

Role of Rebamipide in Treatment of Aphthous Ulcers: A Systematic Review

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HOW TO CITE:

Anlin Anto, Jayanth Kumar Vadivel, Ashir KR, Anuna Laila Mathew (2026). Role of Rebamipide in Treatment of Aphthous Ulcers: A Systematic Review. International Journal of Special Education, 41(2), 624-634

ABSTRACT:

Aphthous ulcers, also known as aphthous stomatitis, particularly affect the non-keratinized mucosa of the oral cavity. Although the precise cause of aphthous ulcers remains uncertain, several factors such as stress, trauma, immune responses, and viral infections are believed to play a role. Given the multifactorial nature of this condition, treatment primarily targets the relief of symptoms like pain or burning, typically using topical anesthetics or antiseptics. The aim of this review was to assess the efficacy of Rebamipide in achieving these therapeutic outcomes, including pain relief, reduction in ulcer size and duration, and prevention of recurrence. Search was conducted by electronic databases to determine the clinical trials on Rebamipide use in aphthous ulcers and Behçet's disease. Randomized controlled trials, cohort, and case-control studies were included. Data extraction and quality assessment were conducted independently by two reviewers. There were 3 RCTs included in the present systematic review. Clinical evidence shows Rebamipide has anti-inflammatory and mucosal-protective properties. Additionally, it reduces the pain significantly, size of ulcers and healing period. Few studies noted that decreased rate of recurrence with prolonged therapy. Rebamipide seems beneficial in reducing the symptoms and healing of ulcer. Large-scale, high-quality randomized controlled trials are essential to confirm the efficacy for the development of standardized treatment protocols. Clinical significance: This analysis examines current trial data through strict appraisal methods, seeking coherence amid variation. Insights gathered may guide medical professionals, while also highlighting the directions of further studies.

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Keywords: Aphthous Ulcers, Behçet disease, Drugs, Management, Oral ulcers, Rebamipide

INTRODUCTION

RAS is a common oral mucosal condition characterized by recurrent, painful ulcers on non-keratinized surfaces such as the labial or buccal mucosa, soft palate, and floor of the mouth. It usually appears erythematous border with shallow base, affect 5–25% of the global population. Adolescents and young adults are commonly

affected (Porter & Scully, 2007; Preeti et al., 2011). RAS can significantly affect the mastication, speech, and quality of life, although it is self-limiting.

Local trauma, food hypersensitivity, nutritional deficiencies, hormonal changes, stress, microbial factors, systemic diseases, and genetic predisposition are the multiple causative factors (Preeti et al., 2011; Altenburg et al., 2014; Mattioli et al., 2021). Intriguingly, chewing tobacco can cause partial protection through keratinization of mucosa (Queiroz et al., 2018).

First-line management include local anesthetics, topical corticosteroids, antiseptics, and amlexanox, while refractory cases may require systemic agents such as thalidomide, colchicine, dapsone, or other immunosuppressants (Porter & Scully, 2007; Altenburg et al., 2014). Due to adverse effects, delayed onset, relapse after discontinuation, systemic options have limitations (Preeti et al., 2011; Porter & Scully, 2007; Oray et al., 2016). Formerly, Rebamipide a 2-(1H)-quinolinone derivative introduced for gastric ulcers (Verma et al., 2023; Takeuchi et al., 2003; Takeuchi et al., 2010; Kak, 2025). It has multifaceted mechanism of action, includes synthesis of prostaglandin, scavenges ROS, enhance epithelial regeneration, and healing of mucosa without the systemic toxicity of immunosuppressants (Matsuda et al., 2003; M K et al., 2014; Hasan et al., 2022). It is beneficial in both RAS and systemic disease-associated aphthous ulcers, and provide a superior safety compared to Levamisole (Bhargava et al., 2023; Lau & Smith, 2022; Chiang et al., 2019). Combination therapy with 5% amlexanox paste may further accelerate healing (Binnie et al., 1997; Khandwala et al., 1997). Because of adverse effects associated with conventional treatment

modalities, attention remains on supplementary options capable of supporting natural repair processes without compromising safety in management of aphthous ulcers. Despite multiple trials examining rebamipide for aphthous ulcers, findings span varied causes, preparations, and evaluation methods; thus, a systematic analysis remains absent. The novelty of this review emerges through its systematic appraisal of current data, assessing effectiveness and tolerability while mapping inconsistencies - offering clarity where prior work falls short, shaping the future in study and practice.

This systematic review sought to examine how well rebamipide works, along with its safety, when used for aphthous ulcers. Objectives focused on healing speed, lessening discomfort, and recurrence rate - measured against standard treatments or inactive controls. The research question centers on whether Rebamipide lessens discomfort/pain among individuals suffering from recurring aphthous ulcers.

The hypothesis of the present review was that rebamipide, serving as both a protective shield for mucosal tissue and an agent against inflammation, might outperform placebos or standard therapies when used in treating aphthous ulcers. Owing to its ability to boost natural defenses within the oral cavity - through enhanced prostaglandin activity, support of cell regrowth, and reducing inflammation - the rebamipide shows promise. This review aims to locate applicable research on rebamipide's role in treating aphthous ulcers through structured methods. Pain reduction, changes in lesion dimensions, time until recovery, along with frequency of reappearance form the core outcomes under scrutiny. Instead of merely listing findings, it weighs how consistently results appear across trials. Safety considerations emerge by examining adverse reactions documented during usage periods. Evidence strength surfaces when study designs face methodical inspection. Clinical relevance follows only after weighing consistency, precision, and limitations present within data. Relevance in practice hinges less on isolated reports but more on reproducible patterns seen throughout available literature.

METHODS

The review process adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021), ensuring methodological rigor and transparency with PROSPERO ID CRD420250652184

Focused question:

"What is the efficacy and safety of Rebamipide in reducing pain, ulcer size, healing time, and recurrence in patients with aphthous ulcers?"

The research question was formulated based on the PICO framework: [Table 1]

Table 1: PICO criteria for the current systematic review

Study (Author, Year)	Randomization	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Parvathi Devi et al. (2014)	Some concerns	High	Low	High	Some concerns	High
Matsuda et al. (2003)	Low	Low	Low	Low	Low	Low
Hasan et al. (2022)	Some concerns	High	High	High	Some concerns	High

Eligibility criteria:

This review includes randomised clinical trials, text in English language. Studies comparing the efficacy of rebamipide with placebo, other biological agents, or standard treatments. Inclusion criteria include a study reporting at-least one clinical outcome, such as pain reduction, ulcer size reduction, and recurrence rates.

Exclusion criteria were studies not involving recurrent aphthous ulcers, those where Rebamipide was not the primary intervention, and non-original research such as systematic reviews, case reports, or case series. Studies published only as abstracts, lacking full-text, without relevant outcomes, or without a suitable comparator group were also excluded.

Information sources and Search strategy:

The data search was primarily conducted through electronic searches of well-known databases, including PubMed, Google Scholar, Scopus, and The Cochrane Central Register of Controlled Trials (CENTRAL). The search was limited to

articles published between January 1, 1995, and January 31, 2026.

A set of keyword combinations: "Recurrent aphthous ulcers"[Mesh] OR "aphthous stomatitis"[Mesh] OR "recurrent mouth ulcers" [Title/Abstract] OR "RAU" [Title/Abstract] OR "oral ulcers"[Title/Abstract] AND "Rebamipide"[Mesh] OR "Rebamipide"[Title/Abstract] AND "placebo"[Title/Abstract] OR "control group" [Title/Abstract] OR "standard treatment" [Title/Abstract] OR "comparison group" [Title/Abstract] AND "pain reduction" [Title/Abstract] OR "ulcer size" [Title/Abstract] OR "recurrence" [Title/Abstract] OR "healing time" [Title/Abstract] OR "treatment outcome" [Mesh] OR "treatment efficacy" [Title/Abstract] were used to search the literature in all the databases to ensure that all relevant articles were screened.

Study selection:

It was a two-stage process performed by two reviewers (NC and RD) independently. Titles and

abstracts were evaluated. Using predefined selection criteria, the studies were performed. Any disagreements during the selection process were resolved through conversation among the reviewers.

Data collection process:

Two reviewers (NC and RD) manually extracted information using a pre-designed MS Excel sheet, which includes study and participant characteristics (sample size, demographics), intervention and comparator details, outcome measures, and results.

Risk of bias and quality of assessment:

Based on the type of study, ROB was categorised. In the current review for included RCTs, the Cochrane Collaboration's ROB 2 tool (Sterne et al., 2019) was used to evaluate validity.

Data synthesis:

Findings were narratively synthesized based on intervention type, population characteristics, outcome measures, and intervention details. Meta-analysis was not performed due to insufficient suitable data.

RESULTS

Literature search:

A total of 51 studies were identified through a database search. After removing irrelevant, non-clinical, and duplicate studies based on title and abstract screening, 41 articles remained. Further, 34 studies were excluded due to non-randomized designs, irrelevant outcomes, or methodological limitations. Ultimately, 3 studies met the inclusion criteria and were included in the final analysis. The detailed selection process is illustrated in [Figure 1] The kappa value was 0.98, indicating strong agreement among the investigators.

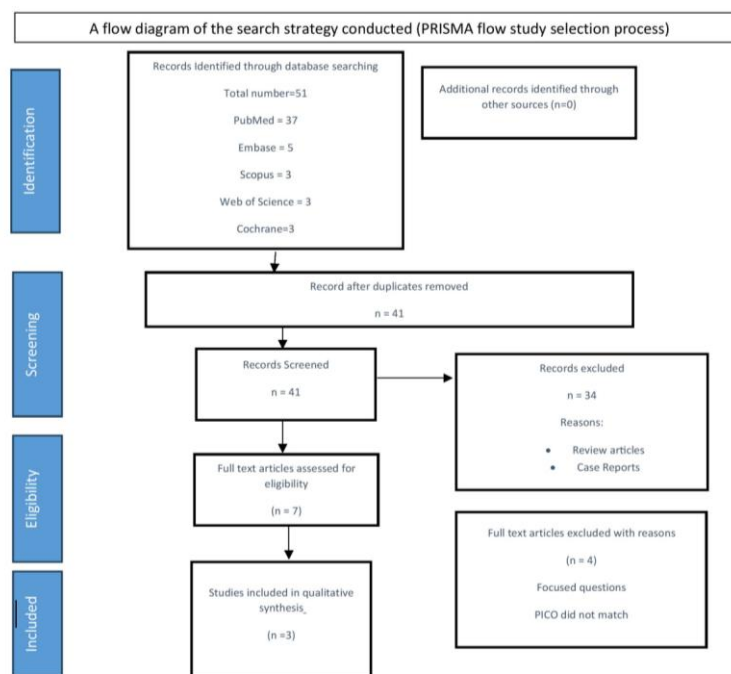


Figure:1 Prisma Chart

General characteristics of included studies:

Parvathi Devi et al. (2014) conducted a randomised controlled study with 100 RAS patients. They are divided equally into two groups receiving oral Rebamipide or Levamisole. Ulcer size, count, pain scores, and recurrence over three

months were the outcomes mentioned. Results were analyzed using t-tests and Mann-Whitney tests which is reported as means and standard deviations. No significant differences were observed in groups such as number of episodes ($p = 0.43$), number of ulcers ($p = 0.75$), and ulcer

size ($p = 0.91$). Both groups showed clinical improvement across outcome measures, indicating comparable tolerability and effectiveness of Rebamipide and Levamisole.

Shamimul Hasan et al (2022) carried out a randomized clinical trial which includes 150 healthy patients aged 15–65 years. Group A received Rebamipide tablets (100 mg orally) combined with 5% Amlexanox paste, while Group B was treated with Dologel CT. The follow-up for 30 days. Ulcer size decreased in Group A by day 5 (–85.2%), and day 10 (–98.8%), compared with Group B, which decreased from (–68.5%) by day 5, and (–96.1%) by day 10, with a significant difference at day 5. Pain scores (VAS) in Group A dropped by day 5 (–85.3%) and by day 10 (–99.2%), while Group B reduced (–66.7%) by day 5 and (–98.3%) by day 10. Erythema scores in Group A improved (–84.5%) by day 5, whereas Group B improved (–60.9%), with differences approaching statistical

significance ($p \approx 0.07$). Most ulcers in Group A healed within 10–15 days, compared with 15–30 days in Group B.

Matsuda et al (2003) performed a multicentre, double-blind, placebo-controlled trial in 35 Behçet's disease patients with recurrent oral aphthae. Rebamipide (300 mg/day) or placebo was administered for 12–24 weeks, with daily ulcer and pain logs plus global improvement scores. 65% of patients in the Rebamipide group achieved moderate to marked improvement

compared with 36% in the placebo group. Pain scores initially improved in both groups, but after 3 months worsened in the placebo group, whereas they continued to decline in the Rebamipide group, demonstrating sustained benefit. In patients with severe baseline disease, Rebamipide consistently reduced ulcer burden and pain, while the placebo group worsened during months 4–6 ($p < 0.01$).

Table 2: Literature Search Strategy

Database	Search Terms Used	Number of items found
PubMed/MEDLINE	(“Recurrent aphthous ulcers”[Mesh] OR “aphthous stomatitis”[Mesh] OR “recurrent mouth ulcers” OR “oral ulcers” OR RAU) AND (“Rebamipide”[Mesh] OR Rebamipide) AND (“placebo” OR “control group” OR “standard treatment” OR “comparison group”) AND (“pain reduction” OR “ulcer size” OR “recurrence” OR “healing time” OR “treatment outcome” OR “treatment efficacy”)	37
Scopus	(“recurrent aphthous ulcers” OR “aphthous stomatitis” OR “oral ulcers” OR “RAU”) AND (Rebamipide) AND (placebo OR control OR comparison) AND (pain OR recurrence OR healing OR efficacy)	3

Web of Science	("aphthous stomatitis" OR "oral ulcers" OR "RAU") AND (Rebamipide) AND (placebo OR control OR comparison) AND (pain OR recurrence OR healing OR efficacy)	3
Cochrane Library	Rebamipide AND (aphthous OR stomatitis OR "oral ulcer*") AND (placebo OR control OR comparison) AND (pain OR recurrence OR healing OR efficacy)	3
Embase	Rebamipide AND recurrent aphthous OR oral ulcers AND placebo OR control OR standard treatment AND pain reduction OR ulcer size OR recurrence OR healing time OR efficacy	5

Risk of bias (ROB) assessment:

The quality of these included trials was assessed for risk of bias using the ROB 2.0. Among these three trials, Matsuda et al (2003) remain rather rigorous compared with Parvathi Devi et al (2014) and Hasan et al (2022) regarding randomization methods. Even though they have randomization, they have not mentioned these methods. Both have no blinding technique, which might

increase risk and bias regarding subjective parameters, such as pain and size of ulcers. But they have no missing participants. None were externally registered, so there might be some selective reporting.

On the whole, Matsuda et al (2003)¹¹ had a low risk, and the remaining two trials (Parvathi Devi et al 2014; Hasan et al., 2022) were at a high risk. Based on these values, the remaining three trials were eligible for pooling. [Figure 2]

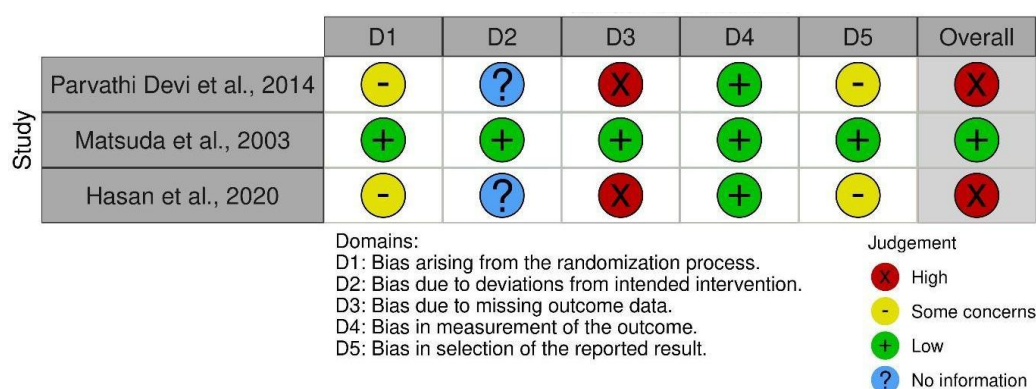


Figure 2: The ROB of RCT a) Individual study, and b) the overall summary

DISCUSSION

RAS is a chronic inflammatory condition with multifacet causative factors. Therapeutic effect of Rebamipide plays a increased role in RAS and

Behçet's disease (Kudur & Hulmani, 2013). Rebamipide has a property of mucosal protection, improves healing and reduce ulcer recurrence (Arakawa et al., 1998).

In a study conducted by Parvathi Devi et al (2014) Rebamipide and Levamisole shows decreased ulcer counts, size, pain and recurrence for 3 months. Better tolerability and compliance were offered by Rebamipide sensing it more appropriate for long-term use. It can be used in place of immunosuppressants with high risk.

Hasan et al (2022) performed a study that the combination of Rebamipide (100 mg) and 5% Amlexanox paste shows accelerated healing in 10 to 15 days and progressively asymptomatic in 15 to 30 days compared with control, suggesting synergistic benefits. Other study conducted by Matsuda et al (2003) on Behçet's disease, seems that satisfactory improvement in

Rebamipide-treated patients (64%) and placebo group (36%), with benefits stands for 24 weeks.

Formerly Rebamipide's was developed for gastric ulcers, it enhances regeneration, secretion of prostaglandin E and I, mucosal blood flow by nitric oxide synthase and ROS scavenges (Kak, 2025). Studies conducted by Yoshikawa et al (1993) and Suzuki et al (2008) justified antioxidant effect. Another study conducted by Tanigawa et al (2011) stated that COX-1/COX-2 upregulation and tight junction preservation (ZO-1), proves increased mucosal protection.

In the present study shows the marked improvements in pain, ulcer size, erythema, and healing time in both Rebamipide alone and combination with Amlexanox. These is similar to the previous research where significant benefits with Rebamipide alone was observed (Oh et al., 2022).

Other than RAS, Rebamipide has a promising role in mucositis induced by cancer therapy. Elsaadany et al (2024) developed gargle from Rebamipide which is as effective as benzydamine. It has marked improvement and superior tolerability for WHO grade 3 mucositis. Akagi et al (2019) confirmed its potential role in reducing the risk of severe mucositis.

This systematic review shows clear methodical advantages. Following PRISMA standards, it had prior registration in PROSPERO, which supports transparency while limiting biased results. Across

many key databases, a broad search was done, improving chances of finding pertinent studies. Instead of single reviewers, two worked separately on selecting research and gathering data, adding reliability. Evidence is strictly from randomized trials, ensuring stronger conclusions could be drawn. Evaluation of bias used the Cochrane ROB 2 instrument, giving structure to quality checks. Notably, findings cover both aphthous ulcers and those linked to Behçet's condition, pointing toward wider uses for Rebamipide in treatment settings

Even with clear advantages, certain drawbacks must be recognized. Due to limited qualifying studies and fairly small sample size, the strength of conclusions weakens. Differences across trials - in how they were structured, what interventions were used, how results were measured, and how long participants were followed up - made combining data impractical. Concerns in research quality appeared in two out of three analyzed trials, especially around randomization, blinding, and possible measurement bias when evaluating self-reported effects like pain. Long follow up remained rare, meaning lasting patterns in symptom recurrence and prolonged safety remain uncertain.

To validate Rebamipide's effectiveness and its ability to reduce recurrences, future work must include broad, coordinated studies across multiple centers using rigorous trial designs. Alongside this, consistency in measuring results and extended observation periods will strengthen reliability. Comparisons directly pitted against current standard treatments - both oral and applied locally - stand to reveal where it fits within existing treatment methods. Attention might shift toward how dose, dosage, and delivery forms influence real-world benefits of Rebamipide. Localized applications may open new routes for better performance. Insight into biological signals that predict individual responses may guide more tailored approaches over time. As patterns emerge from cellular clues or genetic hints, treatment decisions could become less generic. Safety tracked consistently over years would ground recommendations firmly in proof rather than assumption. Guidance meant for

everyday clinics gains strength only when rooted in long term monitoring.

CONCLUSION

Rebamipide is an emerging therapeutic option for recurrent aphthous stomatitis (RAS) and associated oral ulcers, with efficacy shown in pain relief, size, erythema, and rate of healing alone and with medications like Amlexanox. Safer and more tolerable compared with Levamisole or corticosteroids, it promotes term use. It works mechanistically by promoting prostaglandin production, epithelial regeneration, tight junction integrity and functions as an antioxidant and anti-inflammatory, helping with symptomatic relief and recurrence prevention. Evidence from Behçet's disease and radiation-induced mucositis substantiates its validity. However, large-scale and properly structured research should be conducted to validate recurrence prevention and refine procedures. At present, Rebamipide is still a highly effective and safe alternative for RAS treatment.

CLINICAL SIGNIFICANCE:

Despite their frequent occurrence, recurrent aphthous ulcers cause notable pain, interfere with daily functions like eating and speaking, thus diminishing overall well-being. Though rebamipide acts by shielding mucosa and reducing inflammation, its actual benefit for such mouth ulcers lacks clear consensus across studies. While some trials suggest faster recovery with rebamipide use, results differ widely in strength and design. Because findings remain fragmented, drawing firm conclusions becomes challenging.

This analysis examines current trial data through strict appraisal methods, seeking coherence amid variation. Insights gathered may guide medical professionals, while also highlighting the directions of further studies.

PROSPERO ID: CRD420250652184

Acknowledgements: Nil.

Funding: Nil.

Conflicts of Interest: None.

List of Abbreviations

RAS – Recurrent Aphthous Stomatitis

RAU – Recurrent Aphthous Ulcer

RCT – Randomized Controlled Trial

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO – International Prospective Register of Systematic Reviews

PICO – Population, Intervention, Comparison, Outcome

ROB – Risk of Bias

ROB 2 – Risk of Bias 2 Tool

VAS – Visual Analog Scale

ROS – Reactive Oxygen Species

COX – Cyclooxygenase

ZO-1 – Zonula Occludens-1

WHO – World Health Organization

TDS – Three Times Daily

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TABLES

Table 3: Characteristic table of included studies

Study	Participants/Sample size	Treatment	Pain reduction	Ulcer size reduction	Recurrence
Parvathi Devi et al. (2014)	100 RAS patients; Group A: 50 RAS patients receiving Rebamipide Group B: 50 RAS patients receiving Levamisole	No significant difference vs. Levamisole at all time points	No significant difference vs. Levamisole	Not recorded	
Hasan et al. (2022)	150 RAS patients	Group A: 5% Amlexanox + Rebamipide 100 mg TDS × 7 days	Significant reduction in pain, erythema	Faster ulcer size reduction in Group A	Not recorded
Matsuda et al. (2003)	35 Behçet's disease patients	Rebamipide 300 mg/day vs. placebo × 12–24 weeks	65% improvement vs. 36% placebo	Higher efficacy vs. placebo	Placebo: increase; Rebamipide: decrease over 2–6 months

Table 4: Risk of bias of included studies

Study (Author, Year)	Randomization	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Parvathi Devi et al. (2014)	Some concerns	High	Low	High	Some concerns	High
Matsuda et al. (2003)	Low	Low	Low	Low	Low	Low
Hasan et al. (2022)	Some concerns	High	High	High	Some concerns	High

FIGURES

