30 ± 10.63 years, respectively (p=0.378). Male/female ratio in the intervention group was 11/12 while, this was 12/10 in the control one (p=0.488). The inner aspect of the lower lip was the most common site of RAS in the participants (48.8%) and the lowest site went for hard palate (2.4%) although there was no difference between the groups in this regard (p=0.355).

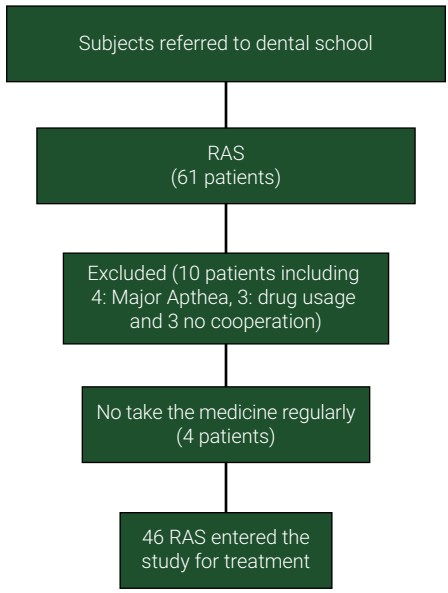

Figure 1. Flowchart of enrolling the subjects to this study

The results of the present study showed that the efficacy of honey-lemon oral spray was similar to the conventional treatment of triamcinolone in accelerating the healing process and pain relief of lesions. The baseline factors such as pain, burning, size of necrosis area and size of red area (erythema) before intervention in the two groups were not significantly different (p <0.05). On the second and seventh days after intervention, pain was significantly reduced in the both groups but, comparison between two groups showed that there was not any significant difference between them (p-value = 0.849 for 2nd day, and p-value = 0.986 for 7th day).

Four items including pain, burning sensation, necrosis area, and erythematous area were evaluated in both groups. There was no significant difference in all parameters before the treatment period (day 0). As shown in table 1, the mean pain score was not different in days 0, 2 and 7 between groups (p=0.849). Moreover, other assessed items showed the same results in the current study.

Table 1. Studied parameters before and after the treatment period in RAS patients

Parameter		Day 0 Mean ± SD	Day 2 Mean ± SD	Day 7 Mean ± SD	p-value
Pain	Int. group	4.14±2.99	1.0±1.95	0.0	0.849
	Con. group	4.80±2.66	1.40±1.43	0.0	
Burning sensation	Int. group	5.52±3.03	1.57±2.06	0.14±0.65	0.105
	Con. group	7.01±2.05	3.10±1.97	0.90±1.52	
Necrosis area (mm)	Int. group	2.79±1.94	1.74±1.97	0.12±0.38	0.917
	Con. group	3.20±1.81	1.95±2.06	0.25±0.54	
Erythematous area (mm)	Int. group	3.48±3.47	1.43±3.15	0.14±0.65	0.442
	Con. group	4.10±4.56	2.10±2.28	0.60±0.95	

Abbreviations: SD: standard deviation; Int.: Intervention; Con.: Control; mm: millimeter

Also, total painless sensation and treatment period were assessed for the intervention and control groups. Both records did not show any significant difference statistically (Table 2). Six patients recorded mild burning for seconds while using honey-lemon spray without any impact on their consistent usage. In the control group, 2 patients reported moderate itching sensation but, they regularly continued the medication.

Table 2. Painless sensation and treatment period in studied participants

Parameter	Intervention group Mean ± SD	Control group Mean ± SD	p-value
Total painless sensation (days)	2.76 ± 1.79	1.70 ± 1.25	0.231
Treatment period (days)	4.95 ± 2.85	4.50 ± 1.84	0.897

Discussion

This study was conducted to compare the effects of a honey-lemon spray that named Mucotin, with triamcinolone ointment on RAS. The results showed that both treatments were effective in reducing the pain, burning sensation, necrotic area, and erythematous area of RAS lesions. However, there was no significant difference between the two groups in terms of these parameters. This suggests that Mucotin and triamcinolone ointment have similar effects in treating RAS.

Ameri et al.[20] conducted a randomized and double-blind clinical trial to compare the effect of honey-lemon spray with benzydamine hydrochloride spray on radiation-induced acute oral mucositis in head and neck cancer patients. The results showed that honey-lemon spray significantly improved the mean score of radiation-induced oral mucositis, the amount of pain that patients experienced based on the VAS indicator, and the mean score of quality of life. The results also showed that honey-lemon spray had similar effects as benzydamine hydrochloride on the symptoms of radiation-induced acute oral mucositis. Our study is consistent with Ameri's study that demonstrated the beneficial effects of honey-lemon in the improvement of oral ulcers[20]. Ghalayani et al.[21] in a randomized double-blind study evaluated the efficacy of Punica granatum extract in the management of RAS and showed that Punica granatum extract in the form of oral gel (10%) may be beneficial in reducing RAS pain and has a positive effect in reducing the overall time period of complete healing. The results of Ghalayani's study are similar to our study, but in Ghalayani's study, the patient's quality of life was not examined[21].

Li et al.[22] in a systemic review of thirteen trials with a total of 1,515 patients investigated the efficacy and safety of topical herbal medicine remedies on RAS and results showed favorable benefits of the topical treatment of RAS with natural herbal medicines and few side effects during the clinical trial period. Also, Shavakhi et al.[23] in a systemic review of randomized clinical trials (2022), with thirty-three articles comprising 2,113 patients investigated the efficacy of herbal medicine in the treatment of RAS. The results of Shavakhi's study suggested medicinal plants and phytochemicals as effective and safe agents for the treatment of RAS, as well few adverse events were reported[23]. The results of our study confirm the results of Chun-Lei Li's[22] study and Shavakhi's[23] study.

It is likely that oxidative stress caused by systemic inflammation plays a major role in the pathogenesis of RAS[24]. A cell-mediated immune response mechanism is the probable immunopathogenesis of RAS which comprises activation of T cells and tumor necrosis factor α (TNF-α) by other leukocytes such as macrophages and mast cells[2]. Although finding the mechanism of honey-lemon spray was not a defined outcome for current study, the anti-inflammatory, antioxidant, anticancer, antibacterial, and wound healing effects of lemon and honey may be helpful in this regard[25,26]. Honey is a good source of amino acids, absorbable carbohydrates, and vitamins, expressly vitamin C, resulting in tissue regeneration and wound healing[16].

Decrease in pain in both groups was predictable as there were plenty of evidence supporting the effect of herbal products for this issue but, this item is controversial while reviewing a wide range of literature[6,27-30]. This controversy may be attributed to route of drug delivery, plant components, and dose of active agents. The dosage form could also play a role to the level of patients' response rate to pain stimuli. On the other hand, the superiority of honey against topical corticosteroid has been demonstrated in a randomized clinical trial. They showed that honey could reduce ulcer size, duration of pain in days, and erythema. Another pilot trial on a bee product showed effective reaction in decreasing the number of recurrences in patients suffering from RAS[6,31]. The findings were in line with the current study except for erythema which was not reviewed in our trial.

Assessment of total painless sensation in patients in days showed similar results between the intervention and control groups (p=0.897). This point was in accordance with Saleh et al.[32] which showed the efficacy of an herbal formula to decrease the pain sensation in patients with RAS. It is of worth mentioning that the treatments were not similar but, both of them showed a significant pain sensation reduction in a limited time period. This may support the evidence using herbal compounds for common problematic issues like aphthous ulcers in patients with poor dental hygiene and related problems.

Remarkable side effects are among important reasons causing insufficiency in the current therapeutic approach in the field of dental medicine[33]. In a systematic review on 25 randomized clinical trials assessing the pain reduction linked with RAS or decrease in pain duration, the rate of side effects was small[34]. This finding was in line with our study as there was no life-threatening side effects reported. Acceptable safety profile and the prescribed drug quality to improve quality of life are among important indices for choosing a new preparation in clinical setting. These findings may make the use of honey-lemon spray for the treatment of RAS more judicious.

Small sample size, subjective evaluation of pain in patients, absence of negative control, and lack of the mechanism of action are our limitations in the current trial. To the best of authors' knowledge, this is the first trial on the effect of a natural remedy (honey and lemon) for the treatment of RAS. The dosage form is unique in this regard, too. The similarity of findings for triamcinolone, as a potent drug for treatment of RAS, and honey-lemon spray to reduce pain, burning sensation, necrotic area, and erythematous extent is a promising point to investigate its efficacy in next randomized controlled trials with large populations. It is of more important considering its trivial charge, lower side effects, and patients' enthusiasm for natural products.

In conclusion, considering to the results, Mucotin (honey-lemon spray) and topical corticosteroid have similar effects in RAS treating, So Mucotin can be used as the first line of treatment for recurrent aphthous stomatitis lesions. This herbal medicine has no side effects.

Acknowledgements

The authors would like to extend their appreciation to the vice chancellor for research, Zahedan University of Medical Sciences for their financial support.

Data availability

Datasets related to this article cannot be shared at this moment because they are part of an ongoing research.

Author Contribution

Masoomeh Shirzaiy: Principal investigator, patients' evaluation

Ghazale Heydarirad: Drug preparation

Bakhshi Pour Samane: Patients' evaluation, patients' treatment.

All authors actively participated in the manuscript's findings, revised, and approved the final version of the manuscript.

References

1. Krawiecka E, Ślebioda Z, Szponar E, Kowalska A, Dorocka-Bobkowska B. Vitamin D status in recurrent aphthous stomatitis. Postepy Dermatol Alergol. 2017 Dec;34(6):612-17. doi: 10.5114/pdia.2017.69683.
2. Cui RZ, Bruce AJ, Rogers RS 3rd. Recurrent aphthous stomatitis. Clin Dermatol. 2016 Jul-Aug;34(4):475-81. doi: 10.1016/j.clindermatol.2016.02.020.
3. Scully C, Porter S. Oral mucosal disease: recurrent aphthous stomatitis. Br J Oral Maxillofac Surg. 2008 Apr;46(3):198-206. doi: 10.1016/j.bjoms.2007.07.201.
4. Edgar NR, Saleh D, Miller RA. Recurrent Aphthous Stomatitis: A Review. J Clin Aesthet Dermatol. 2017 Mar;10(3):26-36.
5. Chiang CP, Yu-Fong Chang J, Wang YP, Wu YH, Wu YC, Sun A. Recurrent aphthous stomatitis - Etiology, serum autoantibodies, anemia, hematinic deficiencies, and management. J Formos Med Assoc. 2019 Sep;118(9):1279-89. doi: 10.1016/j.jfma.2018.10.023.
6. El-Haddad SA, Asiri FY, Al-Qahtani HH, Al-Ghmlas AS. Efficacy of honey in comparison to topical corticosteroid for treatment of recurrent minor aphthous ulceration: a randomized, blind, controlled, parallel, double-center clinical trial. Quintessence Int. 2014 Sep;45(8):691-701. doi: 10.3290/j.qi.a32241.
7. Zeini Jahromi N, Ghapanchi J, Pourshahidi S, Zahed M, Ebrahimi H. Clinical Evaluation of High and Low-Level Laser Treatment (CO2vsInGaAlP Diode Laser) for Recurrent Aphthous Stomatitis. J Dent (Shiraz). 2017 Mar;18(1):17-23.
8. Bardellini E, Amadori F, Conti G, Majorana A. Clinical efficacy of a solution composed by sodium bicarbonate and alginate, aloe vera, propoli, chamomile, calendula and honey, in the treatment of minor recurrent aphthous stomatitis in children. Minerva Pediatr. 2016 Dec;68(6):507-9.
9. Heydarirad G, Choopani R. "Dry mouth" from the perspective of traditional Persian medicine and comparison with current management. J Evid Based Complementary Altern Med. 2015 Apr;20(2):137-42. doi: 10.1177/2156587214558596.
10. Aghamohamamdi A, Hosseinimehr SJ. Natural Products for Management of Oral Mucositis Induced by Radiotherapy and Chemotherapy. Integr Cancer Ther. 2016 Mar;15(1):60-8. doi: 10.1177/1534735415596570.
11. Ahmed S, Othman NH. The anti-cancer effects of Tualang honey in modulating breast carcinogenesis: an experimental animal study. BMC Complement Altern Med. 2017 Apr;17(1):208. doi: 10.1186/s12906-017-1721-4.
12. Almasaudi SB, Al-Nahari AAM, Abd El-Ghany ESM, Barbour E, Al Muhayawi SM, Al-Jaouni S, et al. Antimicrobial effect of different types of honey on Staphylococcus aureus. Saudi J Biol Sci. 2017 Sep;24(6):1255-61. doi: 10.1016/j.sjbs.2016.08.007.
13. Sarkar R, Ghosh A, Barui A, Datta P. Repositing honey incorporated electrospun nanofiber membranes to provide anti-oxidant, anti-bacterial and anti-inflammatory microenvironment for wound regeneration. J Mater Sci Mater Med. 2018 Mar;29(3):31. doi: 10.1007/s10856-018-6038-4.

14. Fazalda A, Quraisiah A, Nur Azlina MF. Antiulcer effect of honey in nonsteroidal anti-inflammatory drugs induced gastric ulcer model in rats: a systematic review. Evid Based Complement Alternat Med. 2018 Jul;2018:7515692. doi: 10.1155/2018/7515692.

15. Khanal B, Baliga M, Uppal N. Effect of topical honey on limitation of radiation-induced oral mucositis: an intervention study. Int J Oral Maxillofac Surg. 2010 Dec;39(12):1181-5. doi: 10.1016/j.ijom.2010.05.014.

16. Halim DS, Mahanani ES, Saini R, Marzuki Omar, bt Ibrahi NR, Alam MK. A comparison study on the effectiveness of local honey and salicylate gel for treatment of minor recurrent aphtous stomatitis. Int Med J. 2013;20(6):770-2.

17. Vissink A, Mitchell JB, Baum BJ, Limesand KH, Jensen SB, Fox PC, et al. Clinical management of salivary gland hypofunction and xerostomia in head-and-neck cancer patients: successes and barriers. Int J Radiat Oncol Biol Phys. 2010 Nov;78(4):983-91. doi: 10.1016/j.ijrobp.2010.06.052.

18. Dongmo PMJ, Tchoumbougnang FT, Boyom FF, Sonwa ET, Zollo PA, Menut C. Antiradical, antioxidant activities and anti-inflammatory potential of the essential oils of the varieties of Citrus limon and Citrus aurantifolia growing in Cameroon. J Asian Scient Res. 2013;3(10):1046-57.

19. Hamdan D, Ashour ML, Mulyaningsih S, El-Shazly A, Wink M. Chemical composition of the essential oils of variegated pink-fleshed lemon (Citrus x limon L. Burm. f.) and their anti-inflammatory and antimicrobial activities. Z Naturforsch C J Biosci. 2013 Jul-Aug;68(7-8):275-84.

20. Ameri A, Poshtmahi S, Heydarirad G, Cramer H, Choopani R, Hajimehdipoor H, et al. Effect of Honey-Lemon Spray Versus Benzydamine Hydrochloride Spray on Radiation-Induced Acute Oral Mucositis in Head and Neck Cancer Patients: A Pilot, Randomized, Double-Blind, Active-Controlled Clinical Trial. J Altern Complement Med. 2021 Mar;27(3):255-62. doi: 10.1089/acm.2020.0468.

21. Ghalayani P, Zolfaghary B, Farhad AR, Tavangar A, Soleymani B. The efficacy of Punica granatum extract in the management of recurrent aphthous stomatitis. J Res Pharm Pract. 2013 Apr;2(2):88-92. doi: 10.4103/2279-042X.117389.

22. Li CL, Huang HL, Wang WC, Hua H. Efficacy and safety of topical herbal medicine treatment on recurrent aphthous stomatitis: a systemic review. Drug Des Devel Ther. 2015 Dec 31;10:107-15. doi: 10.2147/DDDT.S96589.

23. Shavakhi M, Sahebkar A, Shirban F, Bagherniya M. The efficacy of herbal medicine in the treatment of recurrent aphthous stomatitis: A systematic review of randomized clinical trials. Phytother Res. 2022 Feb;36(2):672-85. doi: 10.1002/ptr.7332.

24. Tugrul S, Koçyiğit A, Doğan R, Eren SB, Senturk E, Ozturan O, et al. Total antioxidant status and oxidative stress in recurrent aphthous stomatitis. Int J Dermatol. 2016 Mar;55(3):e130-5. doi: 10.1111/ijd.13101.

25. Yaghoobi R, Kazerouni A, Kazerouni O. Evidence for Clinical use of honey in wound healing as an anti-bacterial, anti-inflammatory anti-oxidant and anti-viral agent: a review. Jundishapur J Nat Pharm Prod. 2013 Aug;8(3):100-4. doi: 10.17795/jjnpp-9487.

26. Klimek-Szczykutowicz M, Szopa A, Ekiert H. Citrus limon (Lemon) Phenomenon-A review of the chemistry, pharmacological properties, applications in the modern pharmaceutical, food, and cosmetics industries, and biotechnological studies. Plants (Basel). 2020 Jan;9(1):119. doi: 10.3390/plants9010119.

27. Kia SJ, Mansourian A, Basirat M, Akhavan M, Mohtasham-Amiri Z, Moosavi M-S. New concentration of curcumin orabase in recurrent aphthous stomatitis: A randomized, controlled clinical trial. J Herbal Med. 2020;22(2):100336. doi: 10.1016/j.hermed.2020.100336.

28. Giroh VR, Hebbale M, Mhapuskar A, Hiremutt D, Agarwal P. Efficacy of aloe vera and triamcinolone acetonide 0.1% in recurrent aphthous stomatitis: A preliminary comparative study. J Indian Acad Oral Med Radiol 2019 Jan-Mar;31(1):45-50. doi: 10.4103/jiaomr.jiaomr_203_18.

29. Deshmukh RA, Bagewadi AS. Comparison of effectiveness of curcumin with triamcinolone acetonide in the gel form in treatment of minor recurrent aphthous stomatitis: A randomized clinical trial. Int J Pharm Investig. 2014 Jul;4(3):138-41. doi: 10.4103/2230-973X.138346.

30. Babaee N, Zabihi E, Mohseni S, Moghadamnia AA. Evaluation of the therapeutic effects of Aloe vera gel on minor recurrent aphthous stomatitis. Dent Res J (Isfahan). 2012 Jul;9(4):381-5.

31. Samet N, Laurent C, Susarla SM, Samet-Rubinsteen N. The effect of bee propolis on recurrent aphthous stomatitis: a pilot study. Clin Oral Investig. 2007 Jun;11(2):143-7. doi: 10.1007/s00784-006-0090-z.

32. Saleh MF, Othman A, Ibrahim A. The Efficacy of essential oils (lavender oil and flaxseed oil) in treatment of recurrent aphthous ulceration. Indian J Public Health Res Devel. 2019;10(5):1325-9. doi: 10.5958/0976-5506.2019.01180.x.

33. Queiroz SIML, Silva MVAD, Medeiros AMC, Oliveira PT, Gurgel BCV, Silveira ÉJDD. Recurrent aphthous ulceration: an epidemiological study of etiological factors, treatment and differential diagnosis. An Bras Dermatol. 2018 Jun;93(3):341-6. doi: 10.1590/abd1806-4841.20186228.

34. Brocklehurst P, Tickle M, Glenny AM, Lewis MA, Pemberton MN, Taylor J, et al. Systemic interventions for recurrent aphthous stomatitis (mouth ulcers). Cochrane Database Syst Rev. 2012 Sep 12;(9):CD005411. doi: 10.1002/14651858.CD005411.pub2.