Natural and Synthetic Drugs Approached for the Treatment of Recurrent Aphthous Stomatitis Over the Last Decade

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Abstract: Recurrent aphthous stomatitis (RAS) refers to a sore and frequently recurring inflammation of the oral tissues, distinguished by the presence of small ulcers that cause significant discomfort and cannot be attributed to any underlying disease. Different treatments have been used for RAS. This review aims to provide a comprehensive overview of the treatment options over the past decade for recurrent aphthous stomatitis (RAS), encompassing both natural and synthetic treatments. It will utilize clinical efficacy studies conducted in vivo and in vitro, along with a focus on the pharmaceutical approach through advancements in drug delivery development. We conducted a thorough literature search from 2013 to 2023 in prominent databases such as PubMed, Scopus, and Cochrane, utilizing appropriate keywords of recurrent aphthous stomatitis, and treatment. A total of 53 clinical trials with 3022 patients were included, with 35 using natural materials in their research and a total of 16 articles discussing RAS treatment using synthetic materials. All the clinical trials showed that natural and synthetic medicines seemed to benefit RAS patients by reducing pain score, ulcer size, and number of ulcers and shortening the healing duration.

Keywords: recurrent aphthous stomatitis, drug therapy, natural products, treatment outcome, clinical trial

Introduction
RAS is an oral mucosa disease characterized by recurrent, painful, single or multiple well-demarcated ulcers with peripheral red halo where healing occurs with or without scarring. In the adult population, 60–85% of patients experience their first ulceration before age thirty. Although the primary causes of RAS remain unknown, certain factors have been identified as triggers for RAS outbreaks, including mental stress, trauma, lack of sleep, iron and folic acid deficiencies, menstruation, anemia, and changes in women’s sex hormones.

With a 39% frequency, children are more likely to experience it. The prevalence rises with the female gender and a higher socioeconomic level and falls with age. Numerous perspectives have proposed that the oral microbiota could be the cause of RAS. Among the possibly significant components of the core microbiota responsible for this condition are Streptococcus, Helicobacter pylori, CMV (Cytomegalovirus), and a host of other unknown microorganisms. The presence of ulcers as a significant phenotype in systemic illnesses such as Crohn’s disease, Behçet’s illness, herpes stomatitis, and ulcerative colitis further compounds the difficulty in determining the etiologic cause. Stress may contribute to the likelihood of developing RAS; hence, it is crucial to address stress management in patients as a means of controlling its recurrence.
Numerous therapies for RAS have been studied, such as topical steroids, local anesthetics, topical antibiotics, antiseptics, and analgesic/anti-inflammatory medications. Not every patient will respond well to topical therapies, despite the fact that they can be useful. Several systemic drugs have been investigated to treat RAS, including colchicine, thalidomide, dapsone, and corticosteroid. The current therapeutic options can only lessen the frequency or severity of the lesions. In most cases, the primary goal of RAS treatment is to achieve pain reduction (Visual Analog Scale Score), decrease in ulcer size, decrease in ulcer count, and acceleration of ulcer healing duration.12

Herbal supplements and natural items have been used for a long time and are recommended as an alternative to systemic pharmaceuticals due to their potential side effects. For them to serve as a resource and be considered while developing a treatment for RAS, this literature review addresses the natural and synthetic drug-based therapies for RAS that have been demonstrated, as well as the results of their potential.

Methods
We searched journals with the keywords “Recurrent Aphthous Stomatitis”, and “Treatment”, in 3 journal sources: PubMed, Scopus, and Cochrane. This narrative review was prepared based on studies related to the implementation of natural or synthetic products for “Recurrent Aphthous Stomatitis” AND “Treatment”. The authors use all original research and clinical reports published from 2013 to September 2023 regarding the use of treatment in recurrent aphthous stomatitis. The authors exclude irrelevant articles, which are the results of clinical research, but the results do not evaluate the effect on the health of research subjects, RAS treatment with laser or other physical intervention, research articles that do not clearly state the interventions, and other sources such as book chapters, article abstracts only, conference reports, reviews, posters, discussion results, and articles that only contain research designs. Authors C.V. and G.N.I. examined all the articles identified for inclusion. The authors later discussed the findings to reach a consensus. The procedure for selecting research articles is shown in Figure 1.

Result
Numerous treatment methods have been reported to treat RAS. Natural and synthetic treatments are the most frequently reported among the various treatments. Other strategies involve physical interventions such as diode laser, Er, Cr:YSGG laser irradiation, and low laser therapy, to name a few. According to the results obtained from journal sources, treatment for RAS mainly uses topical medication in the form of gels, patches, ointments, and mouthwash. However, there are also therapies using oral drugs that work systemically. Data and explanations regarding natural and synthetic drug-based treatments used as RAS treatments are shown in Tables 1 and 2. The positive overall effect showed that the test materials produced a better outcome than the comparator or control material, as evidenced by the Negative overall impact, which
<table>
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<th>No.</th>
<th>Materials</th>
<th>Activity</th>
<th>Form</th>
<th>Dosage</th>
<th>Comparator</th>
<th>Subjects</th>
<th>Study Design</th>
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**Table 1 (Continued).**

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<td>Camel whey protein</td>
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<td>24</td>
<td>Fenugreek seed (Trigonella foenum graecum L.)</td>
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<td>Mouthwash</td>
<td>Topical application, TID</td>
<td>Dexamethasone</td>
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<td>25</td>
<td>Licorice extract 5%</td>
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<td>Bioadhesive paste</td>
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<td>Diphenhydramine</td>
<td>60</td>
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<td>N/A</td>
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### Table 1 (Continued).

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[^14]: [doi.org/10.2147/DDDT.S449370](https://doi.org/10.2147/DDDT.S449370)
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<th>Subjects</th>
<th>Study Design</th>
<th>Overall Effect (Compared with Comparator)</th>
<th>Source</th>
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</table>
| 1.  | Zinc Sulfate | Anti-inflammatory and wound-healing | Mucoadhesive paste | Topical application, TID | Placebo | 55 | Double blind, RCT | Positive | Positive | N/A | N/A | Ghorbani et al (2020), Iran
t | |
| 2.  | Tetanus and diphtheria toxoid vaccine – Colchicine 1 mg | Immunomodulator | Tablet & injection | Oral application, QD Intramuscular injection, Single dose | Colchicine & Vitamin B6 | 66 | Triple blind, RCT | Positive | Positive | N/A | Positive | Habibzadeh et al (2019), Iran
t | |
t | |
| 4.  | Doxycycline hyclate 100 mg | Antimicrobial, prostaglandin inhibitor, leukocyte suppression | Tablet | Oral application, QD | Placebo | 50 | Single blind, RCT | Positive | N/A | N/A | Positive | Vijayabala et al (2013), India
t | |
| 5.  | Amlexanox 5% | Anti-inflammatory | Paste | Topical application, TID/QID | Triamcinolone acetonide | 60 | Single blind, RCT | Negative | Negative | N/A | Negative | Shrivastava et al (2020), India
t | |
t | |
t | |
| 8.  | Topical insulin-liposomal | Wound-healing | Gel | Oral application, QD | Placebo | 80 | Double blind, RCT | Positive | N/A | N/A | Positive | El-Wakeel et al (2018), Egypt
t | |

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<th>Form</th>
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<td>Anti-inflammatory</td>
<td>Tablet</td>
<td>Oral application, QD</td>
<td>Prednisolone 0.4mg</td>
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<td>Positive Positive Positive Positive</td>
<td>Zeng et al (2019), China(^{26})</td>
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<td>Ibuprofen, diphenhydramine, Aluminum Magnesium Sulfate (AlMgS)</td>
<td>Analgesic, anti-inflammatory</td>
<td>Gel</td>
<td>Topical application, TID</td>
<td>Diphenhydramine and Aluminum Magnesium Sulfate (AlMgS)</td>
<td>31</td>
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<td>Minocycline 0.2%</td>
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<td>Triester Glycerol Oxide</td>
<td>Anti-inflammatory, Reduce moisture loss</td>
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<td>Not Significant Not Significant N/A N/A</td>
<td>Devi et al (2014), India(^{30})</td>
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Abbreviations: QD, Once a day; BID, Twice a day; TID, Thrice a day; QID, 4 times a day; RCT, Randomized Controlled Trial.
indicates that the comparator or control materials outperformed the test materials, and not significant overall effect indicates that the materials indicated a better outcome with no significant difference with the comparator material.

A total of 3072 RAS patients were studied in this review. The sample size ranged from 15 to 210 patients in each study. Twenty-one different types of formulations were used in the articles, such as pasta, tablet, injection, mouthwash, gel, nanomicelle gel, powder, pill, film, lozenges, patch, capsule, buccal film, liquid, ointment, membrane piece, oil, gelatin, orabase, and tincture. The experimental period ranged from 5 days to 12 months.

Natural Treatment

Natural treatment is a naturally occurring secondary metabolite with possible clinical activity that is taken from living things like fungi, bacteria, plants, and animals. It is remarked that natural treatments are excellent sources for creating and manufacturing anti-inflammatory, analgesic, antimicrobial, and immunomodulator agents. Medicinal plants and natural remedies have long been conventionally used for various pharmacological uses.

Numerous varieties of natural substances are employed in the research article that has been compiled. Each of these materials possess distinct components and activities in managing Recurrent Aphthous Stomatitis (RAS). Typically, medications for RAS treatment are formulated in topical forms, including gels, patches, pastes, or mouthwash. This formulation is selected due to its capacity to endure in the oral cavity for an extended period, offering ulcer protection to mitigate deterioration and facilitating a swifter wound healing process.

The entire study incorporated pain reduction as one of its outcome measures. Out of the 37 studies, 25 demonstrated that natural substances yielded superior therapeutic effects compared to the control materials. Pain assessment was conducted using the Visual Analog Scale (VAS) score, where a score of 1 signified minimal pain, and a score of 10 indicated maximum pain. Three studies, however, reported negative results or lower therapeutic effects compared to the comparator. The remaining 9 articles indicated better therapeutic effects than the comparator, although the differences were not statistically significant.

The reduction in ulcer size represented the second most frequently measured outcome in the trials. Out of 28 articles reporting on ulcer size reduction, 18 trials yielded positive results, 7 articles showed not statistically significant results, and 3 articles reported negative outcomes compared to the reference materials. Only 7 articles assessed the difference in the number of ulcers in the trials, with 3 showing results that were not statistically significant and 4 articles demonstrating a positive effect for RAS compared to the control materials. As for the reduction in healing duration, it was evaluated in 16 articles, with 12 reporting positive results and 2 articles each indicating results that were not statistically significant and negative compared to the control.

Synthetic-Based Treatment

Synthetic pharmaceuticals are formulated to address symptoms associated with specific diseases based on the scientific understanding of pathology. Synthetic drugs are pharmaceuticals derived from synthetic compounds and are typically prescribed by medical professionals to treat specific diseases. These synthetic medications represent a modern approach, often synthesized from artificial or naturally occurring substances that have undergone contemporary processing techniques.

Therapeutic strategies for RAS primarily focus on alleviating pain and expediting wound healing. The management of minor aphthous ulcers involves supportive care, such as topical analgesics and protective bio-adhesive agents, while topical corticosteroids have been employed for both major and minor RAS ulcers. However, the frequent use of corticosteroids is often limited due to topical side effects and the risk of systemic absorption, including oral candidiasis, mucosal atrophy, susceptibility to infections, and gastrointestinal complications.

There are 16 articles discussing the use of synthetic drugs in the management of RAS. Fifteen of these articles evaluate the effects of drug utilization on pain control, with 12 articles reporting positive outcomes, 1 article yielding negative results, and 3 articles indicating superior effects, albeit with non-significant differences.

Discussion

RAS is an oral mucosa disease characterized by recurrent, painful, single or multiple well-demarcated ulcerations with peripheral red halo where healing occurs with or without scarring. In the adult population, 60–85% of patients...
experience their first ulceration before age thirty. Although the primary causes of RAS remain unknown, certain factors have been identified as triggers for RAS outbreaks, including mental stress, trauma, lack of sleep, iron and folic acid deficiencies, menstruation, anemia, and changes in women’s sex hormones. The current therapeutic options can only lessen the frequency or severity of the lesions. In most cases, the primary goal of RAS treatment is to achieve pain reduction, decrease in ulcer size, decrease in ulcer count, and acceleration of ulcer healing duration.

Various medications, whether derived from natural or synthetic sources, are employed as therapies for RAS, each with diverse mechanisms of action, including anti-inflammatory, antioxidant, immunomodulatory, analgesic, wound healing, antiulcer, antibacterial, antiviral, and antibiotic effects as depicted in Figure 2.

Immune alterations are among the factors that contribute to the development of RAS. It starts with antigen secretion on keratinocytes that activates T lymphocytes, causing TNF-α secretion and leukocyte chemotaxis. Studies have demonstrated a 2–5-fold increase in the secretion of TNF-α in the saliva of individuals suffering from RAS. Therefore, anti-inflammatory agents are essential to cure RAS, such as thalidomide, which speeds up messenger RNA degradation to reduce TNF-α activity, and pentoxifylline, which inhibits TNF-α production. Another example is chitosan, which can suppress TNF-α production and inhibit cytokine synthesis. These actions trigger re-epithelialization and contribute to the rejuvenation of the mucous layer.

The treatment of choice for RAS often includes natural immunomodulatory agents like Lactobacillus acidophilus and Lactobacillus reuteri and synthetic options like Levamisole. These drugs regulate both cellular and humoral immunity in individuals with RAS. Furthermore, levamisole exerts effects on T suppressor cells in vitro. Suppressing specific T-cell responses can result in immunosuppression, which is advantageous in managing RAS. This drug’s mechanism of action helps normalize the CD4+/CD8+ cell ratio and enhances IgA and IgM levels.

Antioxidants also have a crucial role in the treatment of RAS. This condition can arise due to an elevated level of reactive oxygen species (ROS) that suppresses the activity of the immune system and induces cellular damage. Sage extract, a natural antioxidant, has been employed as a treatment for RAS. The phenolic and flavonoid compounds present in sage extract can enhance blood oxygen levels and protect the body against oxidative stress and free radicals that can

**Figure 2** Mechanism of action for pharmacological active agents in RAS therapy. Created with Biorender.com.
cause cell damage, thus protecting against various types of ulcers.\textsuperscript{85} N-acetylcysteine (NAC), recognized for its potent antioxidant properties, is utilized as a therapy for RAS. In clinical scenarios characterized by glutathione deficiency and/or oxidative stress, the use of NAC has demonstrated effectiveness.\textsuperscript{86}

The clinical presentation of RAS involves inflammation in the oral mucosa, manifesting as yellowish-white ulcers with clear boundaries and surrounded by an erythematous halo.\textsuperscript{87} Hence, substances with antiulcerogenic properties represent a viable therapeutic approach for RAS. Limonene, the primary component in citrus essential oil, exhibits antiulcerogenic activity.\textsuperscript{88} The antiulcerogenic effect of limonene acts as an immunomodulatory agent for oral aphthous ulcers.\textsuperscript{82} The mechanism of these properties is attributed to its capacity to enhance mucus secretion, heat shock protein-70, vasoactive intestinal peptide, and prostaglandin E2.\textsuperscript{88} In addition, rebamipide, which has activity as a gastro protective agent, is also recommended as RAS therapy, especially to improve ulcer conditions. It works by diminishing oxygen radicals, enhancing blood flow, and promoting the production of protective prostaglandins in the ulcerated mucosa, thereby expediting the healing process.\textsuperscript{89}

In the management of RAS, supportive treatment is often advised, which aims to reduce pain, accelerate healing, and prevent recurrence.\textsuperscript{90} To reduce pain, it is essential to utilize medications with analgesic properties. Diphenhydramine and aluminum magnesium simethicone (AlMgS) syrup are often prescribed as an analgesic mouthwash to mitigate various symptoms of oral ulcers, including aphthous ulcers. Ibuprofen is a potent non-steroidal anti-inflammatory drug (NSAID) with significant anti-inflammatory capabilities and is frequently recommended in dental care.\textsuperscript{67} Moreover, natural substances like cannabidiol, aloe vera, fenugreek seed, and chamomile are known to possess analgesic properties and can be employed as therapeutic options for RAS.\textsuperscript{40,47,52,54}

Supportive treatment to accelerate wound healing is important, and substances like alum and \textit{Ageratina pichinchensis} can be valuable. Alum, for instance, induces tissue contraction, which reduces mucous membrane inflammation and accelerates wound healing.\textsuperscript{91} \textit{Ageratina pichinchensis} also exhibits wound healing properties. In vitro studies have shown that the compound 7-O-(β-D-glucopyranosyl) galactin, found in \textit{Ageratina pichinchensis}, can stimulate the proliferation of normal human skin cells (HFS-30), thereby promoting the acceleration of wound healing.\textsuperscript{92} Other natural compounds that significantly accelerate wound healing are propolis, honey, and aloe vera.\textsuperscript{33,38,47} Additionally, a synthetic compound known as topical insulin-liposomal has demonstrated its potential in this regard. Insulin, when applied topically, can enhance the healing process by accelerating re-epithelialization, promoting angiogenesis, and stimulating the secretion of extracellular matrix components in keratinocytes, endothelial cells, and fibroblasts.\textsuperscript{65,92}

The antibacterial properties are also crucial for treating RAS because open sores on mucosal tissues make it easy for bacteria to colonize, especially Gram-positive bacteria, which can slow down the healing process.\textsuperscript{93} Bacterial infections disrupt the regeneration of the oral mucosa. Eradicating microbes within the oral cavity supports the normal wound healing process.\textsuperscript{94} The presence of catechins in gambier extract possesses the ability to reduce bacterial populations in oral ulcers. Catechins modify membrane fluidity, resulting in a loss of membrane integrity and, ultimately, bacterial cell death.\textsuperscript{95} Other studies have also indicated the effectiveness of gambier extract in reducing the levels of \textit{Streptococcus mutans} in saliva.\textsuperscript{44} By maintaining a sterile wound environment, gambier extract expedites the wound healing process by promoting angiogenic responses.\textsuperscript{96}

From the analysis of a total of 53 clinical trials conducted by the authors in the last 10 years, natural-based medicines have shown significant improvement in patients’ symptoms, including the reduction of pain scores, ulcer size, the number of ulcers, and a decrease in ulcer healing duration. However, when compared with the control group, natural-based medicines provided better therapeutic effects compared to negative control or placebo but did not demonstrate significantly different or superior therapeutic effects compared to positive control or triamcinolone acetonide.

The drug delivery system also plays a crucial role in influencing the effectiveness of RAS therapy.\textsuperscript{97} Typically, medications intended for RAS treatment are formulated in topical forms, such as gels, patches, pastes, or mouthwash.\textsuperscript{9} This choice of the formulation is made because it can persist in the oral cavity for an extended period, providing protection against ulcer deterioration and facilitating a more rapid wound healing process.\textsuperscript{98,99} For instance, in the case of curcumin nanomicelle gel, it has shown better therapeutic outcomes than curcumin gel.\textsuperscript{20} This is because nanomicelle gel does not readily dissolve in saliva, making it highly suitable for the physiological conditions of the oral cavity and facilitating easy absorption by the mucosa.\textsuperscript{100} Furthermore, the development of drug delivery systems for RAS is an
ongoing endeavor, encompassing research conducted in both in vitro and in silico settings. These developments include muco-adhesive sponges containing tenoxicam and miconazole nitrate,\textsuperscript{101} hydrogel formulations with alpha mangostin,\textsuperscript{102} adhesive buccal films comprising alginate and ambroxol,\textsuperscript{103} prednisolone,\textsuperscript{104} and benzydamine hydrochloride,\textsuperscript{105} as well as mucoadhesive films containing betamethasone valerate,\textsuperscript{106} and clobetasol propionate.\textsuperscript{107}

The trial duration also shows a rather significant difference, with synthetic-based drugs having trial periods ranging from 3 days to 12 months. Topical and systemic corticosteroids, antibiotics, and analgesics are highly recommended for RAS patients.\textsuperscript{80} However, extended treatment periods and frequent exposure to these medications can lead to fungal infections and drug resistance, which can subsequently result in more severe side effects or even life-threatening complications.\textsuperscript{75} Therefore, the long-term use of these medications for RAS management should be avoided.\textsuperscript{108}

Finding effective treatment for oral disease is among the most critical challenges of oral medicine. Consequently, there is a demand for therapy that can be effectively administered to the oral mucosa, withstand the washout effect of saliva, maintain a good safety profile, and minimize adverse side effects.\textsuperscript{109} Research in RAS therapy is an ongoing endeavor encompassing various stages of development, starting with drug formulation, pre-clinical testing, and clinical trials. An example of such research is the study conducted by Milanda et al, in which the compound alpha mangostin was utilized as a hydrogel film formulation based on chitosan alginate. This formulation demonstrated in vivo efficacy in the context of RAS therapy in white mice. The efficacy was indicated by the swiftest healing process, as determined through slope calculations.\textsuperscript{110}

In summary, current data indicate a favorable benefit from both synthetic and natural remedies for the treatment of recurrent acute stomatitis (RAS). These remedies have demonstrated effectiveness in reducing pain, the number of ulcers, ulcer size, and healing duration. Natural remedies are recognized for their therapeutic benefits in RAS treatment but have yet to surpass the effectiveness of corticosteroid therapy. Conversely, the use of synthetic remedies, such as corticosteroids, tends to be of longer duration and raises concerns regarding potential side effects. The development of RAS therapy, including active ingredients, formulations, and delivery systems, must continue to be pursued in order to obtain effective, safe, and minimally side-effect-inducing treatments from both natural and synthetic sources.

**Conclusion**
The utilization of natural and synthetic medicinal approaches for the treatment of recurrent aphthous stomatitis (RAS) has exhibited considerable success in enhancing the well-being of patients, as evidenced by the reduction in pain, ulcer size, ulcer count, and the duration required for complete healing. Nevertheless, natural-based medicines necessitate further investigation and research to establish their therapeutic effectiveness equivalent to or surpassing that of corticosteroids, intending to potentially be integrated as a standard treatment modality for RAS. The progression of RAS therapy, encompassing the exploration of active constituents, formulations, and delivery systems, must persist in attaining effective and safe treatments while inducing minimal side effects originating from both natural and synthetic sources.

**Abbreviations**
RAS, Recurrent Aphthous Stomatitis; CMV, Cytomegalovirus; NAC, N-Acetylcysteine; VAS, Visual Analog Scale; AlMgS, Aluminum Magnesium Simethicone; NSAID, Non-steroidal Anti-inflammatory Drug; RCT, Randomized Controlled Trial; QD, Once a day; BID, Twice a day; TID, Thrice a day; QID, 4 times a day.

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