

Comparison of Anti-Inflammatory Efficacy of Curcumin in *Curcuma Longa L.* with Triamcinolone Acetonide for Minor Recurrent Aphthous Stomatitis: A Systematic Review

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Abstract

Recurrent aphthous stomatitis (RAS) is the most common inflammatory disorder in oral mucous characterized by recurrent ulceration. This review's objective was to compare the efficacy of curcumin (diferuloylmethane) in turmeric (*Curcuma longa L.*) with triamcinolone acetonide as an anti-inflammatory agent for minor recurrent aphthous stomatitis (RAS). Articles were searched according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines 2020 with studies published between 2011 and 2021 in six digital databases, namely PubMed, Scopus, EBSCOHost, Cochrane Library, ScienceDirect, and Google Scholar. The keywords were aphthous stomatitis, aphthous ulcers, and curcumin. The risk of bias was assessed using the RoB-tools JADAD Oxford Quality Scoring System. A total of 5 articles were included and eligible for analysis.

All of the articles showed that curcumin is as effective as triamcinolone acetonide required for regression in pain and size of the ulcers in RAS. In conclusion, curcumin in turmeric (*Curcuma longa L.*) is as effective as triamcinolone acetonide and can be used as an alternative treatment modality to topical corticosteroids in the therapy of minor RAS.

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Introduction

Recurrent aphthous stomatitis (RAS) is the most common inflammatory disorder in oral mucous, characterized by recurrent ulceration.¹ Recent studies estimate that the prevalence of RAS ranges between 5% and 66%, with a global mean of 20 % in the population.² RAS is classified into three clinical manifestations: minor, major, and herpetiform. Minor RAS is the most common manifestation of RAS, in about 85% of RAS patients.³ Minor RAS ulcer has 0.3 - 10 mm in size, oval in shape, a concave surface covered with a yellowish pseudomembrane surrounded by an erythematous halo, 1-10 in number, seen

in the nonkeratinized mucosal surfaces like labial mucosa, buccal mucosa, and floor of the mouth, and heal in 10 – 14 days without scarring.⁴ The ulcers of minor RAS cause various problem, such as taste disturbances, difficulties while talking, pain while eating and swallowing, and disrupt the ability of performing oral hygiene procedures so that patients need to seek treatment in order to solve the problems and increase their quality of life.⁵

Since the etiology of RAS is multifactorial and unknown, the absolute treatments for RAS are still questionable.^{4,6} RAS can be influenced by several predisposing factors, including genetic factors, stress, nutritional deficiencies, hormonal changes, and immunological diseases.⁷ RAS can represent the mucosal manifestation from various conditions and require a complete patient evaluation, including accurate diagnosis, classification of RAS, causative factors, and identification of diseases that may be associated to decide an appropriate therapy administration and reduce its recurrence.⁸ The therapy aims to

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decrease the severity of pain, ulcer number and size, and prevent the recurrence of the disease.⁹ The most effective therapy can control the onset of RAS and limit the risk of recurrence without causing side effects.¹⁰

Topical therapy that can be given for minor RAS patients includes anesthetics, antiseptics, steroid or non-steroidal anti-inflammatory drugs, and antibiotics.¹¹ Topical corticosteroids are widely used in RAS patients and can inhibit the inflammatory process in ulcer formation.¹² Triamcinolone acetonide is one topical corticosteroid commonly administered in immune-mediated oral mucosal diseases for reducing or suppressing the pain and shortening the ulcer healing time.¹³ Nevertheless, corticosteroids as anti-inflammatory agents to continuously treat minor RAS in the long term may cause side effects in the form of increased growth and fungal infections in oral mucous, namely candidiasis.^{3,14} These side effects can limit the goal of minor RAS therapy. Thus many scientists are currently researching alternative therapies with the same anti-inflammatory potency as conventional medicine without any side effects.^{15,16}

Scientists have found an alternative to RAS therapy using herbal medicines which aim to prevent problems arising from conventional medicine side effects, in addition to increasing the potential for healing the inflammation and providing a high protective effect on the oral mucosa.^{6,17} Several studies indicate that herbal remedies are safer, more effective, and suitable for long-term usage.¹⁸ In developing countries, about 80% of people still rely on therapy with herbal medicines as the primary choice in various disease treatments.¹⁹ In Indonesia, particularly Javanese people, therapy with herbal ingredients has been used for a long time to maintain health or treat a disease.⁹

One of the herbal plants used for RAS therapy is turmeric (*Curcuma longa L.*), a rhizome of the *Zingiberaceae* family, along with ginger, an annual shrub-shaped and commonly used as a culinary spice.¹⁹ In Asia, including India, China, and other tropical and subtropical nations, turmeric grows abundantly.²⁰ According to the history of traditional medicine in India, also known as Ayurveda, and traditional Chinese medicine, turmeric can prevent and cure various health conditions.²¹ Turmeric is widely utilized in numerous Asian nations due to its active

constituent curcumin (diferuloylmethane). Curcumin has various therapeutic properties, including antioxidant, anti-inflammatory, antibacterial, and anticancer.²⁰

Several studies have been conducted to evaluate the effects of curcumin as a therapy for various diseases associated with the inflammatory process and the mechanism underlying the anti-inflammatory activity of curcumin.²² However, there is no systematic review explaining specifically the efficacy of curcumin as an anti-inflammatory for the therapy of minor RAS. In 2020, a systematic review conducted by Al-Maweri SA, *et al* evaluated the efficacy of curcumin as a treatment for RAS, using inclusion criteria for randomized controlled and uncontrolled trials.¹⁶ Gharibpour F *et al.* also investigated the therapeutic advantages of curcumin against RAS by conducting a systematic review in 2021.²³ However, no systematic review for randomized controlled trials has compared the efficacy of curcumin in turmeric (*Curcuma longa L*) to triamcinolone acetonide in treating minor RAS. On this basis, our study aims to investigate curcumin's anti-inflammatory efficacy in turmeric (*Curcuma longa L*) with triamcinolone acetonide in minor RAS. The results of this systematic review are intended to provide information and become references concerning herbal-based treatments from turmeric related to the therapy of minor RAS for future research.

Materials and methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines 2020. The research question was arranged by the PICO (Population, Intervention, Comparison, and Outcome) framework with the following details: The population was patients with the diagnosis of minor RAS; the intervention was curcumin; the comparison was triamcinolone acetonide; the outcomes were reduction of pain severity and ulcer size. The articles were searched using the keywords ((aphthous stomatitis) OR (aphthous ulcers)) AND (curcumin), and the database filter applied was articles published from 2011 to 2021. The digital databases in this study were PubMed, Scopus, EBSCOHost, Cochrane Library, ScienceDirect, and Google Scholar.

The inclusion criteria in this study were limited to a randomized controlled trial (RCT) study design with the topic of curcumin compared to triamcinolone acetonide, human study, in English, full paper available, published in the past ten years (range between 2011-2021). The exclusion criteria were articles with a non-randomized controlled trial (non-RCT) design (serial case report, study in vivo dan in vitro, systematic review, meta-analysis review) and only abstracts. The article selection process was conducted by one independent reviewer (A.R.P). All articles were checked for duplication and eliminated using the Mendeley reference manager.

After screening, risk of bias and quality assessment was carried out for each selected article using the RoB-tools JADAD Oxford Quality Scoring System. This instrument could assess the quality of randomized controlled trial (RCT) articles by answering the five questions point in Table 1. The total score would be the conclusion of risk of bias and quality assessment. The maximum score is five and the minimum score is -2. If the score ≥ 3 shows articles with a high range of quality, while when the score ≤ 2 shows articles with a low range of quality.²⁴

The data for each study were extracted using data extraction form in Microsoft word with the following format. Table 2 consists of the author (year), country of research, title, study design, aim, and the subject of research (age range and number of patients). Table 3 consists of the author (year), intervention, treatment duration, outcome parameter, and outcome.

Results

Fig 1 shows a complete process flowchart of the article search strategy based on PRISMA guidelines 2020. Articles identification process using keywords in six digital databases found a total of 1085 articles, six articles from PubMed, 276 articles from Scopus, six articles from EBSCOHost, 13 from Cochrane Library, 65 articles from ScienceDirect, and 719 articles from Google Scholar. A total of 276 articles were removed due to duplication. The first screening process using database filters and inclusion criteria from 818 articles found that 812 articles were excluded as they did not meet the criteria. Therefore, six articles were assessed for eligibility using the risk of bias and quality

assessment JADAD Oxford Quality Scoring System. The detailed summary of the questions proposed in the risk of bias and quality assessment for six articles reviewed were presented in table 1. Five relevant articles, three low range of quality articles and two high range of quality articles, are included for further review qualitatively.

Table 2 presents a general summary of the reviewed article. Three articles were conducted in India^{17,25,26}, two articles in Malaysia¹⁸ and Iran²⁷. All selected articles are randomized controlled trial (RCT) studies, with three articles using a single-blinded method^{18,25,26} and two articles using a double-blinded method.^{17,27} The total sample size was 133 patients for the treatment group and 134 for the control group, ranging from 9 to 66 years old. Four articles aimed to assess and compare the efficacy of curcumin with triamcinolone acetonide for minor RAS^{17,18,25,27} and another article aimed to assess and correlate the pain score with ulcer size between topical curcumin 2% gel and triamcinolone acetonide oral paste 0.12% in minor RAS.²⁶

The detailed intervention and the result of each study can be seen in table 3. The primary outcome measures or parameters assessed in our study are pain score and ulcer size. Deshmukh and Bagewadi were not only using pain score and ulcer size, but also the number of ulcers and duration of ulcers.¹⁷ Raman *et al.*, added healing time and recurrence rate as the parameters of the results.²⁵ Pain scores in 4 articles were determined by the Visual Analogue Score (VAS)^{17,18,26,27} and one article by NIPC Pain Assessment Scale.²⁵ For ulcer size, three articles measured the diameter of the ulcer using a calliper in millimeter and two articles used william's periodontal probe.^{25,26} Three reviewed studies reported no statistical significance ($p>0.05$) in reducing pain score and ulcer size between the two groups, curcumin and triamcinolone acetonide.^{17,18,27} Raman *et al.*, reported statistically significant ($p<0.05$) in reducing pain scores on day 1, day 2, day 3, day 4, and day 5, also in reducing ulcer size on day 2, day 3, day 4, dan day 5.²⁵ Raman and Pitty reported no positive correlation between pain score and ulcer size with the management of Curcumin and Triamcinolone acetonide.²⁶

Reference	Question No					Total Score	Result
	(1)	(2)	(3)	(4)	(5)		
Halim et al., 2013 ¹⁶	1	1	0	-1	0	1	Low Range of Quality
Deshmukh dan Bagewadi, 2014 ¹⁷	1	1	1	1	0	4	High Range of Quality
Singh et al., 2018 ²⁸	0	-1	0	-1	0	-2	Low Range of Quality
Kia et al., 2020 ²⁷	1	1	1	1	0	4	High Range of Quality
Raman et al., 2020 ²⁵	1	1	0	-1	1	2	Low Range of Quality
Raman and Pitty, 2021 ²⁶	1	1	0	-1	0	1	Low Range of Quality

Table 1. Assessment of Risk of Bias.

Note: Question No. 1. Was the study described as random? (Yes = 1, No = 0); 2. Was the randomization scheme described and appropriate? (Yes = 1, No = -1); 3. Was the study described as double-blind? (Yes = 1, No = 0); 4. Was the method of double-blinding appropriate? (Yes = 1, No = -1); 5. Was there a description of dropouts and withdrawals? (Yes = 1, No = 0). If The total score of -2 to 2 shows a low range of quality score, while the total score of 3 to 5 shows a high range of quality score.

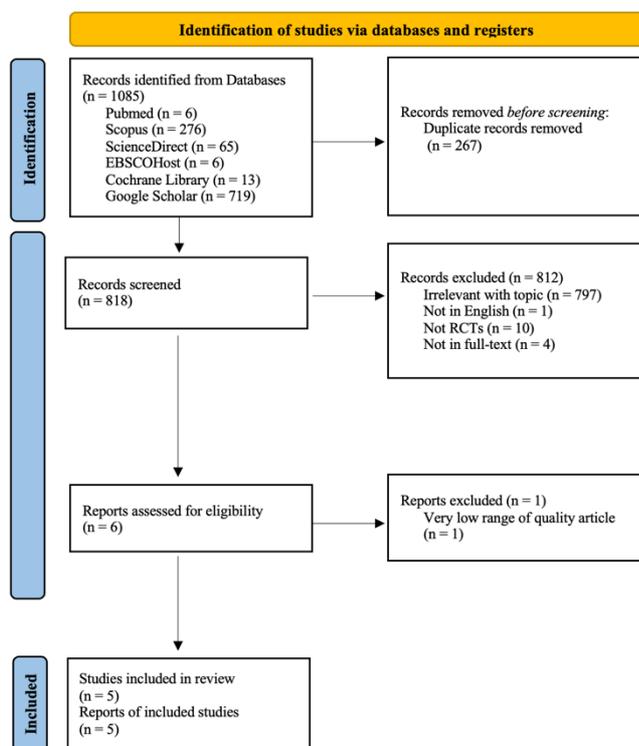


Figure 1. Flowchart of article searching based on the PRISMA guidelines 2020.

Discussion

Table 2 shows the research related to comparing the efficacy of curcumin and triamcinolone acetonide that was conducted on populations in Malaysia, Iran, and India, which are part of the Asian continent. Turmeric (*Curcuma longa L*) is cultivated extensively in the south and southeast tropical Asia, such as India, China, Japan, and is widely consumed through foods as a popular dietary spice and pigment.²¹ It has been used to prevent and cure various health-related problems in the Indian

subcontinent from ancient times, namely Ayurveda medicines.^{20,21} It is also usually used in Hindu religious ceremonies in India.²⁰

3 of the 5 articles' design studies used in this review are single-blind randomized controlled trials.^{18,25,26} This design study is conducted when only subjects are blinded to the intervention because the researcher requires knowledge of treatment allocation. Nonetheless, the problem of a single-blind randomized controlled trial is prone to bias from the researcher rather than a double-blind randomized controlled trial.²⁹

A total of 267 subjects in 5 included articles were analysed, consisting of females and males. The subjects ranged from 9 to 66 years old, with a range mean above 18 years old. This is based on the prevalence of recurrent aphthous ulcers that greatest for persons aged 17 to 29 years.³⁰

In table 3, the duration of treatment for each group in the articles ranges from 5 to 10 days based on the time that minor RAS ulcers can heal in the range of 7-10 days with or without treatment.⁷ The preparations of curcumin and triamcinolone acetonide in each article vary from powder, gel, orabase or oral paste. The gel form can easily expand, absorb liquids well, and be more stable, although this formula's water content can increase microbial attack and make it slower in releasing the drugs.³¹ The orabase or oral paste formula consists of pectin 1–5%, silica 5–10%, sodium carboxymethylcellulose 5–10%, paraffinum liquidum 75–100% that have the advantages of being a protective, hydrophobic, and anhydrous adhesive vehicle, used to retain the application of active pharmaceutical ingredients to the oral mucosa.^{32,33}

The primary outcome parameters observed in this study were pain score and ulcer size. Our study found the measurement of pain score was 0 (zero) in 5 articles on the last day of treatment, both the treatment group and the control group.^{17,18,25–27} This results from the suppressed inflammation response of the ulcer, including inhibition of COX-2, which decreases the production of prostaglandins that can mediate the development classic signs of inflammation such as pain, redness, and swelling.³⁴ The result of ulcer measurements in 5 articles showed that the mean lesion size decreased gradually in both groups.^{17,18,25–27} Anti-inflammatory properties in curcumin can accelerate the wound healing process consisting of hemostasis and

inflammation processes, proliferation phase, and remodelling phase.³⁵ An experimental study on the efficacy of curcumin as a therapy in animal ulcer lesions conducted by Lim *et al.*, showed an increase in the healing of ulcers on the labial gingival oral cavity of rabbits after topical administration of curcumin by the formation of granulation tissue, and collagen deposition.³⁶ Three articles^{17,25,26} reported that curcumin was safe and did not cause side effects to be used in the treatment of minor RAS because it has been investigated as a potential RAS treatment and little side effects even used at high dosages so that it can be consumed by children, pregnant or lactating women, and immunocompromised patients.³⁷

The inflammation of minor RAS involves a cell-mediated immune response mechanism. This immunopathogenesis begins with the activation of T cells, which release different pro-inflammatory cytokines and increase tumor necrosis factor α (TNF- α) by macrophages and mast cells.⁸ TNF- α is an essential cytokine for host self-defense.³⁸ The effect of TNF- α on endothelium followed by the effect of neutrophils will initiate a cascade of inflammatory processes that cause ulceration in RAS.⁸ The inflammatory process that occurs in RAS is initiated by the activation of TNF- α , interferon-gamma (IFN- γ), and interleukin 2 (IL-2) (a pro-inflammatory cytokine) released by Th1 cells.³⁹ Interleukin 6 (IL-6) is also elevated in RAS patients, resulting in a pro-inflammatory action that stimulates the development of RAS lesions in oral mucous.³⁸ In this inflammatory state, cyclooxygenase-2 (COX-2) will increase, resulting in the production of prostaglandins, particularly prostaglandin E2 (PGE₂), which is involved in leading to signs of inflammation, such as swelling, redness, and pain.³⁴ Both curcumin and triamcinolone acetonide can decrease the generation of inflammatory mediators in minor RAS, including

prostaglandin, neutrophils, eosinophils, monocytes, lymphocytes, and different cytokines (IL-2, IL-6, IFN- γ , and TNF- α).^{20,40}

This study provides evidence that when compared to triamcinolone acetonide, a conventional medicine commonly used for therapy in minor RAS, curcumin has equal efficacy as an anti-inflammatory in reducing pain and ulcer size. Therefore, it can be utilized as an alternative to triamcinolone acetonide-based therapy. There are several limitations in this systematic review, such as 3 of 5 selected articles had a low range of quality and small sample sizes in some included studies. Interpreting the results of comparing the efficacy of curcumin with triamcinolone acetonide is hampered by the heterogeneity of the variety of dosage forms, preparation of curcumin, and treatment period employed in each study. For recommendation, a further well-designed randomized controlled trials research, with standardized curcumin formulations, adequate sample sizes, low study subjectivity, and observation of side effects that may occur in the curcumin group is required. The results of this study become evidence and reference that support the consideration of alternative medicine based on turmeric with the active ingredient curcumin (diferuloylmethane) for patients with minor RAS and be used as the basis for future research on the development of curcumin as an anti-inflammatory for other inflammatory diseases in oral mucous or research on the formulation of drugs based on curcumin.

Conclusions

Curcumin in turmeric is as effective as triamcinolone acetonide and can be used as an alternative treatment modality to topical corticosteroids in treating minor RAS.

Author (Year)	Country of Research	Title	Study Design	Aim	Subject of Research	
					Age Range	Number of Patients
Halim <i>et al.</i> , (2013) ¹⁸	Malaysia	Novel Material in Treatment of Minor Oral Recurrent Aphthous Stomatitis	Single-blind randomized controlled trial	To compare the effectiveness between turmeric and triamcinolone in treating minor RAS in the oral cavity.	≥18 years old	20 patients 10 patients treatment group 10 patients control group
Deshmukh and Bagewadi, (2014) ¹⁷	India	Comparison of Effectiveness of Curcumin with Triamcinolone Acetonide in The Gel Form in Treatment of Minor Recurrent Aphthous Stomatitis: A Randomized Clinical Trial	Double-blind randomized controlled trial	To assess and compare the efficacy of Curcumin with Triamcinolone acetonide in the gel form in the treatment of minor RAS.	13 – 66 years old	60 patients 30 patients treatment group 30 patients control group

Kia <i>et al.</i> , (2020) ²⁷	Iran	New Concentration of Curcumin Orabase in Recurrent Aphthous Stomatitis: A Randomized, Controlled Clinical Trial	Double-blind randomized controlled trial	To compare the efficacy of the administration of 5 % of Curcumin (new concentration) and 0.1 % of triamcinolone acetonide (standard control) for treating RAS.	9 – 53 years old	58 patients 29 patients treatment group 29 patients control group
Raman <i>et al.</i> , (2020) ²⁵	India	Topical Curcumin and Triamcinolone Acetonide in Recurrent Minor Aphthous Ulcers: A Pilot Trial	Single-blind randomized controlled trial	To evaluate the efficacy of topical curcumin and topical triamcinolone acetonide in a professional population with minor RAS by assessing six clinical variables: site, size, pain, healing period, frequency of recurrence and number of ulcers.	18 – 30 years old	69 patients 34 patients treatment group 35 patients control group
Raman and Pitty, (2021) ²⁶	India	Correlation of Pain Score with Ulcer Size in Oral Aphthous Ulcers using 2% Curcumin Gel and 0,1% Triamcinolone Oral Paste – A Parallel Comparison Study	Single-blind randomized controlled trial	To assess and correlate pain score with ulcer size using topical curcumin 2% gel and triamcinolone acetonide oral paste 0.12% in minor RAS.	18 – 30 years old	60 patients 30 patients treatment group 30 patients control group

Table 2. General summary of the reviewed articles.

Author (Year)	Intervention	Treatment Duration	Outcome Parameter	Outcome
Halim <i>et al.</i> , (2013) ¹⁸	Treatment Group: Turmeric powder Control Group: Triamcinolone acetonide 0,1% Instruction: Apply the medicament for 5 minutes twice a day	5 days	1. Pain Score: Visual Analogue Score (VAS) 2. Ulcer size: calliper in millimeter	No statistical significance (p>0.05) in both groups
Deshmukh and Bagewadi, (2014) ¹⁷	Treatment Group: Curenex <i>oral gel</i> (per gram of gel contained 10 mg of curcuma longa extract) Control Group: Kenacort <i>oral paste</i> (triamcinolone acetonide 0.1%) Instruction: apply the gel and paste three times a day on each ulcer after meals and not consume food or water for 30 minutes after application	7 days	1. Pain Score: Visual Analogue Score (VAS) 2. Ulcer size: calliper in millimeter 3. Number of ulcers 4. Duration of ulcers	No statistical significance (p>0.05) in both groups
Kia <i>et al.</i> , (2020) ²⁷	Treatment Group: <i>Curcumin Orabase</i> Control Group: Triadent (triamcinolone acetonide 0,1% <i>orabase</i>) Instruction: apply the orabase three times a day on each ulcer after meals and not consume food or water for 30 minutes after application	10 days	1. Pain Score: Visual Analogue Score (VAS) 2. Ulcer size: calliper in millimeter	No statistical significance (p>0.05) in both groups
Raman <i>et al.</i> , (2020) ²⁵	Treatment Group: Cumnext (<i>Curcuma longa</i> 10 mg <i>oral gel</i> 2%) Control Group: Kenacort (triamcinolone acetonide <i>oral paste</i> 0,1%) Instruction: apply the gel and paste three times a day on each ulcer after meals and not consume food or water for 15 minutes after application	7 days	1. Pain Score: NIPC Pain Assessment Scale 2. Ulcer size: William's periodontal probe 3. Location of ulcers 4. duration of ulcer healing 5. Recurrence rate 6. Number of ulcers	1. Statistically significant (p<0.05) in reducing pain score on day 1, day 2, day 3, day 4, and day 5, 2. Statistically significant (p<0.05) in reducing ulcer size on day 2, day 3, day 4, dan day 5 3. Predominant on the lower labial mucous 4. Statistically significant (p<0.001) 5. No statistical significance (p>0.05) in both groups 6. Statistical significance was not observed
Raman dan Pitty, (2021) ²⁶	Treatment Group: Cumnext (<i>Curcuma longa</i> 10 mg <i>oral gel</i> 2%) Control Group: Kenacort (triamcinolone acetonide <i>oral paste</i> 0,1%) Instruction: not mentioned	7 days	1. Pain Score: Visual Analogue Score (VAS) 2. Ulcer size: William's periodontal probe	No positive correlation between ulcer size and pain score in both groups

Table 3. Intervention and outcome of enrolled studies.

Declaration of Interest

There is no conflict of interest in this writing.

References

1. Woo S Bin, Setterfield JF, Greenberg MS. Ulcerative, vesicular, and bullous lesions. *Burket's Oral Medicine*. 2021. 35–84 p.
2. Najafi S, Mohammadzadeh M, Zahedi A, Heidari M, Rezaei N. Association of serotonin transporter gene polymorphism with recurrent aphthous stomatitis. *Avicenna J Med Biotechnol*. 2018;10(1):56–60.
3. Tarakji B, Gazal G, Al-Maweri SA, Azzeghaiby SN, Alaizari N. Guidelines for diagnosis and treatment of recurrent aphthous stomatitis for dental practitioners. *Indian J Forensic Med Toxicol*. 2020;14(4):1099–104.
4. Preeti L, Magesh K, Rajkumar K, Karthik R. Recurrent aphthous stomatitis. *J Oral Maxillofac Pathol*. 2011;15(3):252–6.
5. Zakiawati D, Nur N, Setiadi R. Distribution of oral ulceration cases in Oral Medicine Integrated Installation of Universitas Padjadjaran Dental Hospital. 2020;32(3):237–42.
6. Heydarpour F, Abasabadi M, Shahpiri Z, Vaziri S, Nazari HA, Najafi F, et al. Medicinal plant and their bioactive phytochemicals in The treatment of recurrent aphthous ulcers: a review of clinical trials. *Pharmacogn Rev*. 2018;12(23):27–39.
7. Manifar S, Obwaller A, Gharehgozloo A, Boorboor Shirazi Kordi HR, Akhondzadeh S. Curcumin gel in the treatment of minor aphthous ulcer: A randomized, placebo- controlled trial. *J Med Plants*. 2012;11(41):40–5.
8. Cui RZ, Bruce AJ, Rogers RS. Recurrent aphthous stomatitis. *Clin Dermatol*. 2016;34(4):475–81.
9. Hasanah NT, Hidayat W. Clinical efficacy and safety of herbal medicine therapy in recurrent aphthous stomatitis : a systematic review. *Int J Appl Pharm*. 2021;13(4):14–20.
10. Chavan M, Jain H, Diwan N, Khedkar S, Shete A, Durkar S. Recurrent aphthous stomatitis: a review. *J Oral Pathol Med*. 2012;41(8):577–83.
11. Altenburg A, El-Haj N, Micheli C, Puttkammer M, Abdel-Naser MB, Zouboulis CC. The treatment of chronic recurrent oral aphthous ulcers. *Dtsch Arztebl Int*. 2014;111(40):665–73.
12. Pandharipande R, Chandak R, Sathawane R, Lanjekar A, Gaikwad R, Khandelwal V, et al. To evaluate efficiency of curcumin and honey in patients with recurrent aphthous stomatitis: a randomized clinical controlled trial. *Int J Res Rev*. 2019;6(12):449–55.
13. Belenguer-Guallar I, Jiménez-Soriano Y, Claramunt-Lozano A. Treatment of recurrent aphthous stomatitis. a literature review. *J Clin Exp Dent*. 2014;6(2):168–74.
14. Li CL, Huang HL, Wang WC, Hua H. Efficacy and safety of topical herbal medicine treatment on recurrent aphthous stomatitis: a systemic review. *Drug Des Devel Ther*. 2015;10:107–15.
15. Salehi B, Jornet PL, López EPF, Calina D, Sharifi-Rad M, Ramírez-Alarcón K, et al. Plant-derived bioactives in oral mucosal lesions: a key emphasis to curcumin, lycopene, chamomile, aloe vera, green tea and coffee properties. *Biomolecules*. 2019;9(3):1–23.
16. Al-Maweri SA, Alaizari N, Alharbi AA, Alotaibi SA, AlQuhal A, Almutairi BF, et al. Efficacy of curcumin for recurrent aphthous stomatitis: a systematic review. *J Dermatolog Treat*. 2020;33(3):1225–30.
17. Deshmukh RA, Bagewadi AS. Comparison of effectiveness of curcumin with triamcinolone acetonide in the gel form in treatment of minor recurrent aphthous stomatitis: A randomized clinical trial. *Int J Pharm Investig*. 2014 Jul;4(3):138–41.
18. Halim DS, Khalik NIBA, Taib H, Pohchi A, Hassan A, Alam MK. Novel material in the treatment of minor oral recurrent aphthous stomatitis. *Int Med J*. 2013;20(3):392–4.
19. Nagpal M, Sood S. Role of curcumin in systemic and oral Health: an overview. *J Nat Sci Biol Med*. 2013;4(1):3–7.
20. Grover HS, Deswal H, Bhardwaj A. Curcumin: a medicinal plant and its effects in medicine and dentistry. *Int J Contemp Dent Med Rev*. 2015:1–4.
21. Deogade SC, Ghate S. Curcumin: therapeutic applications in systemic and oral health. *Int J Biol Pharm Res*. 2015;6(4):281–90.
22. Razavi BM, Rahbardar MG, Hosseinzadeh H. A review of therapeutic potentials of turmeric (*curcuma longa*) and its active constituent, curcumin, on inflammatory disorders, pain, and their related patients. *Phyther Res*. 2021;1–25.
23. Gharibpour F, Fakheran O, Parvaneh A, Shirban F, Bagherniya M, Sathyapalan T, et al. The clinical use of curcumin for the treatment of recurrent aphthous stomatitis: a systematic review of clinical trials. *Adv Exp Med Biol*. 2021;1291:229–38.
24. Wahyuni IS, Sufiawati I, Nittayananta W, Puspitasari IM, Levita J. Efficacy and safety of plant-based therapy on recurrent aphthous stomatitis and oral mucositis in the past decade: a systematic review. *J HerbMed Pharmacol*. 2021;10(2):179–87.
25. Raman P, Pitty R, Krithika CL, Anand SN, Subramani GP. Topical curcumin and triamcinolone acetonide in recurrent minor aphthous ulcers: a pilot trial. *J Contemp Dent Pract*. 2020;21(8):884–90.
26. Raman P, Pitty H R. Correlation of pain score with ulcer size in oral aphthous ulcers using 2% curcumin gel and 0.1% triamcinolone oral paste - A parallel comparison study. *J Indian Acad Oral Med Radiol*. 2021;33(1):53–9.
27. Kia SJ, Mansourian A, Basirat M, Akhavan M, Mohtasham-Amiri Z, Moosavi MS. New concentration of curcumin orabase in recurrent aphthous stomatitis: a randomized, controlled clinical trial. *J Herb Med*. 2020;22:1–6.
28. Singh H, Singh S, Singh N, Singh P, Sharma K. Comparative analysis of therapeutic efficacy of curcumin & triamcinolone acetonide in recurrent aphthous stomatitis - a clinical study. *J Adv Med Dent Sci Res*. 2018;6(4):136–8.
29. Miller LE, Stewart ME. The blind leading the blind: use and misuse of blinding in randomized controlled trials. *Contemp Clin Trials*. 2011;32(2):240–3.
30. Chattopadhyay A, Shetty K V. Recurrent aphthous stomatitis. *Otolaryngol Clin North Am*. 2011;44(1):79–88.
31. Hedayani I, Wahyuni IS. Effectiveness of the natural-based products and mucoadhesive for recurrent aphthous stomatitis therapy : a systematic review. 2021;13(4):7–13.
32. Marta M, Mart A, Bellowa LH, Granda PC, Lim D, Campmany ACC. Biopharmaceutical study of triamcinolone acetonide semisolid formulations for sublingual and buccal administration. *Pharmaceutics*. 2021;1–15.
33. Hamishehkar H, Nokhodchi A, Ghanbarzadeh S, Kouhsoltani M. Triamcinolone acetonide oromucoadhesive paste for treatment of aphthous stomatitis. 2015;5(2):277–82.
34. Ricciotti E, Fitzgerald GA. Prostaglandins and inflammation. *Arterioscler Thromb Vasc Biol*. 2011;31(5):986–1000.
35. Mohanty C, Sahoo SK. Curcumin and its topical formulations for wound healing applications. *Drug Discov Today*. 2017;1–11.
36. Lim YS, Kwon SK, Park JH, Cho CG, Park SW, Kim WK. Enhanced mucosal healing with curcumin in animal oral ulcer model. *Laryngoscope*. 2016;126:E68–73.
37. Witkin JM, Li X. Curcumin, an active constituent of the ancient medicinal herb *curcuma longa* L.: some uses and the establishment and biological basis of medical efficacy. *CNS Neurol Disord - Drug Targets*. 2013;12(4):487–97.
38. Shen C, Ye W, Gong L, Lv K, Gao B, Yao H. Serum interleukin-6, interleukin-17A, and tumor necrosis factor-alpha in patients with recurrent aphthous stomatitis. *J Oral Pathol Med*. 2021;50(4):418–23.
39. Najafi S, Yousefi H, Mohammadzadeh M, Bidoki AZ, Farhadi E, Rezaei N. Interleukin-2, interferon-gamma gene polymorphisms in recurrent aphthous stomatitis. *Prague Med Rep*. 2017;118(2–3):81–6.
40. Yagiela JA, Dowd FJ, Johnson BS, Mariotti AJ, Neidle EA. *Pharmacology and therapeutics for dentistry*. 6th ed. St. Louis, Missouri: Mosby; 2011. 551 p.