

Effects of Propolis and Persica Mouthwashes on Minor Aphthous Ulcers: A Comparative Study

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Abstract

Background and objectives: Recurrent Aphthous Stomatitis (RAS) is a common disease of the nonkeratinized oral mucosa characterized by painful ulcerations and inflammation, causing difficulty in eating, swallowing, and speaking. Symptomatic treatment is considered for this disease due to the ambiguity of the exact etiology. The beneficial therapeutic effects of Persica and Propolis mouthwashes led us to the objective of studying therapeutic potentials of these herbal mouthwashes.

Material and Methods: The present double-blind clinical trial was conducted on 40 patients with minor aphthous ulcers and no systemic disease, who were divided into two groups of 20 via random allocation (systematic random sampling). Each group received 15 drops of propolis or persica mouthwashes three times a day for 10 days. Pain intensity was recorded by measuring the score of Visual Analogue Scale (VAS) and the diameter of minor aphthous lesions (in mm) at three periods of before treatment, and on the second and sixth days after treatment. Data were analyzed by Mann-Whitney test.

Results: There was no significant difference between pain intensity and ulcer size before treatment and on the second day of treatment. The pain intensity on day 6 was significantly lower in Persica group ($P=0.045$) but no difference was observed in the mean ulcer size on day 6 between the two groups ($P=0.104$). The rate of pain relief ($P=0.031$) and reduction of ulcer size ($P=0.046$) were significantly higher in Persica group.

Conclusion: Propolis and Persica mouthwashes both reduce pain intensity and ulcer size in minor aphthous ulcers, and Persica showed a stronger potential to achieve these goals compared to propolis.

Keywords: Stomatitis, Aphthous [MeSH], Propolis [MeSH], Oral Ulcer [MeSH]

Highlights

Aphthous stomatitis is a multifactorial disease, the exact cause has not yet been determined.

Many drugs are currently used to treat aphthous stomatitis, most of which are chemical and have side effects. Therefore herbal medicine can be promising.

Introduction

Recurrent Aphthous Stomatitis (RAS) is a common disease that affects about 20% of the general population (1), and is a nonkeratinized oral mucosal disorder characterized by painful ulcerations and inflammation, causing difficulty in eating, swallowing, and speaking. The clinical symptoms of the disorder typically include irritation, itching, and local pain for 24-48 hours after the onset of ulcer formation. Aphthous lesions are distinctly round superficial ulcer with a necrotic center surrounded by erythematous haloes. Pain intensity decreases with re-epithelialization after four days (1, 3). The prevalence of RAS is slightly higher in women, and the duration of the ulcer is usually 7-10 days. Eighty percent of RAS cases occur before the age of 30 years (1-4).

Aphthous stomatitis is a multifactorial disease, which may be caused by trauma, infections, deficiency of folic acid and B-complex vitamins, immune factors, psychological stress and food allergens. Most research to date has focused on immune factors. However, the exact cause of RAS has not yet been determined and its treatment is challenging. Most treatments currently focus on symptomatic therapies, including analgesics, anesthetics, antiseptics, anti-inflammatory drugs, steroids, and sucralfate (5, 6).

Possible therapeutic goals for aphthous stomatitis includes alleviating the symptoms, reducing the number and size of ulcers and shortening the duration of disease (1, 3). Various clinical trials have been performed to treat RAS. Their results indicate the effect of chlorhexidine in reducing the

severity and duration of the disease, but not the frequency of ulcers, indicating the presence of an infectious agent for the cause of RAS. In addition, topical steroids have been shown to reduce the severity and duration of ulcers, indicating the involvement of the immune system in the development of aphthous stomatitis (1, 7). The effectiveness of any of these drugs has not been proven in all patients with RAS.

Persica is an herbal mouthwash containing the active ingredients of toothbrush tree, menthe, and yarrow. The most important ingredients are tannins, essential oils, calcium and chloride. Unlike other mouthwash solutions, this solution does not cause any side effects if swallowed and its use is unobstructed in children and pregnant women. The chemical compounds of Persica mouthwash include sodium chloride, silica, sulfur, fluorine, trimethylamine, vitamin C and resin, which together cause antimicrobial, antifungal, anti-plaque, and anti-caries properties of this plant (8). Previous clinical trials have shown that continuous use of the toothbrush tree due to the high level of chloride reduces dental plaque formation, prevents tooth discoloration and gingivitis, and the isothiocyanate compounds of this plant inhibit the growth of oral bacteria. In addition, high levels of available calcium increase mineralization and tooth strength (9-11).

Propolis is a Greek word that means to defend the city, and bees use it for purposes such as patching a hole in a hive, flattening the inner walls of the hive, and Mummification the bodies of insects trapped inside the hive and dead, and the bees are unable to get them out. In addition, propolis protects their colonies from diseases due to antiseptic effect and antimicrobial properties. Propolis is one of the most important bee products which is effective on bacterial growth and enzyme inhibition through inhibition of cell division and protein synthesis, and its effect on the bacterial cytoplasm. Therefore, propolis acts as a natural antibiotic and has no side effects compared to industrial antibiotics, so it can be considered as a suitable alternative. Flavonoids make up the bulk of the propolis resin and are responsible for most of the antioxidant, antibacterial, antiviral,

antifungal, anticancer, and anti-inflammatory properties of propolis. Ethanolic extract of propolis exerts anti-inflammatory and analgesic effects in rat models by inhibiting nitric oxide production. The results showed that even these anti-inflammatory and analgesic effects are equivalent to one 20 mg diclofenac tablet (12). Studies show that propolis has an inhibitory effect on various bacterial strains, some fungal species and protozoa, and a wide range of viruses (11, 13-15). According to the properties mentioned about propolis and persica, the aim of this study was to evaluate and compare the effect of propolis and persica mouthwashes in the treatment of minor aphthous ulcers and reduce their complications including pain and burning.

Materials and Methods

The current study was conducted on 40 patients including 26 males and 14 females aged between 18-56 years. Inclusion criteria were complaining of minor aphthous ulcers on the first day of appearing of ulcers which were approved by an alert clinician based on clinical examination. Exclusion criteria were any history of systemic disease including Bechet syndrome, Granulomatous diseases such as crohn disease and sarcoidosis, Celiac disease and HIV infection. Also, patients with disease or conditions affecting the healing process such as diabetes mellitus, metabolic diseases, any suppression of the immune system, smoking and alcohol consumers were not enrolled in the study (16, 17). The patients were divided into two groups of 20 via systematic random sampling. This study was single-blinded and patients and clinicians were unaware of type of the mouthwashes. Group A received Persica mouthwash (Poursina Pharmaceutical Co., Iran), the group B received propolis mouthwash containing 30% extract (Soren Tech Toos Company, Iran). The method of using mouthwashes was the same and the dosage for the treatment of ulcers was three times a day and each time 15 drops in 15 ml of water (three tablespoons), which was circulated in the mouth for 20 seconds and then discarded according to the manufactures instruction. The patient was

asked to use this mouthwash in the same way from the first day of appearing ulcers for 10 days. The intensity of pain and burning was recorded by measuring the score of Visual Analogue Scale (VAS) (18) and the diameter of minor aphthous lesions (in mm) was recorded using a periodontal probe at three periods before treatment, and on the second and sixth days after treatment. The intensity of pain and burning and the indicators set for healing time were assessed and recorded on days 0 (before treatment), 2 and 6 of treatment, and compared with the pre-treatment scales recorded for the two types of mouthwash (3). Changes in pain intensity and ulcer size scores on the second and sixth days of treatment were calculated as follows. The values of the second or sixth day of treatment were subtracted from the pre-treatment values and divided by the pre-treatment values and finally multiplied by 100 to calculate the percentage of changes (3, 19).

Statistical analysis

The data were analyzed in SPSS 22 software by Man-Whitney test, and $P < 0.05$ was considered a significant difference.

Results

There was no significant difference ($P=0.16$) in the mean pain intensity score before treatment between the two groups receiving propolis (4.0 ± 3.7) and Persica (3.0 ± 1.8) (Figure 1). There was no significant difference in the mean pain intensity score on the second day of treatment between the two groups receiving propolis (5.0 ± 0.5) and Persica (3.0 ± 4.4) according to P-Value ($P=0.29$) but the pain intensity on the sixth day of treatment in the Persica group (2.0 ± 6.0) was significantly lower than in the propolis group (3.0 ± 4.1) ($P=0.05$). There was no significant difference in the mean ulcer size before treatment between propolis (2.0 ± 1.3 mm) and persica groups (3.5 ± 0.2 mm) ($P=0.11$), indicating the homogeneity of the two groups (Figure 2). There was no significant difference in the mean ulcer size on the second ($P=0.97$) day of treatment between the two groups of propolis (2.3 ± 0.2 mm) and Persica (2.3 ± 0.2 mm). There was no

significant difference in the mean ulcer size on the sixth ($P=0.10$) day of treatment between the two groups of propolis (0.8 ± 0.3 mm) and Persica (2.0 ± 6.0 mm). The mean duration of ulcer healing in

the Persica (5.2 ± 0.2) group was significantly shorter than the propolis group (0.6 ± 0.3) ($P=0.03$) ([Table 1](#)).



Figure 1. Patient in Persica group before (right) and after (left) treatment.



Figure 2. Patients in Propolis group before (right) and after (left) treatment.

Table 1. The severity of pain and aphthous of aphthous lesions before treatment, second & sixth day of treatment with Propolis & Persica mouthwashes.

	Propolis	Persica	P-value
Pain severity score before treatment	4.0 ± 3.7	3.0 ± 1.8	0.155
Pain severity score in 2 nd day	5.0 ± 0.5	3.0 ± 4.4	0.287
Pain severity score in 6 th day	3.0 ± 4.1	2.0 ± 6.0	0.045*
Size of lesions before treatment(mm)	2.0 ± 1.3	3.5 ± 0.2	0.107
Size of lesions in 2 nd day	2.3 ± 0.2	2.3 ± 0.2	0.967
Size of lesions in 6 th day	0.8 ± 0.3	0.2 ± 0.1	0.104

The mean percentage of pain intensity reduction on the second day of treatment was not significantly different between the two groups of propolis (32.9 ± 0.54) and Persica (45.3 ± 3.7) ($P=0.07$), but the percentage of pain intensity reduction on the sixth day of treatment in the Persica (92.4 ± 3.2) group was significantly higher than in the propolis group (82.8 ± 3.2) ($P=0.03$) ([Figure 2](#) & [Chart 1](#))

The mean percentage of ulcer size reduction on the second day of treatment was not significantly different between propolis (22.9 ± 5.5) and Persica (34.1 ± 3.8) groups ($P=0.10$), but the percentage of ulcer size reduction on the sixth day of treatment in Persica (95.0 ± 2.4) group was significantly higher than propolis group (76.0 ± 8.9) ($P=0.05$), as seen in [Table 2](#) & [Chart 2](#). Data were reported as mean \pm SEM and analyzed statistically by Man-Whitney test at a significance level (*) of $P < 0.05$.

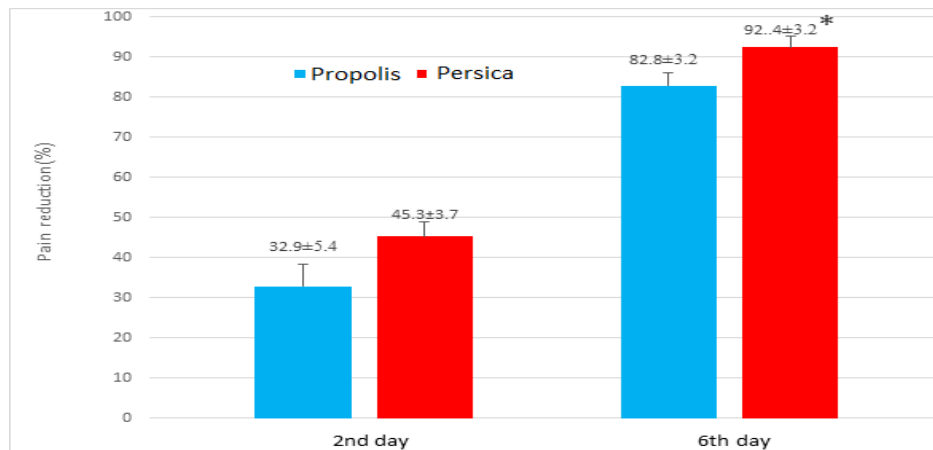


Chart 1. Changes in pain intensity in 2nd & 6th day of treatment in Persica & Propolis groups.

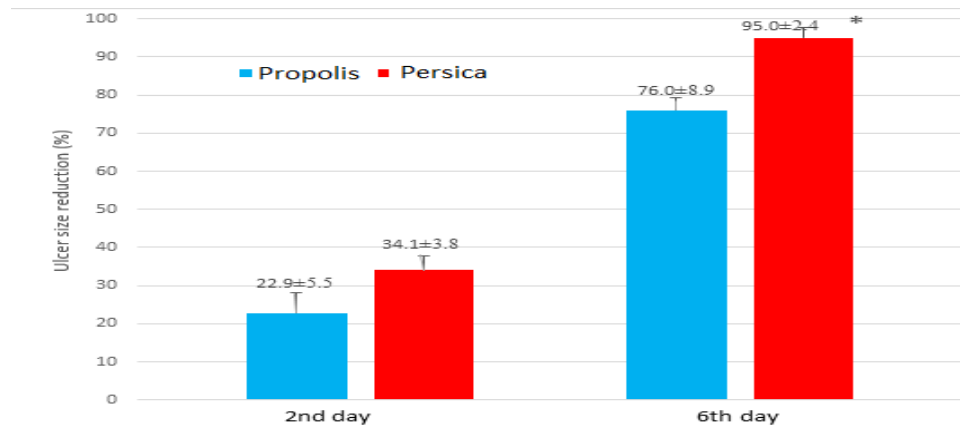


Chart 2. Changes in ulcer size in 2nd & 6th day of treatment in Persica & Propolis groups.

Table 2. Duration of healing and changes in pain intensity and size of the lesion.

	Propolis	Persica	P-value
Healing duration (days)	6.0 ± 0.3	5.2 ± 0.2	*0.029
Reduction of pain intensity on the 2 nd day of treatment (%)	32.9 ± 0.54	45.3 ± 3.7	0.066
Reduction of pain intensity on the 6 th day of treatment (%)	82.8 ± 3.2	92.4 ± 3.2	*0.031
Ulcers size reductonn in the 2 nd day of treatment (%)	22.9 ± 5.5	34.1 ± 3.8	0.103
Ulcers size reduction in the 6 th day of treatment (%)	76.0 ± 8.9	95.0 ± 2.4	*0.046

Data were expressed as mean \pm SD and analyzed by Man-Whitney statistical analysis and $P < 0.05$ was considered significant.

Discussion

Recurrent aphthous stomatitis is a common disease of the oral cavity that affects the mucosa and soft tissues, accounting for about 15-20% of the world's population. Many drugs are currently used to treat aphthous stomatitis, most of which are chemical and have side effects, and because aphthous lesions are recurrent, repeated use of chemical compounds can cause serious complications (20, 21). Many herbal and chemical agents have been applied in the treatment of aphthous stomatitis. In the study of Rajaei-Behbahani *et al.* tetracycline and *Myrtus communis* extract has been compared as treatment of aphthous ulcers. According to this study administration of Myrtex is more effective than tetracycline in reducing the severity of pain and irritation and also improving the quality of life of patients. So, Myrtex 5% based on the mentioned method was recommended for the treatment of minor aphthous (3). The effect of propolis with minimal side effects has been investigated in the treatment of a variety of inflammatory and ulcerative diseases such as contact dermatitis (1, 22-24). In the study of Koo *et al* on the effects of propolis on *Streptococcus mutans* growth and on glucosyltransferase activity it appeared that propolis can be a promising source of new agents that may prevent dental caries and other oral diseases (22). In another study which was conducted by Shoae *et al.* similar results were obtained and anti-microbial effects were seen (25). Niedzielska *et al.* also obtained similar results and it seemed that propolis be a beneficial alternative to preparations containing chlorhexidine or triclosan (26). Momen-Beitollahi *et al.* showed antimicrobial effects of propolis against oral pathogens, too (27). Akhavan Karbasi *et al.* in another study evaluated the efficacy of propolis mouthwash in the treatment of Chemotherapy-Induced Mucositis and positive results were seen (28). In the study of Samet *et al* in 2007 patients were asked to take systemic propolis. It was concluded that Propolis compared to placebo diminished the recurrence rate and improved the quality of life of patients with RAS

(29). Propolis has traditionally been used to treat oral ulcers. Several studies have reported the effectiveness of flavonoids in the treatment of gastrointestinal ulcers (30, 31) Casa *et al* evaluated the gastro protective effects of components of propolis. They concluded that propolis has positive effects in the healing of gastrointestinal ulcers (30). In the study of Boyanova *et al.* effects of propolis on *Helicobacter pylori* strains were assessed and strong and dose-dependent effects of propolis against *H.pylori* were seen (31). Propolis also has antimicrobial effects on oral pathogens. In the study of Sadrzadeh-Afshar *et al* effects of Chlorhexidine and propolis on oral pathogens was compared. It was concluded that propolis showed acceptable results against oral microorganisms but Chlorhexidine was more effective (32). This difference can be interpreted in this way that in this study antimicrobial effects of propolis was evaluated not effects of on the aphthous ulcer which was considered in the present study.

Persica drops have been administered to prevent dental calculus, tooth decay, and bleeding gums, and as a mouthwash and periodontal pain reliever. In the study of Darbandi *et al.* Persica and Irsha mouth rinses were compared and had similar effects on RAS. They both had reduced pain, and duration of healing and can be prescribed for treatment of RAS. These results are similar to our study (19). Studies show that the aqueous extract of yarrow has anti-inflammatory effects due to the presence of azulene in the yarrow essential oil. *Mentha* has analgesic and antiseptic potential due to its menthol content. Accordingly, the present study compared the effectiveness of honey-derived mouthwash, propolis, with Persica herbal mouthwash in the treatment of minor aphthous ulcers. The duration of treatment for aphthous stomatitis is between 10-14 days.

According to the results, the healing time was 6.0 days in the propolis group and 5.2 days in the Persica group. The percentage of ulcer size reduction on the sixth day of treatment was 76% in the propolis group and 95% in the Persica group. The percentage of pain intensity reduction

on the sixth day of treatment was 83% in the propolis group and 92% in the Persica group. Due to the short healing time of aphthous ulcers and pain intensity, two types of mouthwash are likely to be effective; according to results, Persica mouthwash had better effects than propolis mouthwash. Among the reasons for the better effect of Persica mouthwash in relieving pain, in the study of Abbasi et al that is in line with our study, it can be mentioned that Persica can increase salivary pH, which can justify the better analgesic effect of this mouthwash, (33). On the other hand, toothbrush trees and yarrow present in Persica contain large amounts of tannins, which can explain the analgesic and anti-irritation effects of this mouthwash due to its contractile effect on the tissue. In the study of Lewis et al. positive effects of components of persica in aspirin-induced erosions in gastric mucosa had been concluded (34). One of the etiologies of aphthous stomatitis is a weakened immune system that can occur due to an attack by bacteria and viruses. According to studies, Persica has antibacterial and antiviral properties that can strengthen the immune system and thus heal the aphthous ulcers by killing or reducing bacteria or viruses (19, 35).

According to the results, propolis mouthwash is effective in relieving pain and burning and shortening the duration of aphthous stomatitis, which based on studies and hypotheses can be attributed to the presence of caffeic acid and flavonoids in propolis through inhibiting the activity of lipoxygenase and cyclooxygenase and thus exerting an anti-inflammatory effect. It also boosts immune function by stimulating phagocytes, followed by cell-mediated immunity, which may explain the healing of aphthous stomatitis by improving one of its triggers, the weakened immune system. The various enzyme systems in propolis, such as B-complex vitamins, pro-vitamin A, arginine, and minerals such as copper, iron, zinc, and riboflavinoids, are involved in cell metabolism and collagen production, can cause ulcers to heal faster (32,36,37). Another reason for the pain relief and shortening time of ulcer healing in patients receiving propolis can be attributed to the mucosal

surface covering, which prevents aphthous ulcer irritation. Slightly less effective propolis drops than Persica mouthwash can be due to the following reasons: 1- Concentration less than the effective dose of propolis mouthwash and 2- Misuse of propolis mouthwash by patients. Furthermore, some limitations were lack of cooperation of some patients and failure to visit in due time which led to the removal of those patients and admission of new ones. Also, it is recommended to determine the effect of Propolis and Persica mouthwashes on inflammatory factors involved in the pathogenesis of aphthous ulcers such as IL-6 and TNF- α in future studies.

Conclusion

Generally, both types of mouthwash had shown acceptable results with no proven side effects, the results of the present study demonstrated that the Persica mouthwash had slightly better effects in relieving pain intensity, reducing ulcer size, and shortening the duration of the disease in patients with minor aphthous ulcers compared to the Propolis mouthwash. Of course, further studies in this area are suggested for more accurate results as well as comparisons of other Therapeutic modalities.

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Conflict of interests

There is no conflict of interest.

Ethical Approval

The participants willingly filled out the questionnaires and signed written informed consent. The study was approved by the Ethics

Committee of Aja University of Medical Sciences (code: IR.AJAUMS.REC.1398.111).

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