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A SYSTEMATIC REVIEW ON THE EFFECTIVENESS OF *PUNICA GRANATUM* EXTRACT FOR THE TREATMENT OF RECURRENT APHTHOUS STOMATITIS

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ABSTRACT: Recurrent aphthous Stomatitis (RAS) is a painful ulcerous condition that was conservatively treated using topical corticosteroids, immuno-suppressants, thalidomide with some potential risks and reactions. Considering this, herbal extracts are found to be a better alternative with very minimum side effects. *Punica granatum* (pomegranate) extract is one such flavonoid-containing food supplement with excellent antimicrobial, anti-inflammatory, and antioxidant properties used in preventing and treating RAS. The aim of the study is to assess the efficacy of *Punica granatum* extract in treating RAS. **Materials And Method:** Systematic review of randomized, clinical studies were searched using Pubmed, Scopus, Cochrane, Medline, Science direct, Lilacs, and Grey Literature. Research articles were collected using both electronic and manual search methods with a final record of nineteen. Several articles were scrutinized, redundant information was discarded, and based on the study pattern, interventions, outcomes, eight records were taken for consideration. **Results:** Four studies were refined in the systematic review with randomized, clinical studies meeting all criteria. These three were statistically significant and the other did not clearly state the outcome and statistical significance. **Conclusion:** *Punica granatum* extract shows good efficacy in treating RAS. But furthermore, clinical studies and trials have to be done to prove its sustainable and irrevocable existence in the commercial market.

INTRODUCTION: Recurrent Aphthous Stomatitis (RAS) is a very common inflammatory and ulcerative disease of the oral cavity, which is seen primarily due to alteration in the mucosal barrier. It is self-limiting ulceration with a recurrence rate of more than 50%, which is caused by many etiological factors like autoimmune disorders, viral associations, hereditary disorders, hematologic abnormalities.

Based on clinical features, RAS is classified into three types: minor (MiRAS), major (MaRAS), and herpetiformis (HeRAS). The most common type is minor, which is seen as well-demarcated round or oval small, recurrent, painful oral mucosal ulcers^{1, 2}. The size of minor aphthous ulcerative lesions ranges from 2 mm – 4 mm, which is commonly encountered in keratinized mucosa, cheeks, the floor of the mouth.

However, they are rarely seen in the gingiva and palate³⁻⁶. Sometimes it is associated with specific disorders like suite syndrome, Behcet's syndrome, Human immunodeficiency virus⁷. It is most commonly seen in young adults aged 20-30 years and rarely occurs in children.

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Due to many etiological factors, there is no definite treatment for recurrent aphthous stomatitis (RAS). Only symptomatic treatment is available till date, which is done by using several analgesics, local anaesthetics, anti-bacterial, anti-inflammatory and steroids. But most of these drugs have side effects. Hence, herbal extracts were found to be a better alternative with a higher efficacy rate.

All these extracts have antioxidant, antimicrobial properties, which help in treating oral ulcers and other inflammatory conditions. They reduce the discomfort/pain in a shorter period. People nowadays prefer natural medicine to synthetic drugs. Aloe vera extract, Yunnan baiyao (A herbal medicine), Chamomile tincture, Mouthwash containing leaves of Myrtis communis, Pomegranate extract have been the right choices of remedy for RAS⁸.

Punica granatum (Pomegranate) has high antioxidant potential due to the presence of tannins such as ellagic acid, gallic acid, flavonoids. Anthocyanin dye, an important phenolic compound of pomegranate, has been shown to possess anti-inflammatory effects⁹. So, it is widely used for treating various inflammatory conditions, cancer, CVS disease, dental plaque and ulcers¹⁰. Pomegranate extract is useful in accelerating the process of wound healing. The topical use of pomegranate preparations is shown to be effectively helpful in controlling inflammation, as well as bacterial and fungal counts in periodontal disease and Candida-associated denture stomatitis. So, it is particularly used in treating aphthous stomatitis due to its anti-inflammatory, antioxidant, antimicrobial, antiviral and antifungal properties¹¹⁻¹⁵.

Earlier practitioners tried treating RAS using pomegranate extract in comparison with placebo gel and oral trident paste by randomized clinical trial. This systematic review aims to analyze the efficacy rate of *Punica granatum* in treating recurrent aphthous stomatitis.

Objectives: To assess the effectiveness of *Punica granatum* in treating recurrent aphthous stomatitis.

MATERIALS AND METHODS:

Study Design: Randomized control study with inclusion of interventions.

Eligibility Criteria:

1. Randomized, double-blind clinical trials which were published
2. A clinical trial with a minimum sample size of 20 is included
3. Extracts of *P. granatum* in any forms were included
4. Full-text articles published in the English language were included.

Exclusion Criteria:

1. Articles published in other than English languages were excluded.
2. Articles that do not have access to the full text were excluded.
3. Case studies and reports were excluded.

Search Strategy: A systematic search on electronic databases like Pubmed, Scopus, Cochrane, Medline, Science direct, Lilacs, and Grey Literature for published articles on the effectiveness of *Punica granatum* extract for treating recurrent aphthous stomatitis was done. To collect relevant data, keywords like Pomegranate and Recurrent aphthous stomatitis were used, which resulted in more articles. Hence, the search was refined by changing the keywords as “*Punica granatum*” “Recurrent aphthous stomatitis” “Randomized controlled trail,” with Boolean operator as “and”.

Search Engines:

1. PubMed
2. Cochrane
3. SCOPUS
4. Science direct
5. Medline
6. Lilacs
7. Grey literature

RESULTS: Using the above search strategy, 19 articles were obtained, out of which 11 were screened that satisfied the eligibility criteria.

Following scrutinization furthermore, 4 articles were taken for the systematic review. Fig. 1 shows the Prisma diagram indicating the process of

selection of relevant articles from the available database.

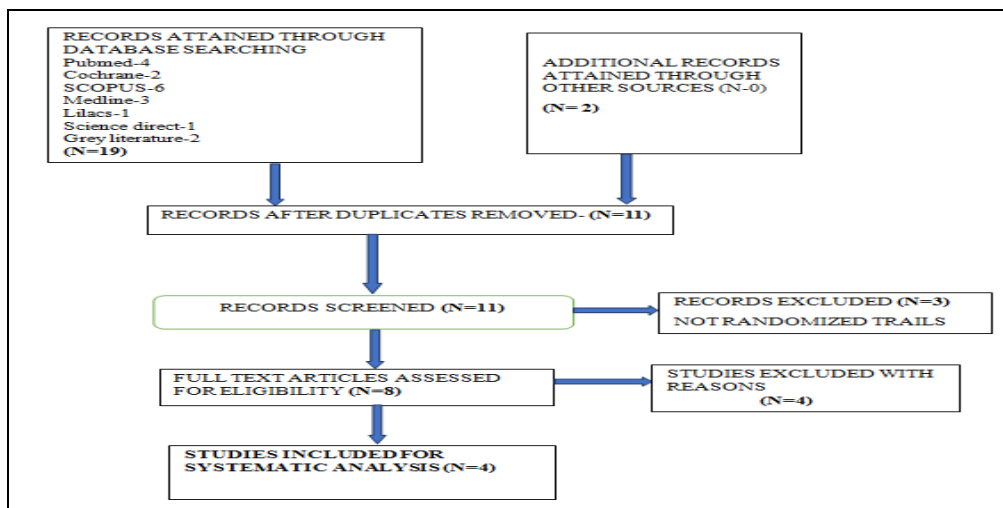


FIG. 1: PRISMA DIAGRAM FOR THE EFFECTIVENESS OF P.GRANATUMIN TREATMENT OF RAS

TABLE 1: CHARACTERISTICS OF INTERVENTIONS FOR INCLUDED ARTICLES IN THE SYSTEMATIC REVIEW

Author Name	Year	Sample Size	Patient Characteristics	Duration	Number (Cases/Controls)
Ghalayani et al. ¹⁶	2013	40	Patients with current recurrent aphthous stomatitis (RAS) on oral mucosa with well demarcated painful ulcer with diameter less than 1 cm surrounded by light red areola	1 week	Group 1: 20 (Pomegranate oral gel 3 times a day) Group 2: 20 (Placebo gel 3 times a day)
Gavanji et al. ⁷	2014	210	Patient with recurrent aphthous stomatitis with sizes of 1 mm to 4 mm and maximum lesion number of 5	10 days	Group A-C: 30 in each group (alcoholic extracts of <i>Punica granatum var. pleniflora</i> , <i>Punica granatum var. sweet alak</i> and <i>Punica granatum var. saveh black</i> mouthwash for about 10 minutes; 4 times a day) Group D: 30 (water extract of <i>Punica granatum var. pleniflora</i> mouthwash for 10 minutes; 4 times a day) Group E: 30 (water extract of <i>Punica granatum var. sweet alak</i> mouthwash for 10 minutes; 4 times a day) Group F: 30 (Water extract of <i>P. granatum of var. saveh black</i> mouthwash for 10 minutes 4 times daily) Group G: 30 (received placebo gel)
Darakhshan et al. ¹⁰	2019	56	Patients with current recurrent aphthous stomatitis of size ranging from 1 mm-5 mm.	1 week	Group A: 28 (pomegranate peel extract gel twice daily) Group B: 28 (placebo gel twice daily)
Tavangar et al. ¹⁷	2019	60	Patient with current recurrent aphthous stomatitis with a well demarcated painful ulcer with diameter less than 1 cm surrounded by light areola	Until ulcer heals completely (approx. 8 days)	Group A: 20 (Pomegranate gel 3 times a day of about 1cm in length on ulcer) Group B: 20 (Triadent oral paste 3 times a day of about 1 cm in length on ulcer) Group C: 20 (Placebo gel 3 times a day)

Table 1 shows the characteristics of intervention for all 4 studies. The efficacy of *Punica granatum* extract on recurrent aphthous stomatitis was compared with placebo gel. Also, one of the studies used trident oral paste as one of the control groups. The sample size, age of the patient, and duration of the intervention varied from one article to another. All the articles stated that the trial was done on

patients with recurrent aphthous stomatitis with a minimum diameter of 1mm, along with the complaint of pain. The duration of the intervention varied among all studies. Two of the studies showed a duration of one week and another study for about 10 days. The period of intervention was not clearly stated in one of the articles.

TABLE 2: OUTCOME DATA FOR INCLUDED ARTICLES IN THE SYSTEMATIC REVIEW

Author Name	Year	Effect Measure	Results
Ghalayani et al. ¹⁶	2013	The mean VAS score, the meantime for pain elimination, the meantime of complete healing were recorded on 0, 1, 3, 5, 7 days	The main intervention of this study was to use <i>P. granatum</i> gel on RAS, and the result of the intervention shows P-value <0.001, which was statistically significant
Gavanji et al. ⁷	2014	The degree of pain,time of pain stopping(hour) and final time of complete treatment recorded on 1, 2, 4, 6, 8, 10 days Also, the values of antioxidant activity of <i>Punica granatum</i> was recorded along with the daily changes of ulcer size.	The main intervention was the effect of <i>Punica granatum</i> on RAS. The result of intervention shows P-value <0.0001, which is significantly indifferent among gender but significantly different for water extracts more than alcoholic extract
Darakshshah et al. ¹⁰	2019	The ulcer size, the pain of the ulcer, healing duration of the ulcer were evaluated on 0, 3, 5, 7 days	The main intervention was the effect of pomegranate peel extract on RAS, and the result of intervention shows P-value <0.05, which was statistically significant
Tavangar et al. ¹⁷	2019	The duration of pain relief by visual analog scale, the duration of ulcer healing, the size of the ulcer were recorded on 0, 3, 5 days.	The main intervention was an effect of <i>Punica granatum</i> gel on RAS with comparison to triadent oral gel, and the result of the intervention shows P-value of 0.05, which was considered to be a significant level

Table 2 shows the outcome data for the effectiveness of *Punica granatum* extract on treating recurrent aphthous stomatitis in all four

studies. The outcome measure and P-value of various studies were explained. P-value <0.05 was considered to be statistically significant.

TABLE 3: BIAS ANALYSIS FOR INCLUDED ARTICLES IN THE SYSTEMATIC REVIEW

Author Name, Year	Random Sequence Generation	Allocation Concealment	Blinding of Outcome	Incomplete Outcome Data	Blinding of Participants and Personal	Selective Reporting	Judgemental Bias
Ghalayani et al. ¹⁶	+	-	-	-	-	-	-
Gavanji et al. ⁷	+	-	+	+	?	+	?
Darakshshah et al. ¹⁰	+	-	-	-	-	-	?
Tavangar et al. ¹⁷	+	-	?	-	?	-	?

Table 3 shows the bias analysis according to the Cochrane risk of bias analysis. Here (-) indicates low risk, (+) indicates high risk and (?) indicates unclear risk.

In such a scenario, we use several medications to treat the infection and relieve pain. Recurrent aphthous stomatitis (RAS) is a common ulcerative disease of the oral mucosa.

DISCUSSION: The dentist's role is always to keep the patient at ease from pain or any discomfort due to underlying medical/oral conditions.

Appropriate treatment procedures have been used to treat RAS. In recent days, herbal remedies have been found useful to reduce pain, burning sensation

and the mean healing period. *Punica granatum* (Pomegranate) has extreme medicinal value that almost all parts of it are used to treat certain medical conditions¹⁸. Usage of *Punica granatum* against RAS is mainly due to its antioxidant, antiviral, anthelmintic activities^{9,13,19}.

Many researchers have discussed the effectiveness of treating RAS with *Punica granatum* extract. Ghalayani et al.¹⁶ experimented with the usage of hydroalcoholic extract of *P. granatum* in treating the RAS. It is a double-blind, randomized placebo-controlled study using pomegranate gel (10%) for 20 patients and placebo gel for the other 20 patients. The mean time for pain elimination, mean-time for complete healing was assessed using VAS score wherein the values were taken periodically during 0, 1, 3, 5, 7 days and analyzed statistically. The literature shows the period was 3.4 days for PG gel and 5.9 days for placebo gel in case of pain elimination, whereas time period for complete healing was 5.3 days for PG gel and 8.6 days for placebo gel. This is because of the anti-inflammatory, anti-bacterial, antioxidant properties of pomegranate which makes it more effective in healing and pain elimination. Gavanji et al.⁷ compared the efficacy of alcoholic water extracts of various *Punica granatum*. This study was also based on a double-blind method showing the meantime for pain elimination, complete healing the antioxidant property, total phenolic content among various species of pomegranate. The result stated that alcoholic and water extracts of *Punica granatum* pleniflora, water extract of *Punica granatum* var sweet alak were effective among the species. Few patients found some discomfort in using alcohol extract. Thus, water extract of *Punica granatum* pleniflora was the most effective form of extract.

Darakhshan et al.¹⁰ used topical form of pomegranate peel extract (PPE) to control RAS using randomized double-blind placebo-controlled study in 56 patients. 28 patients received PPE gel, and other 28 patients received placebo gel for 1 week. The mean value of pain elimination, ulcer size, complete healing was recorded periodically during 0, 3, 5, 7 days. Ulcer healing duration was about 4.9 days for PPE gel and 7 days for placebo gel with p-value <0.001. No side effects were noted for PPE group. At the end of 7th day, the ulcer size

in PPE group was about 0.04 mm-0.41 mm for placebo group. Patients treated with PPE gel felt no pain from 7th day of treatment, and those treated with the placebo group experienced pain which was about 4.38% on the pain scale. Tavangar et al.¹⁷ treated RAS with *Punica granatum* mucoadhesive gel, placebo gel and triamcinolone paste as Group A, B, C. About 60 patients with no other systemic diseases were taken for this randomized, double-blind study and assessed periodically for pain elimination, complete healing.

The mean time for pain elimination for pomegranate gel, placebo group, triamcinolone paste group is 3.85, 5.25, 4.55 days, respectively, with the p-value of p<0.002 whereas mean-time for ulcer healing was found to be 5, 6.5, 5.75 days for the same with the p-value of p<0.05. Thus pomegranate extract was found to be far better than triamcinolone paste and placebo gel. In the current study, Bias analysis was done to assess the risk of bias in primary studies. The process of Random sequence generation, allocation concealment was considered to assess the risk of bias, and all research articles were scanned for any selective reporting, incomplete outcome data. The genuinity of blinding of the outcome, blinding of participants and investigating personal were assessed. Chances of judgemental bias are also evaluated. Hence, herbal remedies like pomegranate extract are economical, simple, safe and highly effective. But it needs some more advanced researches and works to confirm its usage and effectiveness commercially.

Limitations: The main point to consider is that samples taken for the study were not merely uniform in all these compared studies. Also, many articles were rejected since they didn't satisfy the required criteria

CONCLUSION: The role of *Punica granatum* in treating recurrent aphthous stomatitis is indispensable in view of herbal medications. It has magnificent properties ranging from antioxidant, anti-inflammatory, analgesics. Also, the side effects were bare minimal, which is a major advantage when compared to conventional steroids in the treatment of RAS. But further, more clinical studies and trials have to be done to make it an irrevocable commercial product.

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