

Treatment of Recurrent Aphthous Stomatitis by 100% Topical Pumpkin Seed Oil

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How to cite this paper: Sharquie, K.E., Noaimi, A.A. and Latif, T.M. (2017) Treatment of Recurrent Aphthous Stomatitis by 100% Topical Pumpkin Seed Oil. *Journal of Cosmetics, Dermatological Sciences and Applications*, 7, 324-335.

<https://doi.org/10.4236/jcda.2017.74029>

Received: June 3, 2017

Accepted: December 12, 2017

Published: December 15, 2017

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Abstract

Background: Recurrent aphthous stomatitis (RAS) is a major oral health problem, where its etiopathogenesis is not well understood. Accordingly, its therapy whether topical or systemic can induce clearance, but the relapse rate is high. **Objective:** To use 100% topical pumpkin seed oil in RAS as it has many actions as anti-inflammatory and antioxidant effects. **Patients and Methods:** This single, blind, clinical, therapeutic trial was conducted in the Department of Dermatology-Baghdad Teaching Hospital, Baghdad, Iraq, during February 2015-August 2016. Twenty-five patients with RAS were included in this work. After full history and clinical examination, the clinical diagnosis was established. Oral clinical manifestation index score (OCMI) was carried out before, during and after stopping therapy to assess the different parameters of this score. 100% Topical pumpkin seed oil was given two times daily for 3 months during which short term assessment for each patient was done by using OCMI before, after 4 days and after 8 days of therapy in addition to assessing the mean size of largest diameter of ulcers in each visit to evaluate the therapeutic efficacy of the therapy, while long term assessment of the OCMI was done every month for 3 months after starting of the therapy to evaluate the prophylactic effect of the therapy. After 3 months, pumpkin seed oil was stopped and assessment of OCMI was done monthly for another 3 months to evaluate the remission action of pumpkin seed oil. **Results:** Twenty-five patients were included in this study: 15 (60%) males and 10 (40%) females. While their ages ranged from 9 - 60 (27.48 ± 11.97) years. The mean of OCMI before pumpkin seed oil therapy was ranged from 9 - 15 (12.96 ± 1.42), while after the therapy the mean started to decline to lower level within 4 days of therapy and was statistically significant ($p < 0.0001$) and continued to decline significantly till the end of third month of therapy ($p < 0.0001$). The percent reduction was 79.30% after 4 days of therapy and 94.38% after 8 days

of therapy. After stopping therapy, the mean of OCMI started to increase, but it is remained statistically highly significant ($p < 0.0001$) at the end of third months after stopping therapy when it is compared with baseline mean of OCMI. **Conclusion:** Pumpkin seed oil had an effective therapeutic and prophylactic action against RAS, in addition, it induced remission for at least 3 months after stopping therapy. No local or systemic side effects were observed during the course of therapy.

Keywords

Recurrent Aphthous Stomatitis, Pumpkin Seed Oil, Therapy

1. Introduction

Recurrent aphthous stomatitis (RAS) is one of most common cause of oral ulceration that associated with a major health problem as its effect at least 20% of population all over the world [1]. There are many varieties of RAS like minor, major and herpetiform. Minor ulcers (80%) are less than one centimeter in diameter, usually heal within 2 weeks without scarring. Major ulcers (10%) usually one centimeter or more in diameter, take 10 - 40 days to heal and may leave scars, while herpetiform ulcers (10%) are cluster of dozens of smaller ulcers [2].

There are many theories have been suggested to explain its etiopathogenesis but the proper cause is still not fully explained [3]. These theories include: Genetic predisposition [4] [5] [6]; Immunological abnormalities [7]-[13]; Hematological abnormalities [14] [15] Infectious causes [16] [17] [18]; Hormonal factors [19] [20]; Smoking [21] [22] [23]; Trauma [1]; Stress [24]; and Food allergies [19].

There are many therapeutic agents that have been used in treatment of RAS aiming to reduce the frequency of ulceration and to minimize the discomfort that associated with disease activity but the doctors and patients aims are to have full recovery and even cure, these agents include: chlorhexidine [4]; topical honey [25]; 5% lactic acid mouth wash [26]; *Nigella sativa* oil [27]; tetracyclin and their derivative (doxycycline and minocycline) [28]; BCG vaccine [29]; oral dapsone and zinc sulfate [30]; oral steroid [31]-[34]; oral colchicine [35]; and oral clofazimine [31]. Recently, an Iraq study showed that oral isotretinoin had an effective therapeutic and prophylactic role in management of RAS [36].

Pumpkin has been reported in Holy Quran in story of the prophet of the God (Younis).

(In the name of Allah, most Gracious, most Merciful).

(But we cast him forth on the naked shore in state of sickness (145) and we caused to grow, over him, a spreading plant of gourd kind (146). AL-SAFFAT). (Holy Quran).

Pumpkin seed oils are good source of vitamins, minerals and anti-oxidants [37]. Active components include fatty acid, 19.4% saturated fatty acids (palmitic

acid and stearic acid), 80.7% unsaturated fatty acids (linoleic acid and oleic acid) [38], Tocopherol (β -tocopherol, γ -tocopherol, δ -tocopherol), carotenoids including β -carotene and lutein [39], Phytosterols or plant sterols [40], Amino acid Glutamic and aspartic acid, leucine, valine, phenylalanine, and tryptophan are among the amino acids identified [41]. It has many therapeutic activities like antioxidant activity [42] [43] [44], anti inflammatory [45], antimicrobial activity [46] [47], and anti carcinogenic effect [48].

Accordingly, the aim of present work is to use pumpkin seed oil as topical therapy for RAS aiming to find a new safe, effective treatment that could be much more helpful and cost effective than other therapies.

2. Patients and Methods

This is a single, blind, clinical, therapeutic trial to evaluate the effectiveness of 100% topical pumpkin seed oil in treatment and prophylaxis of recurrent aphthous stomatitis (RAS). Twenty-five Patients with RAS included in this study were those who attended Baghdad Teaching Hospital-Department of Dermatology in the period from February 2015 to August 2016.

Inclusion criteria: patients with RAS in the present work were those with early onset ulceration (less than 3 days duration) and had little or no benefit obtained from other conventional therapy in previous attacks and stopped their treatment at least two months before. Patients were requested to avoid the use of any medicaments throughout the trial.

The diagnosis of RAS was based on history and clinical examination. History was obtained regarding age, gender, occupation, history of disease, the recurrence rate, their general health and previous medical history and history of the same condition or other illness in the family. Also, they were asked about any aggravating factors including food, stress, trauma and smoking or associated symptoms. All patients were fully examined regarding shape, size and number of the lesions.

Investigations were done for all patients regarding: pathergy test, complete blood picture, ESR and HLA typing for HLA-B5, 51 and HLA-B27 to exclude patients with Behcet's disease and other internal causes of oral ulcerations. All patients were seen by ophthalmologists, Neurologist and Rheumatologist to exclude findings suggestive for Behcet's disease.

2.1. Drug Preparation

Pumpkin seed oil 100% was ready made in Iraq-Mousl, EMAD trade mark kept in a clean and tight container till usage.

Patients instructed to use pumpkin seed oil topically two times daily for 3 months. All patients instructed not take any other drug for their aphthous ulcer during the course of the study, and to return if they developed drug side effects. An oral clinical manifestations index (OCMI) [26] (**Table 1**), for each patient was calculated before, during and after therapy to assess the response to treatment.

Table 1. Oral clinical manifestation index.

Type	Scoring
Minor ulcer	1
Herpetiform ulcer	2
Major ulcer	3
Number of ulcers/attack	
1 - 3	1
4 - 6	2
7 - 9	3
9 - 12	4
More than 12	5
Duration of the attack	
1 - 4 days	1
5 - 8 days	2
9 - 12 days	3
More than 12 days	4
Frequency (attack/date)	
0 - 2 weeks	5
3 - 4 weeks	4
5 - 6 weeks	3
7 - 8 weeks	2
More than 8 weeks	1
Associated symptoms	
Uncomfortable	1
Painful, but not interfere with eating or swallowing	2
Interfere with solid feeding	3
Interfere with liquid feeding	4

2.2. Follow-Up

* *Short term assessment (The therapeutic effect of drugs):*

An assessment was performed for each patient on day 4 and 8 from starting therapy using OCMI with exclusion of the score of frequency of attacks since we are trying to evaluate the therapeutic efficacy. Also, the size of each oral ulcer was recorded before starting therapy and on day 4 and 8 after starting therapy, then mean size of ulcers was calculated for each patient on each visit. The size of ulcer was estimated depending on the largest diameter of the ulcer.

* *Long term assessment:*

The OCMI score was recalculated for each patient monthly for 3 months after starting the therapy to evaluate the prophylactic efficacy of 100% pumpkin seed oil and monthly for 3 months after stopping the drug to evaluate the remission

efficacy of 100% pumpkin seed oil.

2.3. Statistical Analysis

The data were analyzed, and ANOVA test was used to compare the means of OCMI before, after 4 days and after 8 days of therapy.

The response rate was estimated by calculating the percentage of change in the means of OCMI after 4 and 8 days of therapy from the baseline of mean of OCMI before therapy.

Also, ANOVA test was used to compare the means of OCMI before, after 1 month, 2 months and 3 months of therapy and to compare the means of OCMI before therapy, 1 month, 2 months and 3 months after stopping the therapy. P-value of less than 0.05 was considered to be statistically significant.

3. Results

3.1. Gender and Age

Twenty-five patients were included in this study: 15 (60%) males and 10 (40%) females. Their ages ranged between 9 - 60 years with a mean \pm SD of 27.48 ± 11.97 years. Family history was positive in 12 (48%) of patients.

Age distribution was clarified in the **Table 2** which revealed that higher frequency of patients with RAS involved in this trial in the third and fourth decades of life.

Regarding type of ulcer 20 patients (80%) had minor type and 5 patients (20%) had major type.

3.2. The Therapeutic Effect of Drug

3.2.1. The Effect of Drug on OCMI Score

The OCMI before therapy ranged between 9 - 15 with a mean \pm SD of 12.96 ± 1.42 , and the mean started to decline significantly to a lower level after 4 days of therapy to be 2.76 ± 1.50 , P value < 0.0001 . While after 8 days of therapy a significant lower level of data was recorded, and the mean was 0.72 ± 1.48 , which was statistically significant P value < 0.0001 (**Table 3**).

The percent reduction for mean of OCMI after 4 and 8 days of therapy from the baseline of mean before therapy, was $79.30\% \pm 10.80\%$ after 4 days of therapy and $94.38\% \pm 11.95\%$ after 8 days of therapy.

Table 2. The distribution of age.

Age (yrs.)	NO.	%
<20	5	20
20 - 29	9	36
30 - 39	7	28
40 - 49	3	12
>50	1	4
Total	25	100

3.2.2. The Effect of Drug on Mean Size of Ulcers

The mean size of ulcers before therapy ranged between 3 - 10 mm with a mean \pm SD of 6.20 ± 2.67 , and the mean started to decline significantly to a lower level within 4 days of therapy to be 0.72 ± 1.33 . P value < 0.0001 , and continued to decline till the 8th day of therapy to be 0.04 ± 0.20 , which was statistically significant P value < 0.0001 when compare with 4th day (**Table 4**).

While percent reduction for mean of size was $88.90\% \pm 24.89\%$ after 4 day of therapy and $99.56\% \pm 2.18\%$ after 8 days of therapy.

3.2.3. The Prophylactic Effect of Pumpkin Seed Oil during Three Months Therapy

Before therapy, OCMI was ranged between 9- 15 with mean \pm SD of 12.96 ± 1.42 . after pumpkin seed oil has been given, the mean of OCMI started to decline to be 1.24 ± 3.44 at the end of first month of therapy which was statistically significant (P value < 0.0001), then it continued to decrease to be 1.12 ± 3.11 at the end of second month and 0.84 ± 2.32 at the end of third month of therapy which were statistically significant (P value < 0.0001) (**Table 5**).

Table 3. The effect of pumpkin seed oil on OCMI of the ulcers.

Pumpkin seed oil 100%	OCMI		
	Range	Mean	SD
At day 0	9 - 15	12.96	1.42
At day 4	2 - 7	2.76	1.50
At day 8	0 - 6	0.72	1.48
P value < 0.0001			

Table 4. The effect of pumpkin seed oil on size of ulcers.

Mean size of ulcers	Range	Mean	SD
At day 0	3 - 10 mm	6.20	2.67
At day 4	0 - 4 mm	0.72	1.33
At day 8	0 - 1 mm	0.04	0.20
P value < 0.0001			

Table 5. The prophylactic effect of pumpkin seed oil on OCMI score during course of therapy.

OCMI score	Range	Mean	SD
At day 0	9 - 15	12.96	1.42
At month 1	0 - 11	1.24	3.44
At month 2	0 - 10	1.12	3.11
At month 3	0 - 7	0.84	2.32
P value < 0.0001			

3.2.4. The Remission Effect of Pumpkin Seed Oil during Three Months after Stopping Therapy

After stopping therapy, OCMI started to increase slightly to be 0.96 ± 3.33 at the end of first month after stopping therapy, but remained statistically significant (P value < 0.0001), then it continued to increase to be 3.80 ± 4.80 at the end of second month after stopping therapy which was statistically significant (P value < 0.0001), then it decrease to reach 3.16 ± 4.43 at the end of third month after stopping therapy (P value < 0.0001) (**Table 6**).

3.2.5. Side Effects

No side effects were noticed in all patients.

4. Discussion

Recurrent aphthous stomatitis (RAS) is one of the most common painful oral mucosal disease that probably afflicts at least 20% of population, present first in childhood or adolescence [1]. Multifactorial etiopathogenesis has been suggested to explain the cause of RAS but the exact etiology and pathogenesis still not well elucidated [3].

Despite numerous clinical trials, no medication gives completely reliable cure, Still some patients might get remission either as a result of therapy or spontaneously [30].

A large number of therapies both topical and systemic have been used in treatment of RAS, including tetracycline [28], topical honey [25], Lactic acid 5% mouthwash [26], BCG vaccine [29], *Nigella sativa* oil [27], dapsone and zinc sulfate [30], oral colchicine [30], oral isotretinoin [36], and oral clofazmine [31]. These therapies act through different mechanisms with variable success rate and most of them were associated with a variety of side effects.

Pumpkin seed oil are good source of vitamins, minerals and anti-oxidants [37], it has many therapeutic activities like antioxidant activity [42] [44], anti inflammatory [45], antimicrobial activity [46] [47], and anti carcinogenic effect [48].

The present study using topical pumpkin seed oil 100% showed a significant therapeutic and prophylactic effect in controlling RAS. The effect of this drug on OCMI was statistically significant after 4 days of therapy (P value < 0.0001) and

Table 6. The remission effect of pumpkin seed oil on mean of OCMI during three months after stopping therapy.

OCMI score	Range	mean	SD
At day 0	9 - 15	12.96	1.42
After 1 month	0 - 13	0.96	3.33
After 2 months	0 - 12	3.80	4.80
After 3 months	0 - 12	3.16	4.43
P value < 0.0001			

Table 7. Comparison between prophylactic effect of pumpkin seed oil, lactic acid mouth wash, zinc sulfate mouth wash and *Nigella sativa* oil.

OCMI Score	Pumpkin seed oil	Reduction in mean	Lactic acid MW	Reduction in mean	Zinc sulfate MW	Reduction in mean	<i>Nigella sativa</i> oil	Reduction in mean
At day 0	12.96		17.50		15.45		13.65	
At 1st month	1.24	11.72	6.40	11.1	9.45	6	10.95	2.7
At 2nd month	1.12	11.84	4.90	12.6	3.15	12.3	4.90	8.75
At 3rd month	0.84	12.12	4.10	13.4	4.00	11.45	7.35	6.3

remained statistically significant throughout the course of therapy at the end of third month, with response rate 79.30% after 4 days of therapy and 94.38% after 8 days of therapy.

After stopping therapy, the effectiveness of pumpkin seed oil continued and remained statistically significant ($p < 0.0001$) at the end of third month after stopping therapy, hence, pumpkin seed oil 100% had a remission act in addition to its therapeutic and prophylactic effect in RAS.

No local or systemic side effects were noticed because pumpkin seed oil is edible oil.

The mechanism of action pumpkin seed oil in treatment of RAS cannot be clearly explained, but probable mechanisms of action of pumpkin seed oil may be through its anti-inflammatory [45] and antioxidant actions [42] [44].

When pumpkin seed oil was compared with other studies pumpkin seed oil appeared to be more effective than lactic acid 5% mouth wash which showed response rate of 90.8% in one study, [28] and 69.16% in another study [49].

Also, this oil showed an effectiveness much better than 5% zinc sulfate mouth wash with response rate of 66.33%, and 100% topical *Nigella sativa* oil with response rate of 60.60% [27].

The prophylactic effect of pumpkin seed oil are comparable to 5% lactic acid mouth wash and 5% zinc sulphate mouth wash, and more effective than 100% *Nigella sativa* oil (Table 7).

5. Conclusion

The present work had shown that 100% pumpkin seed oil is a new effective therapeutic and prophylactic agent in management of RAS, in addition to inducing remission in patients with RAS in drug free time, with no local or systemic side effects.

Limitation of Study

Further numbers of patients are needed.

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