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EVALUATION OF THE EFFICACY OF TOPICAL PROPOLIS VERSUS MUCOADHESIVE MYCOPHENOLATE MOFETIL (MMF) IN THE MANAGEMENT OF SYMPTOMATIC ORAL LICHEN PLANUS

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ABSTRACT

Aim: To assess the potential impacts of propolis and mucoadhesive mycophenolate mofetil (MMF) on oral lichen planus.

Methodology: The research was performed on 30 individuals suffering from atrophic-erosive oral lichen-planus. And they were allocated into three groups; Group I: were managed with propolis 5% gel, Group II: were managed with Mycophenolate mofetil (MMF) 2% mucoadhesive and Group III (control group): were managed with triamcinolone acetonide 0.1%. The clinical progress was evaluated utilizing the Visual Analog Scale (VAS) for pain intensity and MOMI scale. The clinical parameters were recorded at the baseline and then every two weeks for two months.

Results: A substantial enhancement existed in all clinical results throughout the follow-up period when compared to the baseline ($P < 0.05$). There was non-significant variation among the among the groups at the end of the eight's week regarding VAS and MOMI scale ($P > 0.05$).

Conclusions: Propolis and MMF might be utilized as alternative treatment for the management of oral lichen-planus.

KEYWORDS: Oral lichen planus, mucoadhesive mycophenolate mofetil, propolis.

INTRODUCTION

Oral Lichen planus (OLP) is a chronic, mucocutaneous, inflammatory, immunological disease. [1] The oral manifestation happens more often compared to the cutaneous manifestation and commonly in females more than males and it is rare in children. Patients of all ages can be affected.[2]

Topical corticosteroid, such as triamcinolone acetonide has been the first line of treatment for several years, as it has lesser adverse impacts compared to systemic prescription. However, prescribing topical or systemic corticosteroids for a long time has many adverse impacts like potential adrenal insufficiency, candidiasis, diabetes mellitus,

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hypertension, and gastrointestinal diseases.[3] So it is meaningful to search for alternative therapeutic approaches**.**

Propolis has attracted a lot of attention recently. It is a resinous, organic, sticky material that honeybees gather from plant leaves, sap, and buds and combine with produced bee's wax [4] It is additionally referred to Russian penicillin and has been utilized for many years in traditional medicine.[5]

Propolis contains a very high concentration of bioflavonoids, which have anti-inflammatory, anti-fungal, anti-bacterial, and anti-viral activities.[4] Because of these characteristics, researchers have been examining its effectiveness in treating a variety of oral disorders, including OLP, oral candidiasis, denture stomatitis, recurring aphthous ulcers, radiation mucositis, and herpes labialis.[6]

On other way, muco-adhesive myco-phenolate mofetil (MMF), a precursor of myco-phenolic acid (MPA), a substance that inhibits of inosine-monophosphate-dehydrogenase (IMPDH), has become an acceptable substitute to corticosteroid therapy for individuals with autoimmune vesiculobullous conditions in order to reduce their dosage and adverse reactions. In general, it is a well-tolerated immunosuppressive drug with fewer nephrotoxic, hepatotoxic, and neurotoxic effects than other immunosuppressive drugs.[7]

Based on the fact that OLP is considered an autoimmune disease we carried out this work to assess the efficiency of topical-propolis as a natural product and MMF as a synthetic product versus corticosteroids which is the treatment of choice in the treatment of symptomatic OLP.

MATERIALS AND METHODS

Study Setting

The participants were selected from the patients attending Periodontology and Oral Medicine Department, Faculty of Dentistry, Tanta University. Informed written approval were obtained by the individuals participating in the study, after they had received all explanations about the materials used and methodology. This investigation was conducted in accordance with the ethical standards set out in the Helsinki declaration regarding experimenting on humans and following consent from Research Ethical Committee of the Faculty of dentistry, Kafr El Shiekh University (MKSU22-12-1)

Sample Size Calculation:

The sample size for this study was calculated according to Arkin, 1984 using the following equation:

$$N= \frac{(Za)^2 *(SD)^2}{(d)^2}$$

N= Total sample size

Zα= Is standard normal variate and its equal 4.7

SD= Standard deviation of variable

d= Absolute error or precision

Zα	SD	d
3.0	2.1	2

The criteria used for sample size calculation were as follows:

-95% confidence limit -82% power of the study

Total sample size $n = \frac{(3.0)^2 *(2.1)^2}{(2)^2}$

= 9.92 ≈ 10 patients in each group, with total 30 patients

Study Design:

This work was performed as a controlled, randomised, clinical-trial.

Patient Selection:

A total of 30 patients suffering from pain and/or burning sensation due to histologically and clinically confirmed (a network of white lines that

are slightly elevated and lace-like - Wickham striae) symptomatic OLP (erosive or ulcerative) were selected based on the following criteria for inclusion: female or male, ages ranged from 25 to 60 years old, medically free (no current systemic medical problem), non-pregnant, non-lactating, nonsmoker, hadn't receive any therapy in the past for the illness and has no prior use of medications that might cause a lichenoid response, (anticoagulant treatment or NSAIDs) for at least the previous five days.

Study groups and Treatment strategy:

The selected participants were divided randomly using sealed envelopes into three groups, 10 each:

Group I: Ten individuals were instructed to place 5% propolis gel* on the lesion (on sterile gauze after good dryness) twice daily for 8 weeks.

Group II: Ten individuals were instructed to place 2% MMF** muco-adhesive on the lesion (on sterile gauze after good dryness) twice daily for 8 weeks.

Group III (control group): Ten patients were instructed to place triamcinolone acetonide 0.1% twice per day for 8-week period.

Each participant received instructions to use the study drugs twice a day, prior to bedtime and another time following the main meal, and avoid drinking, eating, or speaking for at least thirty minutes following applications.

Clinical Assessment:

1-A visual analogue scale (VAS) was used to measure the intensity of the pain:

Each time they visited, participants were required to evaluate their level of discomfort using the following scale: 0 = no pain, 1 = minor pain, 2 = moderate pain, and 3 = severe pain. At follow-up appointments, participants were asked to mark the scale, which allow the collection of the patient's own assessment without intervention from or interpretation by the clinical researchers. [10]

2- Modified oral mucositis index (MOMI):

A semi-quantitative scale (MOMI), [11] validated for evaluation of clinical symptoms of OLP, was used to assess the clinical signs of OLP at baseline. erosive and atrophic alterations were measured during an oral examination depending on their severity and the number of locations they affected.

Erythema intensity was measured using a scale from 0 to 3:

0 represents normal.

1 indicates a little erythema.

2 denotes moderate erythema

3 indicates significant erythema.

The ulceration score was determined by the ulceration's area:

0 indicates no ulcers

1 = 0 to 0.25 cm^2.

2 = 0.25 to 1 cm^2

3= ≥1 cm^2.

All patients underwent baseline (pre-treatment) evaluations, as well as follow-up visits every other week at the second (visit 1), fourth (visit 2), sixth (visit 3), and eighth (visit 4) weeks. Each visit's score was statistically compared to the starting point. The numerical variations among baseline and visit ratings show the clinical and symptomatic improvements.

* Propolis: prepared according to Joshy et al., (2018). 8
** (MMF): prepared according to Samiee et al., (2020). 9
*** triamcinolone acetonide : (Adcortyl, Bristol-Myers Squibb, Anagni, Italy).

Statistical analysis of the data:

With the aid of the IBM SPSS software programme version 20.0 (IBM Corp, Armonk, NY), data was input into the computer for analysis. The Shapiro-Wilk test was used to determine the normality of continuous data. The range (minimum and maximum), mean, standard deviation, and median were used to represent quantitative data. For comparisons among more than two examined groups, apply the Kruskal-Wallis test for quantitative parameters with abnormally distributed distributions. Friedman test for quantitative parameters with abnormal distributions, Post Hoc Test (Dunn's) for pairwise comparisons, and comparing more than two periods or stages. The significance of the obtained results was judged at the 5% level

RESULTS

In this study that included 30 subjects diagnosed with symptomatic OLP (erosive or ulcerative), fulfilling the inclusion and exclusion criteria. No adverse effects or discomfort at the sites of application of the tested material observed throughout the study period.

All patients showed improvement in all clinical outcomes throughout 8 weeks of treatment Figure (1). Intragroup results for the 3 groups showed that, VAS scores and intensity scores for erythema started to decrease at 2 weeks of drug application but with no significant variation as compared to baseline ($P > 0.001$). The scores continued to decrease at 4, 6 and 8 weeks and there was a significant variation as compared to baseline ($P < 0.05$). (Tables 1a & 2a)

Regarding, the intensity score for ulcerations in groups II and III, it started to decrease at 2 weeks of drug application but without substantial variation as compared to baseline ($P > 0.001$). While in group I treated with propolis there was a great significant reduction at 2 weeks ($P < 0.05$). The scores continued to decrease at 4, 6 and 8 weeks with a substantial variation as compared to baseline ($P < 0.05$) for all the studied groups. (Tables 3a)

Comparing the three studied groups, a significant improvement was existed in all clinical results throughout the period of follow-up ($P < 0.05$ for

Table (1a): Comparison between the three studied groups according to VAS

Visual analog scale (VAS)	Group I (n = 10)	Group II (n = 10)	Group III (n = 10)	H	p
Baseline					
Mean ± SD.	2.9±0.32	3±0	3±0	2.00	0.368
Median (Min. – Max.)	3 (2–3)	3 (3–3)	3 (3–3)		
2 weeks					
Mean ± SD.	1.6±0.84	1.6±0.70	1.6±0.84	0.104	0.950
Median (Min. – Max.)	2 (0–3)	2 (0–2)	2 (0–2)		
4 weeks					
Mean ± SD.	0±0	0±0	0±0	0.0	1.000
Median (Min. – Max.)	0 (0–0)	0 (0–0)	0 (0–0)		
6 weeks					
Mean ± SD.	0.10±0.32	0±0	0.30±0.48	3.904	0.142
Median (Min. – Max.)	0 (0 – 1)	0 (0–0)	0 (0–1)		
8 weeks					
Mean ± SD.	0.10±0.32	0.10±0.32	0.30±0.67	0.672	0.715
Median (Min. – Max.)	0 (0–1)	0 (0–1)	0 (0–2)		

***SD:* Standard deviation** ***H: H for* Kruskal Wallis test,**

p: p value for comparing between the studied groups.

all). No substantial differences were existed among the groups under the study at the end of the eight's week regarding VAS and MOMI scores (P > 0.001). (Tables 1b, 2b & 3b)

Intergroups findings revealed a non-statistical variation among the three groups at 2, 4, 6, and 8 weeks follow-up period as (P ≥ 0.05) (Tables 1b, 2b & 3b)

TABLE (1b) Comparison between the different studied periods according to VAS

Visual analog scale (VAS)	Baseline	2 weeks	4 weeks	6 weeks	8 weeks	Fr	p
Group I (n = 10)							
Mean ± SD.	2.9±0.32	1.6±0.84	0±0	0.10±0.32	0.10±0.32	34.733*	<0.001*
Median (Min. – Max.)	3 (2–3)	2 (0–3)	0 (0–0)	0 (0 – 1)	0 (0–1)		
p_0		**0.104**	**<0.001***	**<0.001***	**<0.001***		
Group II (n = 10)							
Mean ± SD.	3±0	1.6±0.70	0±0	0±0	0.10±0.32	37.333*	<0.001*
Median (Min. – Max.)	3 (3–3)	2 (0–2)	0 (0–0)	0 (0–0)	0 (0–1)		
p_0		**0.090**	**<0.001***	**<0.001***	**<0.001***		
Group III (n = 10)							
Mean ± SD.	3±0	1.6±0.84	0±0	0.30±0.48	0.30±0.67	34.591*	<0.001*
Median (Min. – Max.)	3 (3–3)	2 (0–2)	0 (0–0)	0 (0–1)	0 (0–2)		
p_0		**0.056**	**<0.001***	**<0.001***	**<0.001***		

***SD:* Standard deviation** **Fr*: Friedman test, Sig. bet. periods was done using* Post Hoc Test *(*Dunn's)**
p: p value for comparing between the studied groups p_0***: p value for comparing between* Baseline *and each other group***
****: Statistically significant at p ≤ 0.05***

TABLE (2a) Comparison between the three studied groups according to intensity score for erythema

Intensity score for erythema	Group I (n = 10)	Group II (n = 10)	Group III (n = 10)	H	p
Baseline					
Mean ± SD.	3±0	3±0	3±0	0.0	1.000
Median (Min. – Max.)	3(3–3)	3(3–3)	3(3–3)		
2 weeks					
Mean ± SD.	1.5±1.1	2.1±0.74	1.6±1.1	1.917	0.384
Median (Min. – Max.)	1.5(0–3)	2(1–3)	2(0–3)		
4 weeks					
Mean ± SD.	0.10±0.32	0.10±0.32	0.10±0.32	0.0	1.000
Median (Min. – Max.)	0(0–1)	0(0–1)	0(0–1)		
6 weeks					
Mean ± SD.	0.10±0.32	0±0	0.10±0.32	1.036	0.596
Median (Min. – Max.)	0(0–1)	0(0–0)	0(0–1)		
8 weeks					
Mean ± SD.	0.20±0.63	0±0	0.20±0.63	1.036	0.596
Median (Min. – Max.)	0(0–2)	0(0–0)	0(0–2)		

SD: Standard deviation H: H for Kruskal Wallis test, p: p value for comparing between the studied groups

TABLE (2b): Comparison between the different studied periods according to intensity score for erythema

Intensity score for erythema	Baseline	2 weeks	4 weeks	6 weeks	8 weeks	Fr	p
Group I (n = 10)							
Mean ± SD.	3±0	1.5±1.1	0.10±0.32	0.10±0.32	0.20±0.63	32.203*	<0.001*
Median (Min. – Max.)	3(3–3)	1.5(0–3)	0(0–1)	0(0–1)	0(0–2)		
p_0		**0.090**	**<0.001***	**<0.001***	**<0.001***		
Group II (n = 10)							
Mean ± SD.	3±0	2.1±0.74	0.10±0.32	0±0	0±0	38.800*	<0.001*
Median (Min. – Max.)	3(3–3)	2(1–3)	0(0–1)	0(0–0)	0(0–0)		
p_0		**0.322**	**<0.001***	**<0.001***	**<0.001***		
Group III (n = 10)							
Mean ± SD.	3±0	1.6±1.1	0.10±0.32	0.10±0.32	0.20±0.63	32.826*	<0.001*
Median (Min. – Max.)	3(3–3)	2(0–3)	0(0–1)	0(0–1)	0(0–2)		
p_0		**0.090**	**<0.001***	**<0.001***	**<0.001***		

***SD:* Standard deviation** **Fr*: Friedman test, Sig. bet. periods was done using* Post Hoc Test *(*Dunn's)**

p: p value for comparing between the studied groups ***p_0: p value for comparing between* Baseline *and each other group***

****: Statistically significant at p ≤ 0.05***

TABLE (3a): Comparison between the three studied groups according to intensity score for ulcerations

Intensity score for ulcerations	Group I (n = 10)	Group II (n = 10)	Group III (n = 10)	H	p
Baseline					
Mean ± SD.	3±0	3±0	3±0	0.0	1.000
Median (Min. – Max.)	3(3–3)	3(3–3)	3(3–3)		
2 weeks					
Mean ± SD.	1±0.82	1.2±0.63	1.2±0.63	0.464	0.793
Median (Min. – Max.)	1(0–2)	1(0–2)	1(0–2)		
4 weeks					
Mean ± SD.	0.10±0.32	0±0	0±0	2.0	0.368
Median (Min. – Max.)	0(0–1)	0(0–0)	0(0–0)		
6 weeks					
Mean ± SD.	0.10±0.32	0±0	0.10±0.32	1.036	0.596
Median (Min. – Max.)	0(0–1)	0(0–0)	0(0–1)		
8 weeks					
Mean ± SD.	0±0	0.10±0.32	0.10±0.32	1.036	0.596
Median (Min. – Max.)	0(0–0)	0(0–1)	0(0–1)		

***SD:* Standard deviation** ***H: H for* Kruskal Wallis test,**

p: p value for comparing between the studied groups

TABLE (3b): Comparison between the different studied periods according to intensity score for ulcerations

Intensity score for ulcerations	Baseline	2 weeks	4 weeks	6 weeks	8 weeks	Fr	p
Group I (n = 10)							
Mean ± SD.	3±0	1±0.82	0.10±0.32	0.10±0.32	0±0	35.779*	<0.001*
Median (Min. – Max.)	3(3–3)	1(0–2)	0(0–1)	0(0–1)	0(0–0)		
p_0		**0.040***	**<0.001***	**<0.001***	**<0.001***		
Group II (n = 10)							
Mean ± SD.	3±0	1.2±0.63	0±0	0±0	0.10±0.32	37.333*	<0.001*
Median (Min. – Max.)	3(3–3)	1(0–2)	0(0–0)	0(0–0)	0(0–1)		
p_0		**0.090**	**<0.001***	**<0.001***	**<0.001***		
Group III (n = 10)							
Mean ± SD.	3±0	1.2±0.63	0±0	0.10±0.32	0.10±0.32	36.604*	<0.001*
Median (Min. – Max.)	3(3–3)	1(0–2)	0(0–0)	0(0–1)	0(0–1)		
p_0		**0.090**	**<0.001***	**<0.001***	**<0.001***		

SD: Standard deviation ***Fr: Friedman test, Sig. bet. periods was done using Post Hoc Test (Dunn's)***

p: p value for comparing between the studied groups p0: p value for comparing between Baseline and each other group

****: Statistically significant at p ≤ 0.05***

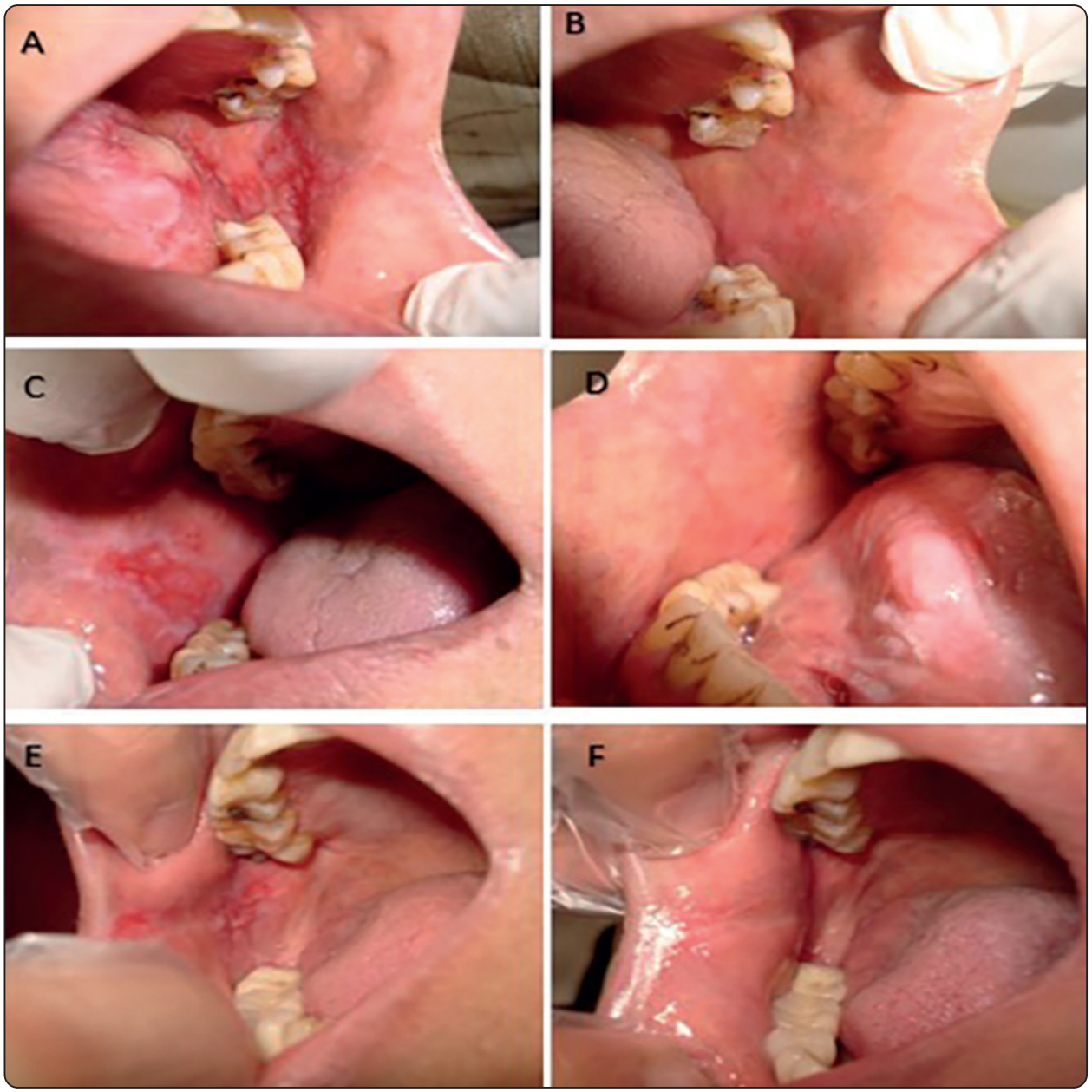

Fig. (1) Clinical outcome: (A) Patient of group I at baseline. (B) Patient of group I 8 weeks post-treatment. (C) Patient of group II at baseline. (D) Patient of group II 8 weeks post-treatment. (E) Patient of group III at baseline. (F) Patient of group III 8 weeks post-treatment.

DISCUSSION

The aim of the current study was to assess the possibility of using Propolis or MMF as a safer substitute to corticosteroids in the management of OLP. Although corticosteroid is an effective treatment of OLP, it comes with many side effects as using it in a topical form is difficult due to its lack of adherence to the mucosa and Some people are resistant to corticosteroid topical treatment. [12] In addition, systemic corticosteroids are administered at larger dosages in severe instances, that may have adverse reactions, particularly if taken for an extended periods. [13] In the current investigation, patients with OLP who received topical propolis, MMF, or corticosteroids noticed substantial improvements in all clinical results. Throughout a two-month study period, 5% propolis, 2% MMF, and 0.1% triamcinolone acetonide treatment reduced pain, decreased erosions, and ulcerations, and enhanced the patient's quality of life.

Regarding the clinical outcomes of OLP after therapy, there were no significant variations in the therapeutic benefits of topical propolis, MMF, or triamcinolone acetonide. Following using the topical medication for two weeks, improvements finally became visible. However, propolis therapy made the ulcerations disappear more obviously and rapidly. These results corroborated those of Wael et al. [14] who claimed that topical administration of propolis sped up the healing of diabetic lesions in experimental animals.

Additionally, Zyada et al. evaluated the effects of topically applying propolis in the form of muco-adhesive gel during the course of therapy of OLP and came to the conclusion that propolis may be a potential pharmaceutical agent for preventing the proliferation of epithelial cells and has potent anti-inflammatory properties. [15]

The use of systemic prescribed MMF leads to minor gastrointestinal disturbances. [16] According to our knowledge, there were a few studies that investigated the topical prescription of MMF. In the present work, we evaluated the use of 2% MMF in a mucoadhesive form as a treatment for OLP. The oral muco-adhesive administration technique increases the medicine's contact with the lesion, allowing for adequate time for drug absorption and high concentrations. [9]

In the current study, there were an improvement in all clinical results after the application of 2% MMF. That was in accordance with Zenus et al., who stated that MMF muco-adhesive was efficient in minimizing severity of VAS and size of ulcers in ulcerative OLP. [17]

Also, Cho et al., stated an 83% reduce in manifestations of refractory lichen-planus after using 0.5 g of oral MMF twice per day for a 4-week period and there were little gastrointestinal problems at the start of MMF medication, which can be explained by the systemic use of MMF. On the other hand, there was no pain or ulcerations after 4 weeks of 2% MMF application in the current study.

Thus, in accordance with this study, propolis, and MMF are comparative in their efficiency to corticosteroids. As, using topical propolis or MMF does not lead to any side effects, unlike topical corticosteroids.

CONCLUSION

In conclusion, propolis and MMF might be utilized as a substitute to topical corticosteroids for the management of OLP.

Conflict of interest Nil

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