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ORIGINAL RESEARCH

Therapeutic Evaluation of 5% Topical Amlexanox Paste and 2% Curcumin Oral Gel in the Management of Recurrent Aphthous Stomatitis

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INTRODUCTION

Recurrent aphthous stomatitis (RAS) is an inflammatory condition affecting the oral mucosa characterized by repeated episodes of painful ulcers that can appear singly or in clusters.Theulcers are often small,round, and have a white or yellowish center surrounded by a red halo(1). The term “aphthae” originated from the Greek word “aphthi” which means “to set on fire” or “to inflame”. It is believed to be coined by the Greek philosopher, Hippocrates.RAS affects 20% of the general population approximately(2).The precise etiology of Recurrent Aphthous Stomatitis remains uncertain,however it has been established that several factors play a direct role in its occurrence.These factors include genetic predisposition ,stress,trauma, exposure to certain food, smoking cessation, nutritionaldeficiencies like iron, vitamin B12, folic acid deficiency and hormonal imbalance. Local and systemic conditions,immunological and microbial factors may also be other contributing elements(3).RAS can manifest as primary,idiopathic condition and as a secondary RAS,which is associated with a systemic disease(4).

This condition is marked by intense pain and discomfort, crippling normal activities of the oral cavity such as chewing and swallowing.Recurrent Aphthous Stomatitis (RAS) is a complex condition that can arise due to multiple factors such as local trauma,psychological stress, allergy to products containing sodium lauryl sulfate (oral care products such as toothpaste), hormonal fluctuations such as ovulation,and menstruation in women, and alterations in oral microbial flora have been related to the occurrence of RAS(5).Although the lesion is typically self-limiting,its painful nature,high recurrence rate,andmultifactorial etiology significantly impact the quality of life and contribute to considerable morbidity.Therefore, an effective therapeutic strategy is essential to alleviate symptoms and improve patient well-being(6).

A variety of therapeutic modalities include topical anesthetics, antibiotics, corticosteroids, nutritional supplements, immune-modulatory drugs, laser therapy, and combination therapies for effective pain management and reduction of recurrence. Amlexanox (C16 H14 N204), a topical anti-inflammatory and anti-allergic drug is the only clinically proven drug approved by the US Food and Drug Administration for the management of RAS.It inhibits the formation and release of histamine and leukotrienes from mast cells, neutrophils, and mononuclear cells(2).

Curcumin,the principal pigment of turmeric,a staple spice in India,is renowned for its vibrant colorand has been celebrated for centuries for its powerful antioxidant,antiseptic,antibacterial,anti-inflammatory,immune-modulatory,anti-allergic properties.Its anti-inflammatory benefits are largely due to its ability to inhibit the biosynthesis of inflammatory prostaglandins,which in turn suppresses cyclooxygenase and lipoxygenase activity.This inhibition reduces the release of prostaglandins and

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leukotrienes and curtails neutrophil activity during inflammatory responses(7).

The primary objective of this study was to evaluate and compare the efficacy of Topical Amlexanox Paste and Curcumin Oral Gel in the Management of Recurrent Aphthous Stomatitis.

MATERIALS AND METHODS

The present study was a single-blinded interventional randomized clinical trial conducted in the out-patient department of a GovernmentDental College and Hospital in Srinagar,Kashmir. The ethical approval was obtained from the Institutional Ethics Committee. A total of 50 participants were included in the randomized clinical trial with an allocation ratio of 1:1. They were divided into two study groups**: Group A received 5% amlexanox oral paste and Group B received 2% curcumin oral gel.**

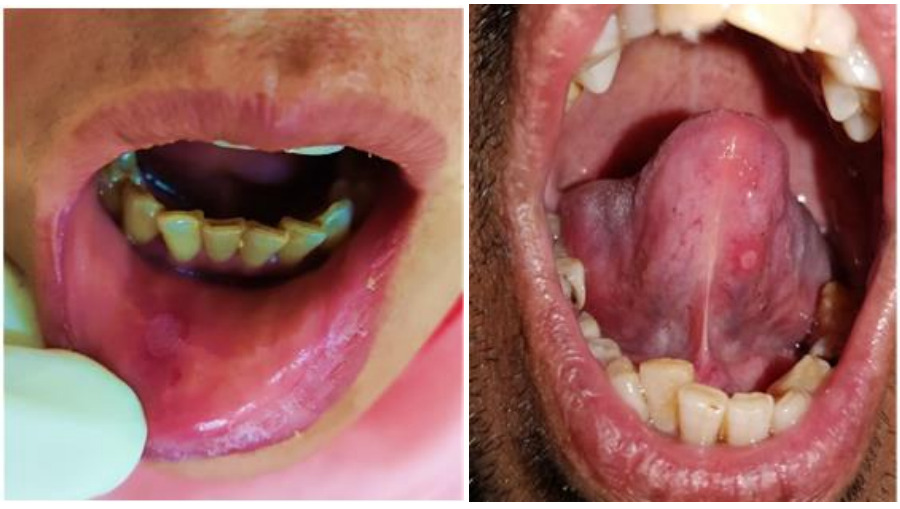
Inclusion criteria

- Age group: 18–30 years
- Participants giving a history of RAS minor (ulcers that measure<10 mm, and heal within 4–14 days without scarring) with a minimum of two episodes in a year
- Participants with 1–3 minor RAS of less than 48 h duration.

Exclusion criteria

- Participants with any systemic disorders
- Pregnant, lactating women
- Participants with the habit of smoking or alcoholism
- Participants undergoing orthodontic therapy
- Participants who had undergone tooth extraction or any dental surgical procedure in the past 2 weeks
- Participants under anyNon-steroidal anti-inflammatory drugs (NSAIDS)/systemic steroids/immune suppressant drugs
- Participants allergic to medicines or foods.

A detailed oral examination was done for all 50 participants and all baseline parameters such as the site, size, number, pain, erythema, and exudation were recorded on the first day. The clinical diagnosis and evaluation were supervised by the staff from the department of oral medicine and radiology. The researcher gave thorough instructions on the application of the drug in both verbal and written format. Topical 5% amlexanox ointment (Lexanox oral paste containing 5% amlexanox,Macleods pharmaceuticals) and 2% curcumin oral gel (curenext oral gel containing 10 mg Curcuma longa extract and colors such as erythrosine from Abbott pharmaceuticals) were randomly packed in identical packages and allotted to the participants. The participants were not aware of the drug. The participants were asked to wipe the affected area clean with a piece of cotton. Group A participants were instructed to take ¼ inch (0.5 cm) of the paste approximately and apply it at the site of the lesion. Group B participants were asked to apply a very little amount of the gel just enough to form a thin smear over the lesions. Both groups were asked to apply the drug four times a day; in the morning after performing oral hygiene, after lunch, after dinner, and before going to bed. The maximum diameter of the ulcers was measured with William's calibrated periodontal probe on days 1,3 and 7. For assessing pain, a Visual Analog Scale (VAS) containing a 10 cm horizontal line between two points connoting no pain and excruciating pain was used. The subjects were asked to identify the line on the scale, which best represented their present pain level. The degree of erythema was evaluated with a 4-point scale (modified Greer et al. scale)(8) in which "0" referred to no erythema, "1" denoted light red/pink color, "2" denoted red but not dark in color, and "3" referred to very red, dark color. All participants were evaluated on days 1, 4, and 7 and checked for all parameters. The subjects were followed up on days 30, 60, 90, and 180 to check for recurrences. Complete oral examinations were performed on all visits, and the subjects were specifically interrogated about any adverse effects.



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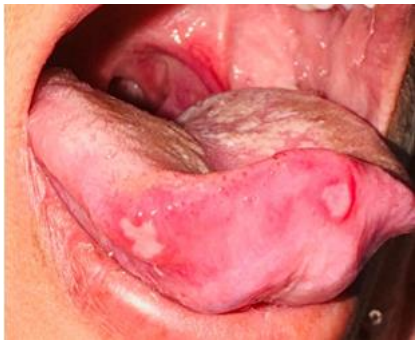

FIG: Clinical pictures of APHTHOUS ULCERATIONS on various mucosal sites (lower labial mucosa,ventral and ventrolateral surfaces of tongue)

Statistical Methods

The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean±SD and categorical variables were summarized as frequencies and percentages. Graphically the data was presented by pie and bar diagrams. The Shapiro-Wilk test was applied to test the normality of data. Student's independent t-test or Mann-Whitney U-test, whichever feasible, was employed for comparing continuous variables. Chi-square test or Fisher's exact test, whichever appropriate, was applied for comparing categorical variables. A P-value of less than 0.05 was considered statistically significant.

RESULTS

Fifty participants were included in the present study of which, 20 were males (40%) and 30 participants were females (60%).(Table 1& diagram 1).

The mean ulcer size on days 1, 3,and 7 in Group B participants were more when compared to Group A participants [Table 2 and diagram 2].

The mean pain scores measured on days 1, 3, and 7 were lower in Group B participants when compared to Group A participants [Table 3 and Figure 3]. When the participants were checked for recurrence, those who used amlexanox had a high recurrence rate (92%) when compared to those who used curcumin (48%).

The mean erythema levels on day 1 for Group A and Group B was 1.67 ± 0.932and 1.73 ± 1.194, respectively. The erythema levels on days 3 and 7 were 1.38 ± 0.783 and 1.21 ± 0.872 for Group A and 0.63 ± 0.452 and 0.32 ± 0.217 for Group B, respectively [Table4&Figure 4]. When the participants were checked for recurrence, those who used amlexanox had a high recurrence rate (92%) when compared to those who used curcumin (48%),[Table 5 and Figure 5].

Table 1: Gender distribution of study patients

Gender	Number	Percentage
Male	20	40
Female	30	60
Total	50	100

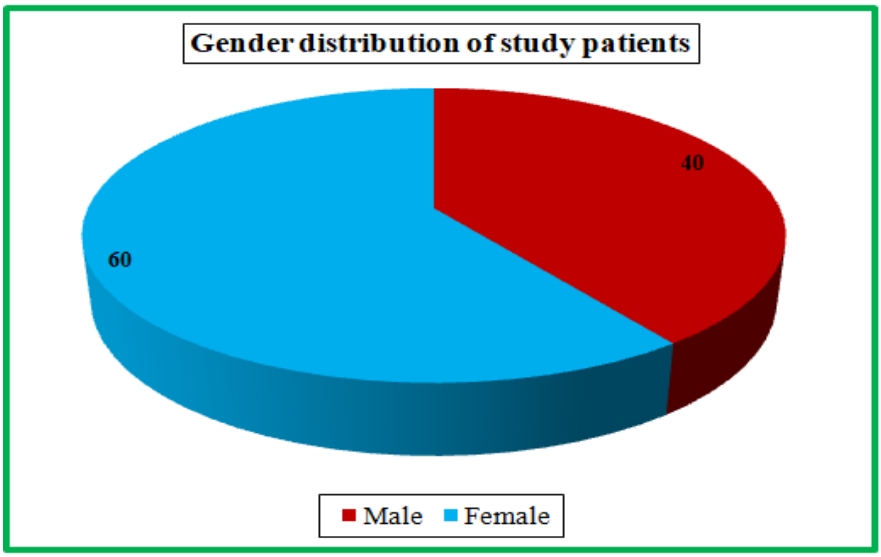

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Table 2: Comparison based on ulcer size in two groups					
Time Interval	Group A		Group B		P-value
	Mean	SD	Mean	SD	
Day 1	3.52	1.247	3.83	1.312	0.396
Day 3	2.71	0.935	2.75	1.058	0.887
Day 7	1.12	0.742	1.23	0.819	0.621

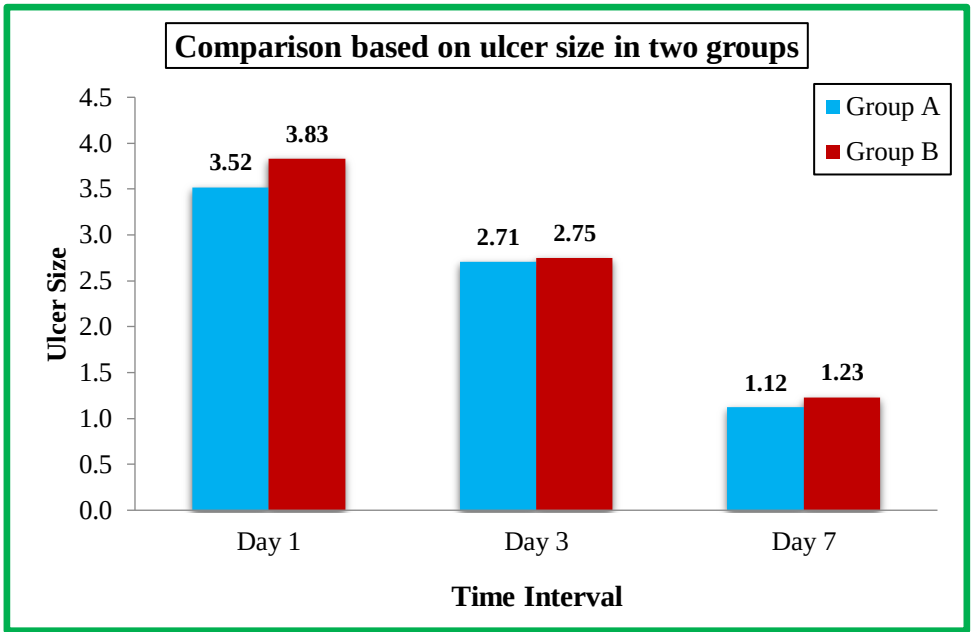

Table 3: Comparison based on pain score in two groups					
Time Interval	Group A		Group B		P-value
	Mean	SD	Mean	SD	
Day 1	3.43	1.395	3.57	1.429	0.728
Day 3	2.14	1.483	1.86	1.518	0.513
Day 7	0.76	0.518	0.25	0.215	<0.001*

***Statistically Significant Difference (P-value<0.05)**

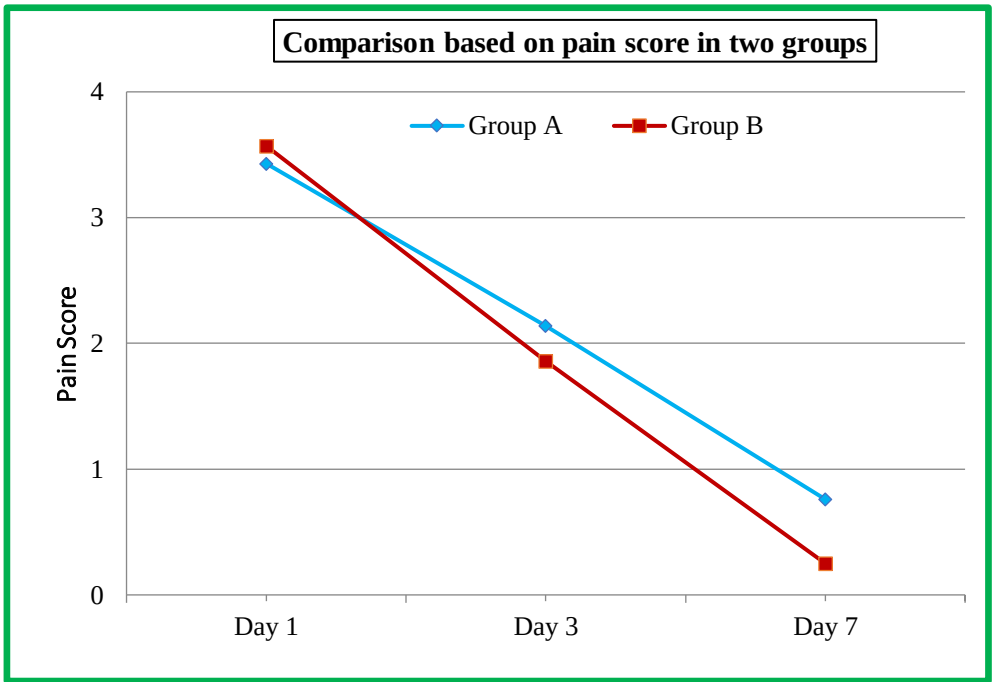

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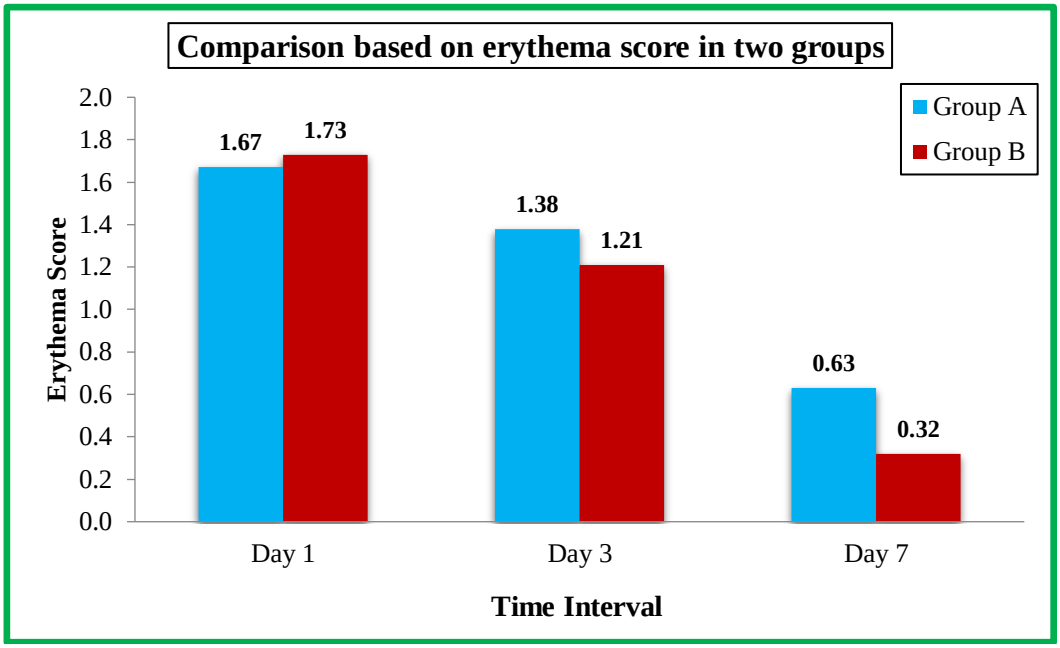
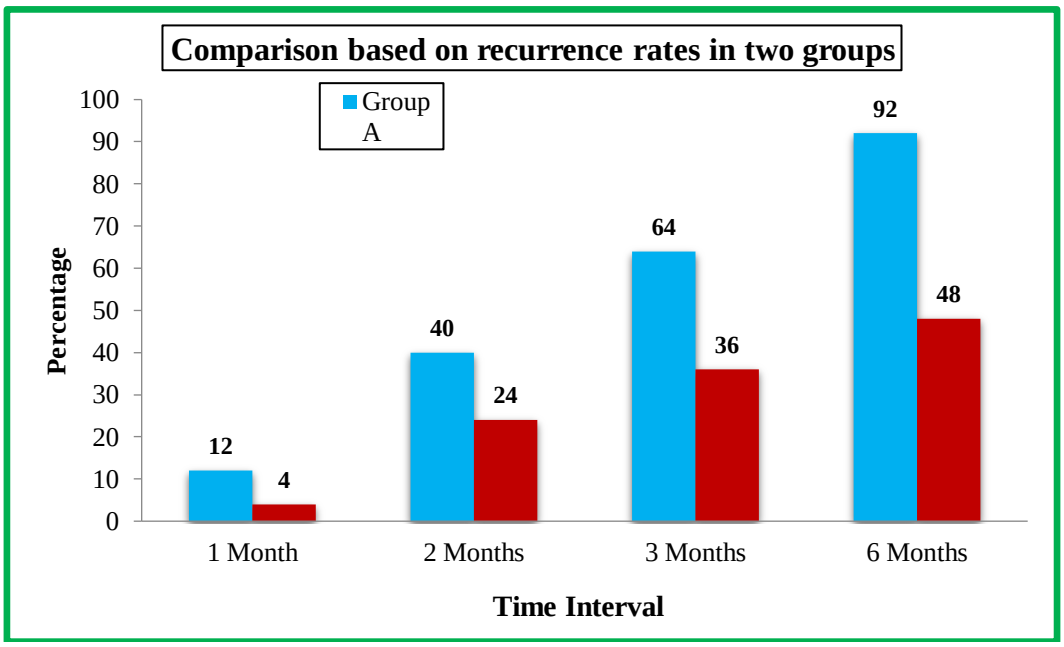
Table 4: Comparison based on erythema score in two groups					
Time Interval	Group A		Group B		P-value
	Mean	SD	Mean	SD	
Day 1	1.67	0.932	1.73	1.194	0.843
Day 3	1.38	0.783	1.21	0.872	0.472
Day 7	0.63	0.452	0.32	0.217	0.003*



***Statistically Significant Difference (P-value<0.05)**

Table 5: Comparison based on recurrence rates in two groups					
Time Interval	Group A		Group B		P-value
	No.	%age	No.	%age	
1 Month	3	12	1	4	0.602
2 Months	10	40	6	24	0.225
3 Months	16	64	9	36	0.048*
6 Months	23	92	12	48	0.002*

***Statistically Significant Difference (P-value<0.05)**



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DISCUSSION

Recurrent aphthous stomatitis(RAS) is a common oral mucosal condition that has a multifactorial etiology. They are recurrent and also known as “canker sores.”. The minor manifestation of the condition is the most common and is characterised by small, shallow, round or oval lesions that are surrounded by a raised erythematous halo and are covered by a grey-white pseudomembrane. Appropriate management of patients with this condition is largely symptomatic and should focus on reducing ulcer duration, relieving pain and reducing or preventing ulcer recurrence(8).The present study is the only investigation that has directly compared topical amlexanox with a competent herbal formulation of curcumin in the management of RAS minor.

In our study 50 patients were included, 20 were males (40%) and 30 participants were females (60%),which shows female preeminence in accordance with the previous studies(9,10,11).

Curcumin is a phytochemical that is obtained from the plant, C. longa, which belongs to the family Zingiberaceae. It has been used in Indian traditional medicinal practices from time immemorial. It is a potent anti-inflammatory and anti-oxidant that is being explored in several clinical trials for its innumerable benefits. Apart from curcumin, the other essential compounds present in C. longa are dimethoxycurcumin and bisdemethoxycurcumin(12).

In our study, the erythema on day 3 was reduced in Group B participants when compared to Group A participants. On day 7, there was a significant reduction in erythema in participants using curcumin oral gel compared to those who used amlexanox ($P = 0.003$).

Pain levels also reduced on 3rd day in the curcumin using group when compared with GroupA. Also, the pain score decreased significantly on day 7 in curcumin-using patients when compared with amlexanox. ($P = <0.001$).Our results aligned with those of a previous randomized clinical trial where curcumin performed comparatively better than the placebo in a 2-week intervention (13).Previous studies had evaluated curcumin and 1% triamcinolone acetonide and both the groups performed equally well in treating RAS(14,15).However,in our study, curcumin demonstrated superior effectiveness in reducing erythema,with significant pain relief observed by day 7.Our results were also consistent with those of prior study done by Gauthaman J, Ganesan A (2).

Many studies have evaluated the anti-inflammatory properties of curcumin and report that curcumin acts through the inhibition of phospholipase, lipidase, and cyclo-oxygenase-2. It also effectively reduces the levels of cytokines namely Interleukin (IL)-2, Tumor Necrosis Factor (TNF)-alpha, IL-6, and IL-1 beta. Further light has been shed on the pathways involved in the process wherein it is hypothesized that curcumin may stimulate cortisol secretion, which in turn reduces the levels of cytokinins(2)This could explain the possible pain control achieved by using curcumin in RAS.

Upon measuring the ulcer size,both groups exhibited a reduction in ulcer size by day 7.Although there was no significance, the group that used amlexanox performed well in reducing the ulcer size with a mean size of 3.52 ± 1.247 on day 1, 2.71 ± 0.935 on day 3, and 1.12 ± 0.742 (mm) on day 7.Our results were contrary to those of earlier studies, which state that there was a significant decrease in the size of the lesion when curcumin was used(16).

Major concerns revolve around the use of corticosteroids and immunomodulatory drugs for RAS as there is an increase in the frequency of episodes, an increase in severity of ulcers, and also reported adverse effects. However, curcumin has been evaluated for its safety and is reported safe even at high doses (12 g/day) (2).

Furthermore,curcumin demonstrated a significant reduction in recurrence rates when participants were evaluated after 1 month,2 months ,3 months and 6 months.Only 4% (1 participant) reported recurrence on day 30 in Group B, 24% (6 participants) on day 60, 36% (9 participants) on day 90, and 48% (12 participants) reported recurrence at the end period of 6 months.These residents showed significantly better outcomes compared to participants who used amlexanox, where aoverarching number of 23 participants(92%) reported recurrence at the end of 6 months.Our results were similar to previous studies where the healing of RAS was satisfactory in participants who used curcumin(12,15).

Various drug therapies have been explored for the management of RAS,withamlexanox demonstrating superior efficacy in most studies.In our study,we aimed to identify a potent herbal alternative with high efficacy, safety, and better symptomatic relief. Curcumin-based oral gels are herbal preparations that have fewer side effects and safety even at high doses. They reduce the size and erythema of the ulcer and the associated pain. Recurrence of RAS minor is very less and so it can be a better alternative to the existing therapeutic options.However, a limitation of the present study is the small sample size. Further long-term studies should be conducted with a larger sample size to evaluate the effectiveness of curcumin in the. management of all clinical variants of RAS.Comparativestudies assessing curcumin alongside conventional therapies will be valuablein determining its overall effectiveness.

CONCLUSION

The widespread use of topical corticosteroid such as triamcinolone acetonide has been associated with a heightened risk of opportunistic fungal infections.This issue can potentially be mitigated by curcumin,which has demonstrated antifungal properties in several studies.The current study indicates that curcumin may serve as a promising alternative to other drug

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therapies in the management of RAS.Similar herbal options with fewer adverse effects should be explored.

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