Triamcinolone versus nonsteroidal treatments for recurrent oral aphthous ulcers: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Recurrent apthous stomatitis (RAS) is associated with small to large ulcers and pain and may cause difficulty in speech and eating. Treatment modalities such as topical applications, mouthwashes, and tablets are available to manage symptoms. The most common pharmacological topical agents are corticosteroids, analgesics, probiotics, and antibiotics. This systematic review and meta-analysis aimed to compare the efficacy of topical triamcinolone with alternative topical treatments for recurrent oral aphthous ulcers, considering factors such as pain reduction, VAS score and ulcer healing time. It was registered in PROSPERO (registration number: CRD420250655772) with the title “Comparative evaluation of pain recovery and healing duration of Triamcinolone with non-steroidal treatment for recurrent oral aphthous ulcers- A systematic review and meta-analysis of Randomized Controlled Trials”. Randomized control trials published in English from March 2014 to March 2025 and available in five electronic databases, viz., Medline, the Cochrane Central Register of Controlled Trials (Central), Embase, Scopus and Web of Science, evaluating treatments for aphthous ulcers and which reported outcomes during follow-up were included. Studies reporting aphthous ulcers with systemic involvement, such as Behcet’s disease, Crohn's disease, and ulcerative colitis and those that included systemic treatment were excluded. A total of 26 studies were included for final qualitative and quantitative review. Risk of bias analysis was performed using the Cochrane ROB version 2 tool. The quantitative analysis and generation of Forest plots were done using the validated web-based tool available at https://metaanalysisonline.com. Natural and synthetic alternatives may provide effective, safer patient options, challenging the traditional reliance on corticosteroids such as triamcinolone. These findings indicate that natural agents such as honey, sage, and pomegranate could be considered first-line treatments for patients with RAS, particularly those who are intolerant to corticosteroids or experiencing frequent recurrences. Laser-based therapies and novel agents such as hyaluronic acid—microbiome combinations may be effective for severe cases with the same efficacy as corticosteroids but fewer side effects. When evaluating patient satisfaction, natural therapies such as curcumin, aloe vera, Rhus coriaria and cannabidiol were preferred over triamcinolone. However, the current study has limitations, including variations in the study outcomes, ulcer types, and follow-up intervals. This study had no funding.

Introduction

Recurrent aphthous stomatitis (RAS) is also known as aphthous stomatitis, canker sores, mouth ulcers and recurrent aphthous ulcers (RAUs). The term recurrent is used when ulcers occur repeatedly in an individual. The oral aphthous is a painful, shallow ulcer 2–5 mm in diameter that occurs on the mucous membrane of the oral cavity at locations that include the inner part of the cheeks, lips, tongue and floor of the mouth [1]. The pathogenesis of RAS is characterized by disruption of the epithelial layer with a local inflammatory response [2]. The exact etiology is unknown, and these RAUs cause patients’ significant discomfort in eating, speaking and drinking along with pain, which affects their quality of life. The contributing factors include a compromised immune system, stress, nutritional deficiencies, trauma, and genetic predisposition [2]. Recurrent aphthous ulcers are commonly classified as aphthous ulcers

minor, aphthous ulcers major and herpetiform ulcerations [3]. Cell-mediated inflammation in the RAU involves T cells and tumor necrosis factor-alpha [4]. Various synonyms and related terms commonly refer to oral aphthous ulcers (OAUs). The minor ulcers are small (less than 1 mm in diameter) and generally heal within 7–10 days without scarring. Major aphthous ulcers that are larger than 1 cm deep and more painful take several weeks to heal and often leave scarring. Herpetiform aphthous ulcers occur in clusters and are difficult to manage [5, 6]. Various treatment modalities, such as topical applications, mouthwashes, and tablets, are available to manage the pain associated with these ulcers. The most common pharmacological topical agents for the management of RAS are corticosteroids, analgesics, probiotics, and antibiotics.

The most often used topical cortisone medications are hydrocortisone (e.g., Orabase), triamcinolone acetonide (e.g., Kenalog in Orabase), salivary cortisol and dehydroepiandrosterone [7]. The second group that is frequently used includes analgesics and anti-inflammatories, such as benzocaine (e.g., Orajel), lidocaine, and amlexanox (e.g., Aphthasol) [8, 9]. Triamcinolone, a synthetic corticosteroid, is often the first-line pharmacological treatment for aphthous ulcers. They work by inhibiting the production of proinflammatory cytokines and thus suppressing the immune response, contributing to ulcer formation and discomfort. Triamcinolone directly suppresses the immune response in affected mucosal tissue, alleviating pain and reducing the size of ulcers [10]. While effective, long-term use is associated with potential side effects such as mucosal thinning and delayed wound healing [11]. Other topical applications include low-level lasers (diodes and Er:Yag) [12], doxycycline [13], probiotics [14], ozone [15], insulin liposome gel [16], chlorhexidine gluconate (e.g., Peridex) [17], and hyaluronic acid [18]. Natural and herbal remedies such as aloe vera [19], chamomilla [20], liquorice root (Glycyrrhiza glabra) [21], coconut oil [22], honey/bee propolis [23], camel whey protein [24], Punica granatum gel [25] and triadent oral paste [26] are also used for managing aphthous ulcers. Many natural and herbal remedies with the same or better efficacy have been studied to avoid the side effects of corticosteroids. Other alternative treatments that have been reported to be effective are laser therapy, ozone, and probiotics. Low-level laser therapy (LLLT) accelerates tissue repair and reduces inflammation by stimulating cellular metabolism and increasing blood flow to the affected area.

The rationale for this review was to compare the efficacy, ulcer size, and pain relief of natural treatment with that of the most common topical medication, as the literature review has scarce reports of comparison between all the variables mentioned. This review aims to compare the efficacy of topical triamcinolone with alternative topical treatments for managing recurrent oral aphthous ulcers, considering factors such as pain reduction, VAS score and ulcer healing time.

Methodology

The systematic review adhered to the principles outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [27]. It was registered in PROSPERO (registration number: CRD420250655772). The current systematic review aims to evaluate the efficacy of the most effective topical treatment for recurrent oral aphthous ulcers by comparing the commonly used medication,

topical triamcinolone, with other topical medications. The data on comparison and efficacy based on pain relief (VAS), pain recovery time, and ulcer healing were collected from randomized controlled trials (RCTs) published from March 2014 to March 2025. The focus questions were as follows:

Question 1. What is the efficacy of topical triamcinolone compared with other topical modalities in the treatment of recurrent oral aphthous ulcers?

Question 2: To compare the ulcer healing time and pain reduction effects of topical triamcinolone with those of other topical remedies in treating recurrent oral aphthous ulcers.

PICO.

P, population of individuals with minor and major recurrent aphthous ulcers.

I, Intervention, pharmacological and nonpharmacological topical treatments for recurrent aphthous ulcer (RAU).

C, Comparison with topical triamcinolone application for the treatment of RAU

O, outcome pain relief, pain recovery time, and overall ulcer healing time

Inclusion criteria:

- RCTs evaluating pharmacological or nonpharmacological treatments for aphthous ulcers (minor or major).
- Studies that reported outcomes such as pain relief, ulcer size reduction, and healing time.
- Studies published in English, with a follow-up duration ranging from 7 days to 1 year.

Exclusion criteria:

- Nonrandomized studies, studies not focusing on treatments for aphthous ulcers, case reports, abstracts, or conference proceedings.
- Aphthous ulcers with systemic involvement, such as Behcet’s disease, Crohn's disease, and ulcerative colitis
- All nontopical applications for the treatment of recurrent aphthous ulcers.

As the review involved the analysis of previously published data, no ethical approval was needed. Five electronic databases were used: Medline, the Cochrane Central Register of Controlled Trials (Central), Embase, Scopus and Web of Science. A comprehensive search was conducted using key terms such as "Aphthous ulcers", "Recurrent aphthous stomatitis", "Treatment", "Randomized controlled trial”, “Corticosteroids", “Triamcinolone” "Topical treatment”, “Pain relief", and “aphthous ulcer healing” from 2014–2025 (Table 1). Three reviewers independently screened the titles and abstracts (R.E., L.A., M.A.)

for relevance. The selected articles were retrieved as full texts and assessed for eligibility per the inclusion and exclusion criteria by six reviewers (R.E., L.A., M.K., R.G., M.A, B.G.). The full-text articles were reviewed independently by six reviewers (R.E., L.A., M.K., R.G., M.A, B.G.), and discrepancies in study selection were resolved by discussion with another reviewer (M.P.). In the initial search, 961 articles were retrieved from the five databases, and 385 remained after eliminating duplicates. Twenty-eight studies remained and were read in full. Two of them were excluded, and 26 studies fulfilled the criteria in the review and were subjected to data extraction (Fig. 1). Risk of bias was assessed for all included studies with the Cochrane ROB version 2 tool [28]. The risk of bias assessment was graphically visualized using the web based robvis tool [29]. The quantitative analysis and generation of Forest plots was done using the validated web based tool available at https://metaanalysisonline.com [30].

Table 1
Search strategy for the systematic review.

1	**Aphthous Stomatitis OR Stomatitis, Aphthous OR aphthous ulcer*.tw. OR canker sore*.tw. OR recurrent aphthous stomatitis.tw. OR mouth ulcer*.tw. OR oral ulcer*.tw. OR herpetiform ulcer*.tw.**
2	Triamcinolone OR triamcinolone acetonide.tw. OR triamcinolone paste.tw. OR Kenalog.tw. OR Corticosteroid OR corticosteroid*.tw.
3	(Aloe vera OR chamomile OR licorice OR Glycyrrhiza glabra OR honey OR bee propolis OR cannabidiol OR CBD OR hyaluronic acid OR salvia OR sage OR curcumin OR turmeric OR Rhus coriaria OR sumac OR Punica granatum OR pomegranate OR amlexanox OR benzocaine OR lidocaine OR doxycycline OR probiotics OR chlorhexidine OR gel OR placental extract OR triester glycerol oxide OR polyherbal).tw.
4	Laser Therapy OR Low-Level Light Therapy OR Laser OR diode laser.tw. OR low-level laser.tw. OR carbon dioxide laser.tw. OR CO2 laser.tw. OR photobiomodulation.tw.
5	randomized controlled trial OR controlled clinical trial OR randomized.tw. OR randomised.tw. OR RCT.tw. OR placebo.tw. OR clinical trial.tw.
6	1 AND (2 OR 3 OR 4) AND 5
7	Limit 6 to (english language and humans and yr="2014–2024")

The search is compatible with OVID EMBASE, Ovid MEDLINE and the Cochrane Library. Keywords were also used for Web of Science and Scopus.

Results

Three reviewers (M.P., B.G., R.E.) extracted data independently via an Excel sheet, including the author(s), year of publication, and study year's location: the study design, sample size, intervention type, mean duration for pain recovery, ulcer size or complete recovery, duration of follow-up and outcome. Finally, 26 studies were included in the systematic review for qualitative and quantitative analysis. Quantitative outcomes such as the mean difference, relative risk and odds ratio were associated with confidence intervals.

Qualitative analysis

The qualitative analysis compared the efficacy of various topical applications with that of triamcinolone acetonide for pain relief, overall healing time, patient satisfaction, and observed side effects. Twenty-six randomized clinical trials were qualitatively evaluated and compared with those of triamcinolone for efficacy in pain relief and overall healing. Salvian gel, Punica granatum and cannabinoid gel resulted in superior pain relief and faster healing than did triamcinolone. Laser therapies such as diodes, low-level lasers and photomodulation provide pain relief with no side effects, but the overall difference in healing time compared with that of triamcinolone was marginal. Compared with triamcinolone, low-level laser therapy (LLLT) provides superior outcomes in terms of pain reduction and ulcer healing [31]. Other laser therapies, such as diode lasers, both in contact and noncontact modes, also resulted in faster pain relief and ulcer healing than did triamcinolone [32]. Similarly, both pulsed and continuous carbon dioxide (CO2) lasers provided better pain relief than did triamcinolone, although no significant difference in ulcer size reduction was noted across the treatment groups [33]. Further research with larger sample sizes and extended follow-up periods is necessary to assess the long-term recurrence rates and cost-effectiveness of laser therapy [34]. (Table 2)

Sage (Salvizan) gel reduced pain at 1.5 days compared with 2.5 days, and overall wound healing occurred at 3.3 days compared with 6 days with triamcinolone. This might be due to the anti-inflammatory properties of sage [35]. Compared with triamcinolone, Rhus coriaria (Sumac) is associated with notable differences in pain reduction and ulcer size but is not significantly different [36, 37]. Punica granatum (pomegranate) gel and pomegranate flower tablets significantly reduce pain and healing time [26, 38]. Cannabidiol gel (CBD) reduced the ulcer size and healing time, but triamcinolone promoted faster healing. Although triamcinolone results in faster healing, CBD is preferred by patients because it does not have any adverse effects [39]. Compared with triamcinolone, aloe vera was superior in reducing pain and burning sensations, although the latter was more effective in ulcer healing [40]. Curcumin has demonstrated efficacy comparable to that of triamcinolone in reducing pain and ulcer size [41–43]. The comparative evaluation of triamcinolone acetonide with honey-based treatments revealed superior pain reduction, ulcer healing, and patient satisfaction while avoiding the side effects of corticosteroids.

The thyme-honey combination reduced the ulcer size and pain intensity. The ulcer size decreased on days 5 and 7, and lower pain scores were reported on days 3, 5, and 7. Additionally, the Oral Health Impact Profile (OHIP-14) scores indicated increased patient satisfaction in the thyme honey group [44, 45]. A honey-lemon spray (Mucotin) was as effective as triamcinolone ointment for reducing pain, burning sensation, necrosis, and erythematous area in RAS patients, with no significant differences between the two groups [46]. Another study revealed that honey is superior to triamcinolone in reducing ulcer size, pain, and erythema [47]. A comparative evaluation of triamcinolone acetonide with various other medications in the management of recurrent aphthous stomatitis (RAS) revealed that alternative treatments, including hyaluronic acid, microbiome therapy, placental extract gel, Triester glycerol oxide (TGO), and polyherbal formulations, show promising efficacy.

Hyaluronic acid (HA) is significantly more effective than triamcinolone in reducing pain and ulcer size because of its bioadhesive and wound-healing properties [48, 49]. Another study combined HA with microbiome therapy and reported that this combination resulted in even faster healing and greater pain relief than did triamcinolone alone[50]. Triester glycerol oxide (TGO) gel, a novel formulation, outperformed triamcinolone in terms of pain reduction and ulcer healing rates. TGO patients reported lower pain scores on days 2, 4, and 6 and faster ulcer size reduction, suggesting its efficacy in promoting mucosal protection and tissue repair [51]. HiOra SG gel, a polyherbal formulation, was as effective as triamcinolone in managing pain and ulcer severity without causing significant adverse effects [52].

A comparison between triadent (triamcinolone mucoadhesive paste) and Ora-Aid (a mucoadhesive patch) revealed that while triadent patches were more effective at reducing lesion size over time, Ora-Aid provided superior pain and burning sensation relief. This suggests that while triamcinolone remains effective, alternative formulations such as mucoadhesive patches may offer additional benefits in symptom management [53]. Compared with other topical treatments, Triamcinolone and Amlexanox (5%) have proven to be significantly more efficacious at reducing the number and size of ulcers, pain, erythema and exudate levels [54]. In addition, Amlexanox 5% oral paste was comparable to triamcinolone in terms of ulcer healing time; nonetheless, it was less effective in terms of peri-ulcer erythema (65%) and pain reduction (70%) than triamcinolone (90%) in the first 5 days in both groups. [55].

Table 2
Summary of studies included in the qualitative analysis

Authors	Sample Size	Efficacy of Triamcinolone (TA)	Efficacy of Compared Alternative Treatment
Tavangar et al. (2019) [26]	60	Less effective regarding pain relief time and wound healing time.	Wound healing time and pain relief in Punica granatum group were significantly lower than TA.
Huo et al. (2021) [31]	Not specified	Provided pain relief and ulcer healing, but slower than lasers	Laser therapy showed significantly faster pain reduction and ulcer healing
Hussein et al. (2021) [32]	Not specified	Effective in pain relief but slower than laser treatment	LLLT provided faster pain relief and better healing
Kour & Dwivedi (2020) [33]	Not specified	Effective but slower healing than lasers	Noncontact diode laser was the most effective in pain relief and ulcer healing
Seyyedi et al. (2020) [34]	Not specified	Effective but comparable to CO_2 laser in ulcer size reduction	CO_2 laser provided superior pain relief but no significant difference in ulcer size reduction
Abbasi et al. (2023) [35]	60 (30 each)	Mean duration of pain recovery 2.5 days for TA Duration of wound healing is 6 days for TA	Mean duration of pain recovery 1.5 days, and wound healing is 3.3 days for Salvizan. Salvizan gel was significantly better than TA in the pain recovery and wound healing.
Lavaee et al. (2022) [36]	22 (11 each)	There were no significant differences between VAS change and lesion size in the intergroup.	In intragroup comparison: significant differences for ulcer lesion in all time points and most time points for pain for Rhus coriaria
Rezvani et al. (2025) [37]	60	Triadent took the longest time to heal ulcers.	Sumac group exhibited the shortest healing time, significantly reduced lesion size, and had lower Visual Analog Scale scores.
Lavaee et al. (2024) [38]	60	Triadent was less effective. The VAS from day 1 to 6 for Triadent and PG flower tablet was significant and noticeable.	Punica granatum was significantly better than TA for all mean values of VAS & size of oral lesions on all days except on day 1 for ulcer size.
Umpreecha et al. (2023) [39]	69	Both groups significantly reduced ulcer size	CBD reduced ulcer size and accelerated ulcer healing without side effects. CBD exerted

Authors	Sample Size	Efficacy of Triamcinolone (TA)	Efficacy of Compared Alternative Treatment
		TA as the most preferred intervention followed by CBD.	anti-inflammatory effects in the early stage and an analgesic effect in the late RAU stage. Thus, CBD might be more appropriate for RAU patients who decline to take topical steroids.
Giroh et al. (2019) [40]	34	TA is more effective than aloe vera in wound healing (measured by the diameter of the ulcer).	Aloe vera gel had a better response regarding pain and burning sensation.
Raman et al. (2020) [41]	60	TA reduced mean ulcer size & pain significantly. TA is able to minimize ulcer size a little earlier than curcumin.	Curcumin is a better choice in children, pregnant women, and lactating mothers, and immunocompromised individuals due to their safety.
Kia et al. (2020) [42]	58	No statistical differences in TA and curcumin in pain severity, lesion size or efficacy index.	Curcumin is as effective as 0.1% of TA and could be used for contraindicated patients against corticosteroids.
Deshmukh & Bagewadi (2014) [43]	60	No statistical significance was noted in the pain, size, number & duration of ulcer, on comparison between TA & Curcumin	Curcumin & TA showed similar efficiency in the treatment of minor RAS. Curcumin gel can be used as an effective and safer alternative to steroids in the treatment of RAS.
Ghalwash et al. (2025) [44]	30 patients (15 per group)	Reduced pain and ulcer size, but slower healing than thyme honey	Thyme honey showed greater ulcer size reduction on days 5 and 7, and greater pain relief on days 3, 5, and 7
Mhapuskar et al. (2022) [45]	60 patients (30 per group)	Effective in reducing pain and ulcer size but associated with mild side effects	Honey effectively reduced ulcer size and pain with better patient compliance and no side effects.
Shirzaiy et al. (2023) [46]	46 patients (23 per group)	Reduced pain, burning sensation, necrosis, and erythematous area	Honey-lemon spray had similar efficacy as triamcinolone and was well tolerated

Authors	Sample Size	Efficacy of Triamcinolone (TA)	Efficacy of Compared Alternative Treatment
El-Haddad et al. (2014) [47]	94 patients, 180 ulcers	Effective but slower healing than honey	Honey was significantly more effective in reducing ulcer size, pain, and erythema.
Mustafa & Alzubaidee (2020) [48]	Not specified	Effective but less rapid pain relief than HA	Hyaluronic acid provided greater pain relief and faster healing
Koray et al. (2016) [49]	60	Provided pain relief but no significant difference in ulcer size and VAS scores on day 0	The pain score in HA group was statistically lower than that of the TA groups at days 4 and 7
Ramesh & Sadaksharam (2021) [50]	Not specified	Effective but slower healing than combination therapy	HA + microbiome therapy showed faster healing and better pain relief
Ofluoglu et al. (2017) [51]	180 patients	Effective but slower pain reduction than TGO	TGO showed greater pain reduction and faster ulcer healing
Nayak et al. (2023) [52]	Not specified	Effective but had some side effects	HiOra SG gel was equally effective and better tolerated
Barzegar et al. (2024) [53]	40 patients	Triadent was more effective in reducing ulcer size over time	Ora-Aid was better for pain and burning sensation relief
Sharma, et al. (2018) [54]	50	TA & Amlexanox proven to be more efficacious in reduction of size, number, pain, erythema and exudate Levels	Amlexanox & Triamcinolone were equally effective in patients suffering from Recurrent Aphthous Ulcers (RAU)
Shrivasta et al. (2018) [55]	40	90% of TA participants showed complete improvement of peri-ulcer erythema & pain reduction and ulcer size from 1st to 5th day. Completely healed ulcers in 70% of TA.	65% of amlexanox participants showed complete improvement of peri-ulcer erythema & 70% for pain reduction. Mean ulcer size reduced from 1st to 5th day. Completely healed ulcers in 75% of participants in the amlexanox group.

Quantitative results

The meta-analysis utilized random effects models to account for variability across studies.

We analyzed 14 RCTs encompassing 836 patients with aphthous ulcers, with 428 patients in the experimental group (Hiora SG gel, curcumin, thyme honey, Punica granatum flower, Rhus coriaria, honey, honey lemon, hyaluronic acid, amlexanox, triester glycerol oxide, and ora-aid) and 408 in the control group (triamcinolone). Quantitative analysis was performed to compare the efficacy of the topical application of triamcinolone with that of other topical applications in treating recurrent apthous ulcers. Efficacy was tested by comparing pain relief via the visual analog scale (VAS), pain recovery time, and overall ulcer healing time.

This plot displays the mean difference in visual analog scale (VAS) scores between the experimental (Hiora SG gel, curcumin, thyme honey, Punica granatum flower, Rhus coriaria, honey, honey lemon, hyaluronic acid, amlexanox, triester glycerol oxide, and ora-aid) and control groups (triamcinolone), providing an estimate of the intervention's effect on pain reduction compared with triamcinolone. The estimated overall effect size was 0.43 (95% CI: 0.08–0.79, p = 0.01), suggesting that the experimental treatment significantly reduced pain compared with the control treatment. (Fig. 2)

The value of I^2 = 82% indicates high heterogeneity, which means that the variability in effect sizes among studies is substantial. The possible reasons for heterogeneity can be differences in study populations (e.g., variations in age, severity of pain), variability in intervention types (different formulations of experimental treatments) or differences in follow-up periods (some studies may have measured VAS reduction at different time points). A funnel plot was also used to review publication bias (Fig. 3). The funnel plot did not indicate any asymmetry. Therefore, there was no publication bias. Additionally, Egger's test did not support the presence of funnel plot asymmetry (p = 0.834).

The next step for quantitative analysis was to test the efficacy of the mean pain recovery time. A forest plot included four studies reporting the mean pain recovery time of patients with recurrent aphthous ulcers as an outcome between the experimental (sage, Punica granatum, curcumin, and rhus coriaria) and control groups (triamcinolone). A total of 182 patients were involved, with 91 in the experimental group and 91 in the control group. On the basis of the analysis performed via the random effects model with the inverse variance method to compare the standardized mean difference (SMD), there was no significant difference between the pain recovery times of the two groups, with a summarized standardized mean difference (SMD) of 2.62 and a p value of 0.36. (Fig. 4)

Significant heterogeneity was detected, suggesting inconsistent magnitude and/or direction effects. The I^2 value indicates that 98% of the study variability arises from heterogeneity rather than random chance. The possible reasons for high heterogeneity may be large variability in patient populations (e.g., different pain severity levels, underlying conditions); differences in pain recovery measurement methods across studies; inconsistent intervention protocols, including dosage, duration, and type of experimental treatment; or outlier studies with disproportionately large effect sizes.

The third parameter, the ulcer healing time, was assessed. Five RCTs encompassing a total of 245 patients with recurrent aphthous ulcers, with 122 patients in the experimental group (sage, diode laser, punica granatum, aloe vera, and curcumin) and 123 in the control group (triamcinolone), compared with the mean difference in ulcer healing time among patients. The negative effect size of – 1.28 (–2.33, –0.23) suggests that the experimental group had a significantly greater reduction in ulcer healing time than the control group did at $p < 0.05$. (Fig. 5)

The high heterogeneity ($I^2 = 92\%$) suggests that the pooled estimate should be interpreted with caution. Possible reasons for high heterogeneity include variability in sample sizes and patient demographics across studies, differences in intervention methods (e.g., dosage, frequency, administration method) or measurement inconsistencies in the recorded outcomes (e.g., variations in how pain or healing was assessed).

A subgroup analysis of the mean difference in visual analog scale (VAS) scores between the natural experimental (Hiora SG gel, curcumin, thyme honey, P. granatum flower, H. coriaria, honey, and honey lemon) and control groups was conducted, providing an estimate of the effects of the natural intervention on pain reduction compared with those of Triamcinolone (Fig. 6). Overall, eight studies were analyzed, with 470 subjects with aphthous ulcers, 240 subjects in the experimental cohort and 230 subjects in the control cohort. According to the analysis performed via the random effects model, there was a significant difference between the two cohorts; the summarized standardized mean difference (SMD) was 0.45, suggesting that the natural form of treatment provides significant pain relief compared with triamcinolone. Significant heterogeneity was detected, suggesting inconsistent magnitude and/or direction effects. The I^2 value indicates that 77% of the study variability arises from heterogeneity rather than random chance.

Subgroup analysis of the mean difference in visual analog scale (VAS) scores between the synthetic experimental (hyaluronic acid, amlexanox, triester glycerol oxide, or ora-aid) and control groups (triamcinolone) was performed, providing an estimate of the effect of the synthetic intervention on pain reduction compared with that of triamcinolone. A total of six studies were included, encompassing 366 patients with aphthous ulcers, with 188 in the experimental group and 178 in the control group. The standardized mean difference from the random effects forest plot was 0.42 (-0.24, 1.09), suggesting that the synthetic intervention reduced pain intensity in patients more than did triamcinolone, but the difference was not significant. (Fig. 7). The I^2 value indicates that 88% of the variability among studies arises from heterogeneity rather than random chance.

Few studies were eliminated from the quantitative analysis because the outcomes did not meet the criteria for parameters in the meta-analysis. A funnel plot was not generated because there were fewer studies on pain recovery and ulcer healing time.

Risk of Bias:

The risk of bias assessment was performed using the Cochrane ROB Version 2 tool to evaluate the transparency of the evidence synthesis results and findings. Each of the selected studies was included for risk of bias assessment. A web based tool “robvis” was used to generate the graphical visualization of the risk of bias analysis. [28, 29].

Discussion

Triamcinolone is an anti-inflammatory agent that inhibits the release of proinflammatory mediators; hence, it is a common topical treatment for RAU [7, 10]. However, alternative effective natural and synthetic treatments have gained attention because of the potential side effects of corticosteroids. Triamcinolone has been reported to have associated side effects such as dry mouth, candidiasis, nausea, immune suppression, fatigue, fluid retention, and osteoporosis, impeding hormonal balance and digestive troubles[11, 44, 45, 56]. As a result of the vast number of side effects, more alternative options have gained patient acceptance[57]. Several natural topical treatments, such as honey[23, 45, 47], sage (**Salvia** officinalis)[35], chamomilla[20], pomegranate (**Punica** granatum) extracts[10, 25, 26, 38, 58], curcumin[41–43] and aloe vera[19, 40], have demonstrated comparable efficacy to corticosteroids while offering minimal side effects. In addition, synthetic alternatives such as low-level laser therapy (LLLT)[12, 31, 32], hyaluronic acid[18, 48, 49], microbiome-based treatments[50] and mucoadhesive patches[53] have effectively reduced pain and promoted healing. Variability across studies suggests that further research is needed to explore subgroup differences and patient population responses.

The current study revealed that natural alternatives such as honey and curcumin provide fast pain relief and healing without side effects. When evaluating patient satisfaction, treatments such as rhus coriaria, honey, curcumin, aloe vera and Punica granatum resulted in greater patient satisfaction than did corticosteroids, as there were no adverse reactions[37–39, 42, 43, 46–48]. This finding is similar to those of many other studies[10, 23, 59–61]. Compared with triamcinolone, synthetic alternatives, such as laser therapy and hyaluronic acid, are more effective in overall healing, including reducing the recurrence of aphthous ulcers for a longer time[31–34, 48–50]. This finding is similar to the findings of other authors[57, 62–64]. The ability of cannabidiol (CBD) gel to reduce ulcer size and healing time, albeit with slower healing than triamcinolone, is a novel finding[39]. This finding adds to the growing body of evidence on the potential therapeutic applications of cannabinoids in oral health[65]. Importantly, the current meta-analysis (Fig. 2) demonstrated a moderate effect size favoring alternative treatments over triamcinolone. These findings indicate that alternative treatments produced, on average, a moderate improvement in outcomes compared with those of triamcinolone. Some studies[38],[53] have reported substantial benefits of alternatives. Conversely, few studies have shown either minimal or negative effect sizes, indicating potential variability in response depending on the agent used and patient population[45, 46, 55].

Among synthetic alternatives, low-level laser therapy (LLLT) and other laser-based modalities, such as diode and CO_2 lasers, provide rapid pain relief with minimal side effects. However, their impact on the overall healing time compared with that of triamcinolone was modest[12, 31–34]. Nonetheless, given the

noninvasive and reproducible nature of laser treatments[12], they offer valuable options for patients seeking steroid-free alternatives, especially in cases of recurrent or refractory ulcers[66], during which the epithelization of the RAS has been considerably accelerated, making the use of LLLT better than the use of pharmacotherapy in the RAS[67]. Similarly, another study revealed that combining laser therapy with hyaluronic acid surpassed triamcinolone in terms of healing time and pain relief [68]. HA, either alone or combined with microbiome-based treatments, has demonstrated superior pain control and mucosal healing outcomes, likely due to its bioadhesive and regenerative properties[18]. This finding is consistent with systematic review observations[64]. Interestingly, topical application of a novel formulation of Triester glycerol oxide (TGO) outperformed triamcinolone in terms of pain reduction and ulcer healing, with an easily applicable and accessible procedure and no side effects, suggesting a potential future role in mucosal protection and repair[51]. When evaluating patient satisfaction, natural therapies such as curcumin[41–43], aloe vera[40], Rhus coriaria[36, 37], and cannabidiol[39] are preferred over triamcinolone because of the lack of adverse effects. This observation is similar to that of various other studies[2, 19, 56, 63], which emphasized the importance of considering patient preferences and quality of life when selecting treatments for recurrent aphthous ulcers.

Strengths and limitations:

This review is one of the first to comprehensively compare topical triamcinolone with a broad range of alternative topical treatments, providing robust quantitative data through meta-analysis. However, the current study has several limitations, including variations in the study outcomes, ulcer types, and follow-up intervals. Additionally, long-term recurrence and cost-effectiveness data for newer therapies are lacking.

Conclusion

These findings suggest that natural and synthetic alternatives may provide effective, safer patient options, challenging the traditional reliance on corticosteroids such as triamcinolone. These findings indicate that natural agents such as honey, sage, and pomegranate could be considered first-line treatments for patients with RAS, particularly those intolerant to corticosteroids or those who experience frequent recurrences. Laser-based therapies may be integrated for severe cases, in addition to novel agents such as hyaluronic acid-microbiome combinations and TGOs, which warrant further investigation. Future research should prioritize standardized outcomes, longer follow-up periods to capture recurrence rates, and cost-effectiveness evaluations, with a focus on patient-reported outcomes to ensure patient-centered care. An important finding from our review is that patients often favor natural remedies or alternative treatments that offer comparable efficacy to that of triamcinolone without the potential side effects associated with corticosteroids. This finding also endorses patient preference toward natural, safe and effective therapies that minimize systemic exposure to corticosteroids.

Declarations

Additional Information:

Competing interests:

The authors declare no competing interests.

Author Contribution

Conception or design of the work, methodology- L.A., R.E., M.K, M.AData collection and validation- R.E., L.A., M.K., R.G., M.A, B.G., M.PAnalysis of data- R.E., L.A., R.G., B.G., M.P.Drafting the work or revising it critically for important intellectual content- R.G., L.A, R.E., B.GReview editing and final approval of the version to be published: B.G., L.A., R.E.

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Data Availability

Not applicable as this is a systematic review of publicly available articles. Any analytical data can be obtained from the corresponding author, if necessary.

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Figures

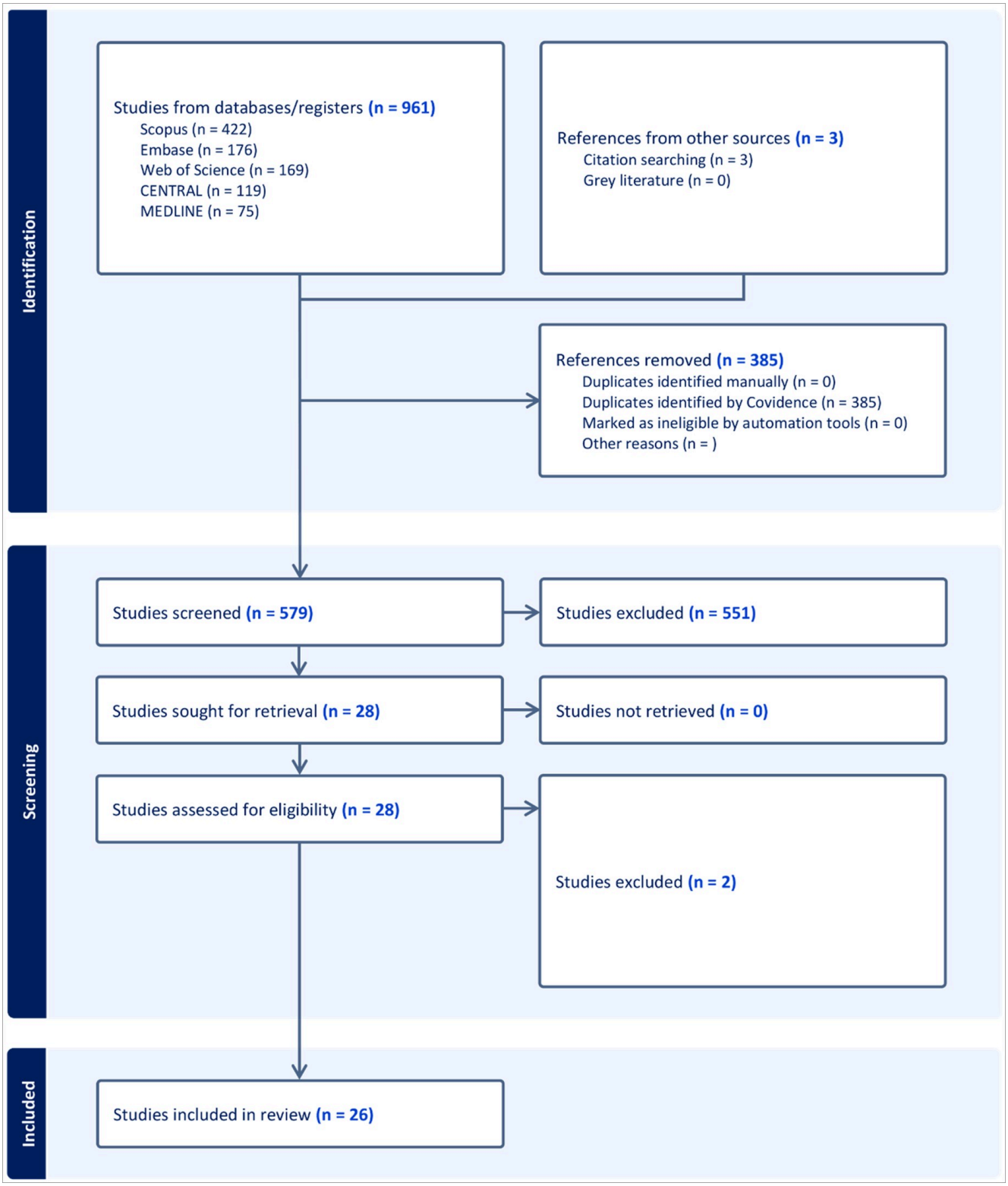

Figure 1

PRISMA chart

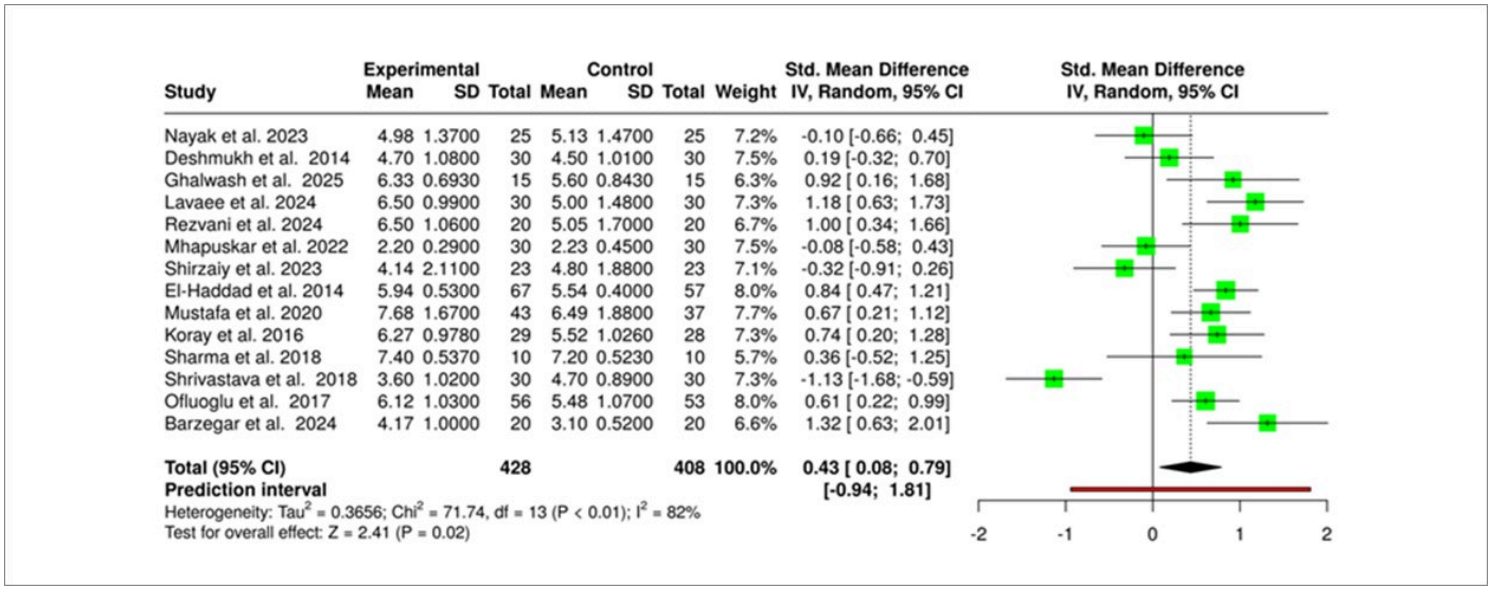

Figure 2

Forest plot denoting the standardized mean difference in visual analog scale (VAS) scores between the experimental and control groups

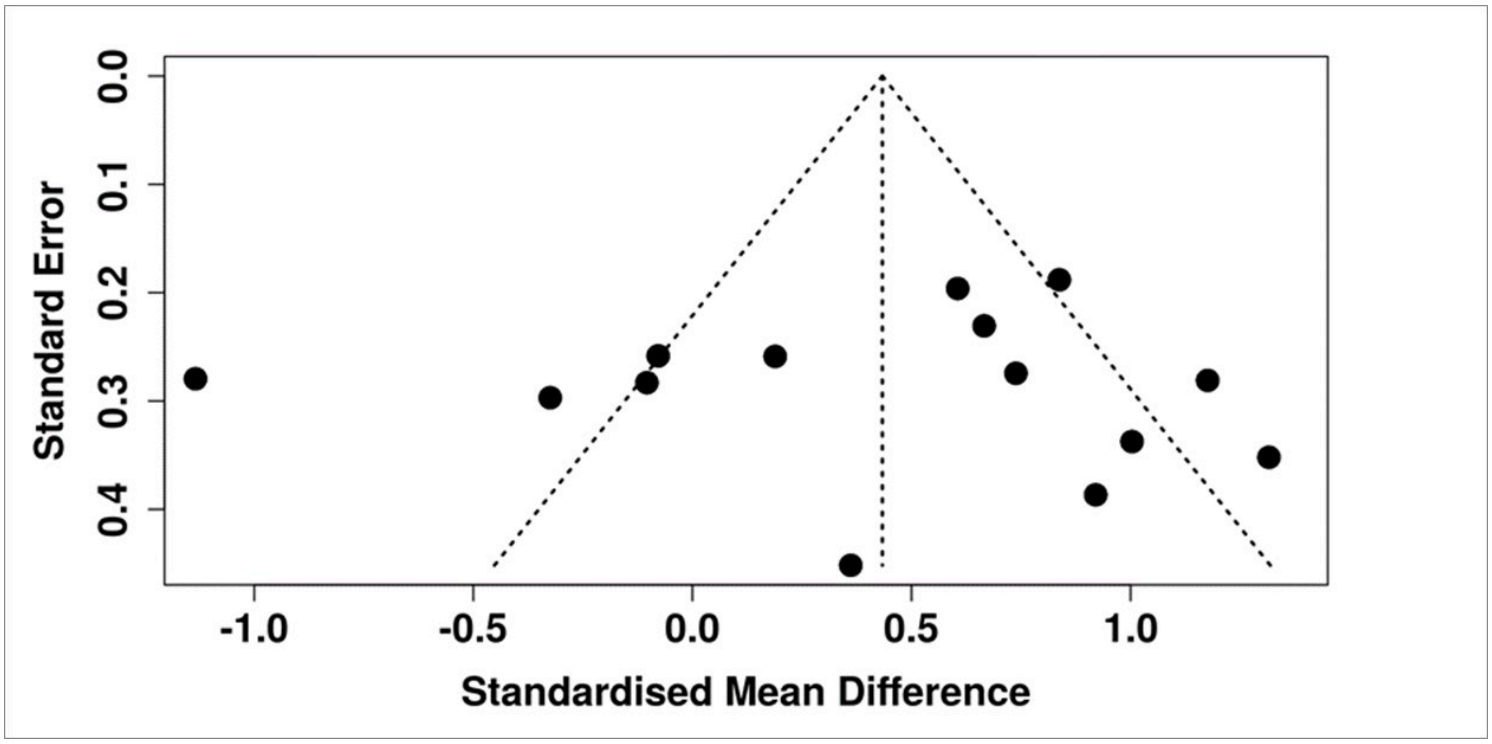

Figure 3

Funnel plot for standardized mean differencesin VAS scores between the experimental and control groups.

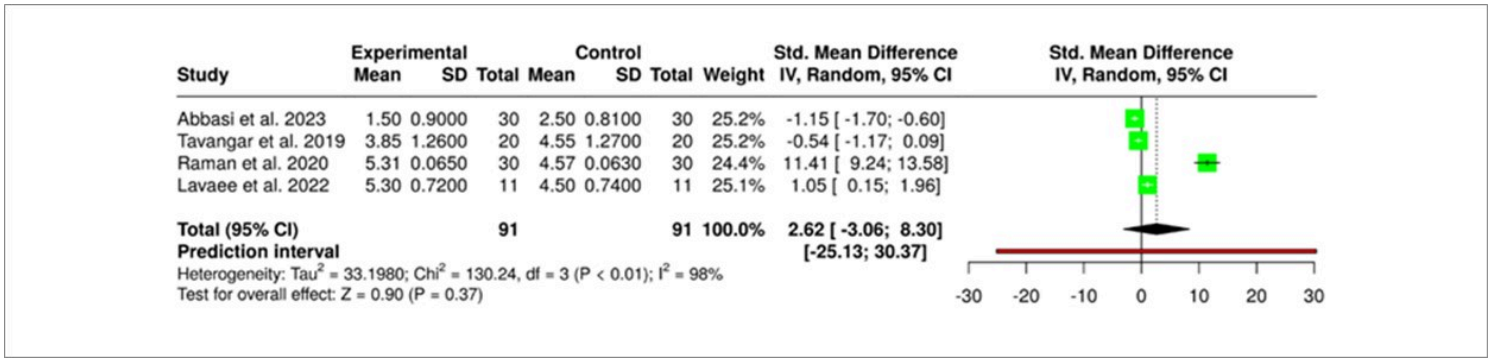

Figure 4

Forest plot denoting the standardized mean difference in pain recovery time between the experimental and control groups.

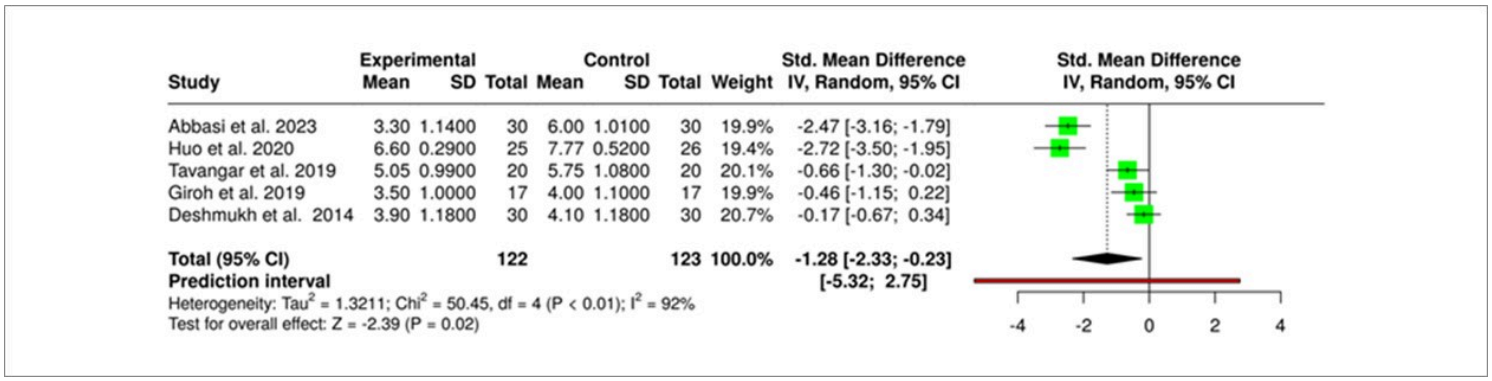

Figure 5

Forest plot depicting the standardized mean difference in ulcer healing time between the experimental and control groups.

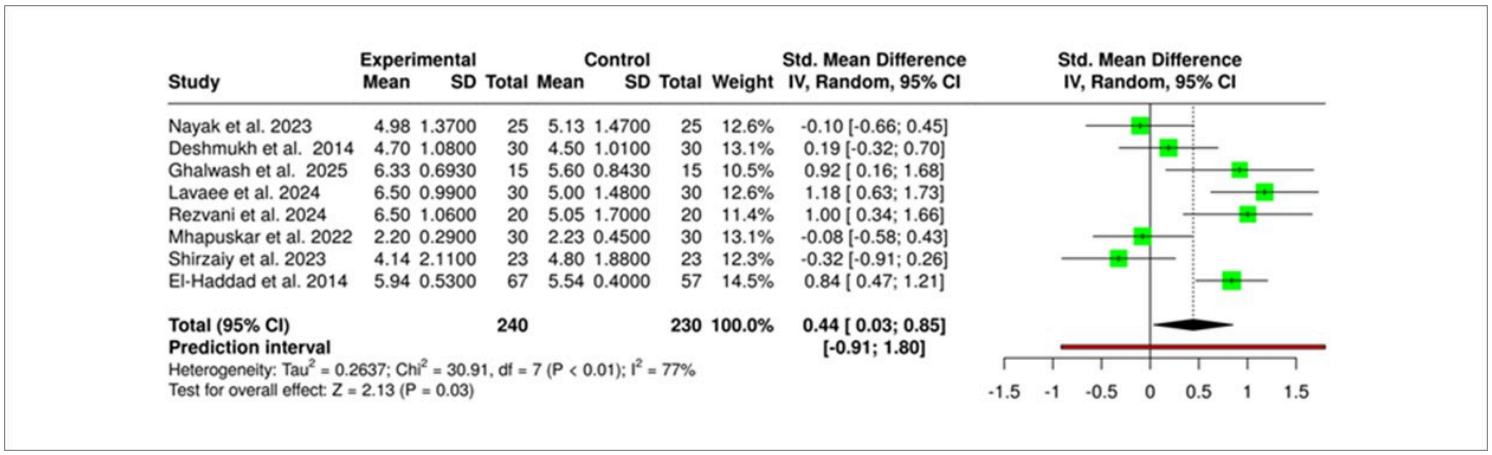

Figure 6

Forest plot depicting the standardized mean difference between natural topical application and triamcinolone.

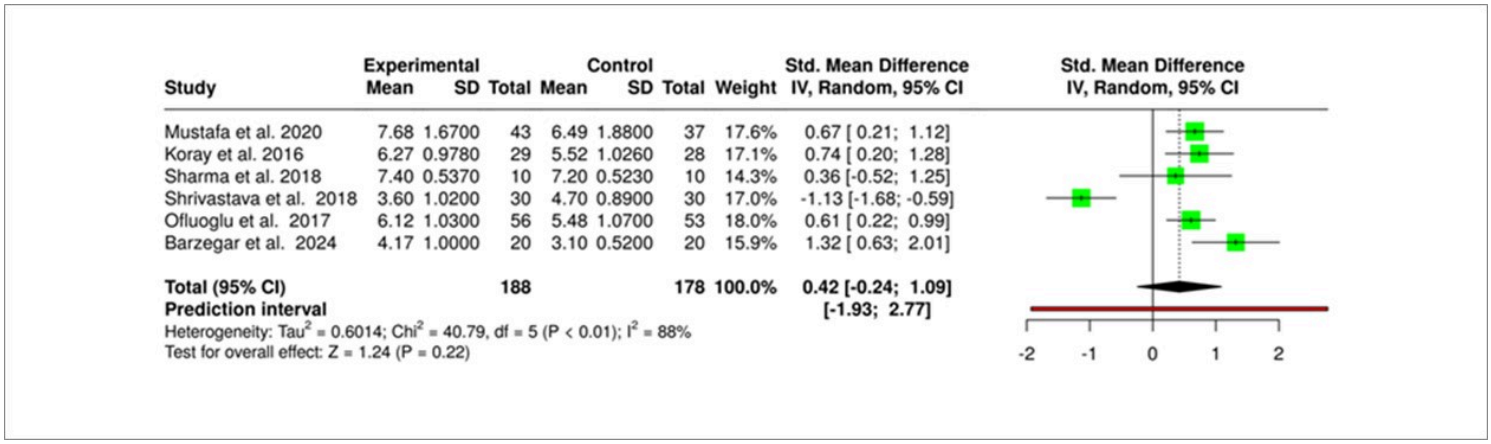

Figure 7

Forest plot depicting the standardized mean difference between synthetic topical application and triamcinolone

Supplementary Files

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