

Systemic and topical treatment methods of recurrent aphthous stomatitis: A systematic review

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SUMMARY

Aim. To analyze the latest systemic and topical recurrent aphthous stomatitis (RAS) treatment methods that could help patients in their daily lives.

Material and methods. A systematic literature review was performed of randomized control trials in English identified in MEDLINE (PubMed), Cochrane Central Register of Controlled Trials (Cochrane Library), Researchgate, published between 2018 and 2023. Studies had to be performed in vivo.

Results. 34 randomized clinical trials matched all criterias and were included in systematic literature review. A wide variety of topical and systemic agents are suggested for the treatment of RAS.

Conclusion. Topical medications can promote the healing time of ulcers and relieve the pain, but most of the time can not decrease the frequency of RAS relapse. However, for continuous RAS, treatment with systemic medication should be considered.

Keywords: recurrent, aphthous, stomatitis, RAS, treatment, systematic review.

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is one of the most common chronic inflammatory disorders in the oral cavity which incidence varies from 5% to 50% depending on the groups under investigation and population (16, 18). This condition presents as recurrent, multiple, small, round, or ovoid ulcers, with circumscribed margins, having yellow or gray floors, and are surrounded by erythematous haloes, manifest first usually in child-hood or adolescence (1). Based on size, number, painful and duration of the lesions, it can be classified into three types: minor, major and herpetiformis ulcer (3, 14). Minor RAS is the most prevalent form which accounts about 70-85% of all RAS lesions (12, 12, 20). The lesions are usually located in the non-keratinized oral mucosa, may persist for days or weeks and present recurrences after very variable remission periods (18).

The specific etiology of RAS is unknown, but there are associated risk factors that have been identified, such as, genetic pre-disposition, atopy, nutrition, drug reactions, microbial factors, stress, menstrual

cycle, immune dysregulation, and deficiencies in hematinic factors such as iron, folic acid (folate), and vitamin B (4, 13). Furthermore, many systemic diseases, such as Bechet's syndrome, gastrointestinal diseases, cyclic neutropenia, periodic fever syndromes and other autoinflammatory diseases, infections and environmental factors, have been associated with oral aphthous lesions (6, 24, 19). Approximately 30% of people who get oral aphthosis have a family history of similar lesions. Human leukocyte antigen alleles such as DR2, B12, A1, and A2 appear to be associated with susceptibility (26). Tumornecrosis (TNF- α), Interleukin (IL-1) and conditions such as Celiac disease, Crohn's disease, Ulcerative Colitis and hormonal changes can be used as indicator for monitoring the occurrence of RAS (2, 7, 24, 20).

In this systematic review, we have analyzed the latest RAS treatment methods that could help patients in their daily lives. The knowledge is based on a systematic search of the current evidence.

MATERIALS AND METHODS

A systematic literature search was performed according to PRISMA guidelines in search of clinical trials. Electronic and manual literature searches were conducted independently by all authors in several databases, including MEDLINE (PubMed),

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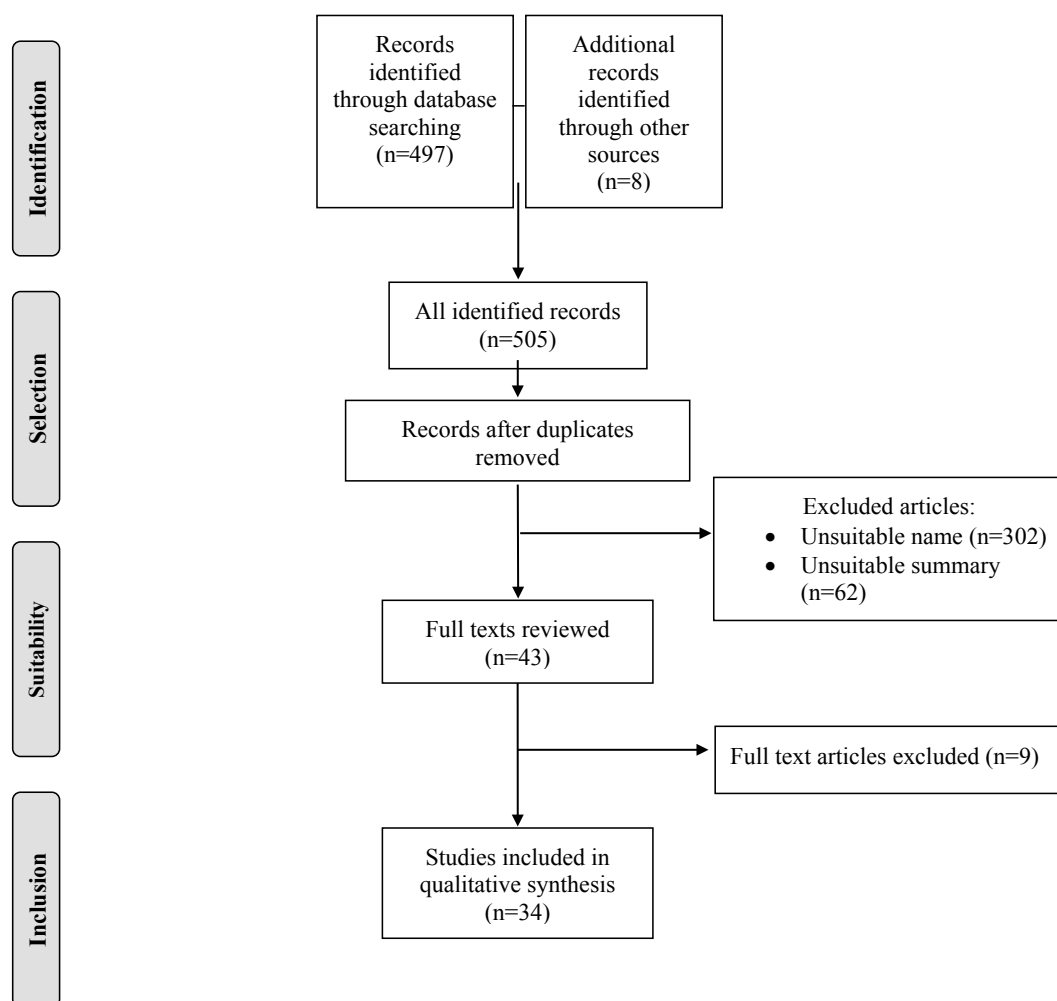


Fig. PRISMA flow chart

Cochrane Central Register of Controlled Trials (Cochrane Library), Researchgate. Databases were searched using different combinations of the following key words: apthous, recurrent, stomatitis, RAS, treatment. The titles and abstracts first were analysed, followed by the selection of complete articles for careful reviewing and analysis according to the eligibility criteria.

Studies inclusion criteria:

- In vivo studies;
- Studies published in English;
- No older than 5 years;
- Systemic treatment methods of RAS;
- Topical treatment methods of RAS;

All case reports or case series, animal and in vitro studies were excluded. Publications that met inclusion criteria were drawn to the qualitative analysis study pool. From this, publications that met qualitative assessment criteria were selected into this literature review.

The quality of selected randomized clinical trials (RCT) was assessed using the Cochrane Risk of Bias Tool (Table 1).

RESULTS

Search outcomes

The combinations of search terms identified a total of 505 titles. After removal of duplicates, 407 records remained. Of these, 364 did not meet the inclusion criteria, leaving 43 manuscripts for more detailed review. Finally, 34 manuscripts fulfilled all inclusion criteria and underwent systematic review. The article search and selection process is presented in PRISMA flow diagram (Figure 1).

Groups of treatment methods

All included studies were in

vivo and published in English. Different topical and systemic treatment methods were compared evaluating: pain relief, ulcer size and healing time. Topical treatment included different lasers therapy, membranes, aerosols, mouth rinses, gels and tablets. Systemic treatment included using probiotic, supplements and immunomodulators therapy.

Topical treatment

Lasers

Soon after the discovery of low level laser therapy (LLLT) by Ender Mester in the 1960s, it was rapidly realized that LLLT had the magic potential to treat numerous diseases and unhealthy conditions involving inflammation, pain, wound healing, regeneration, and abnormal immune responses (12). Four of the included studies assessed different types of lasers as a treatment method of RAS, results are showed in Table 2.

Membranes

Chitosan is an N-deacetylated derivative of chitin. It has antibacterial, anti-inflammatory, wound-healing, hemostatic, and immunomodulatory effects (10).

Dried ginger rhizome (DGR; *Zingiber officinalis*) is a common dietary adjunct contributing to the taste and flavor of foods, and is also an important Chinese herb. Initially, DGR can sensitize sensory endings within inflamed tissue and produced a “warm“ feeling, then desensitize the tissue and relieve pain (14).

The two active medical components from the cannabis plant are Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD). THC has several medicinal effects, including being psychoactive. In contrast, CBD is non-psychoactive and has meaningful analgesic, anti-inflammatory, and anti-convulsant effects. Furthermore, CBD suppresses pro-inflammatory cytokine expression (22).

Cinnamaldehyde is an aromatic aldehyde compound and the main ingredient of cinamon oil. The biological properties of cinamon oil, such as peripheral vasodilatory, antitumor, antifungal, cytotoxic, and anti-mutation characteristics, are mainly attributed to cinnamaldehyde (30). Outcomes of randomized

clinical trials of RAS treatment related to membranes are presented in Table 3.

Aerosols

Alternative therapies have also been proposed for the treatment of RAS, mainly based on the use of different medicinal plants. Although many of these remedies are considered to be fairly safe and maybe valid for the treatment of RAS, consideration should be given to the possibility of interaction with conventional medications (17). The treatment results of included aerosol is given in Table 4.

Mouth rinses

Lactic acid is a natural product of milk sugar (lactose fermentation). Topically applied lactic acid increases spontaneous secretion of vascular endothelial growth factor (VEGF). This factor is a multi-functional angiogenic cytokine involved in angiogenesis and wound healing. Also, it may stimulate the production of collagen and elastic fibers (1).

Table 1. Cochrane Risk of Bias Tool

Authors	Random sequence generation	Confounding variables	Incomplete outcome	Measurment of intervention	Selective outcome reporting	Total risk
Samia A. Ibrahim MD <i>et al.</i> (2019) (1)	-	+	+	+	+	Unclear risk
Siti Rusdiana Puspa Dewi <i>et al.</i> (2020) (2)	+	+	+	+	+	Low risk
Qingwen Guo <i>et al.</i> (2018) (5)	±	+	+	+	+	Low risk
Enrica Giammarinaro <i>et al.</i> (2019) (6)	+	+	+	+	+	Low risk
Hussien G.H. Ghali <i>et al.</i> (2022) (8)	+	+	+	+	+	Low risk
Duygu Ofluoglu <i>et al.</i> (2017) (9)	+	±	±	+	+	Low risk
Yanxiong Shao <i>et al.</i> (2019) (10)	+	+	+	+	+	Low risk
Hasan Guney Yilmaz <i>et al.</i> (2017) (11)	+	±	±	±	+	Low risk
Xiao Huo <i>et al.</i> (2020) (12)	+	±	±	+	+	Low risk
Narjes Akbari <i>et al.</i> (2020) (13)	+	+	+	+	+	Low risk
Qian Du <i>et al.</i> (2018) (14)	+	+	+	+	+	Low risk
Seyed Javad Kia <i>et al.</i> (2020) (15)	+	±	±	±	±	Unclear risk
Hadian Z <i>et al.</i> (2021) (16)	+	+	+	+	+	Low risk
Alberto Rodriguez-Archilla <i>et al.</i> (2017) (17)	+	+	+	+	+	Low risk
Sara Darakhshan <i>et al.</i> (2019) (18)	+	+	+	+	±	Low risk
Fatemeh Abbasi <i>et al.</i> (2023) (21)	+	+	+	+	+	Low risk
Chalapinyo Umpreecha <i>et al.</i> (2023) (22)	+	+	+	+	+	Low risk

Licorice (*Glycyrrhiza glabra*) is one of the oldest medicinal plants, also described by Avicenna, with many therapeutic benefits such as wound healing, improving of asthma, urinary infections, and gastric ulcers. Despite the anti-inflammatory and antimicrobial effects of licorice, few studies have been conducted on its effects on RAS treatment (23).

Minocycline which is a semisynthetic tetracycline has antibacterial properties along with some beneficial effects on controlling non-infectious cutaneous diseases as well. Minocycline was assumed to have a regulatory effect on cytokines that are related to the development of RAS (31).

N-acetyl cysteine (NAC), the derivative of a thiol-containing amino acid, is a precursor for the intracellular antioxidant glutathione. Owing to its potent antioxidant, anti-inflammatory, immunomodulatory, and antimicrobial properties, NAC has received considerable attention in dentistry (32). The

effect of RAS treatment with mouth rinses are given in Table 5.

Gels

Previous study reported that gambier (*Uncaria gambir*) had analgesic, antibacterial and anti-inflammatory activities. Also mentioned, that gambier has antiseptic effect on gingival wounds in rats (2).

Triester glycerol oxide (TGO) gel is a topical agent that has the property of adherence to the oral mucosa by forming a lipid film which protects against mechanical trauma and may help to reduce oral tissue moisture loss and inflammation (9).

Curcuma longa is a perennial plant belonging to Zingiberaceae family which has been used in Indian traditional medicine for centuries due to its anti-inflammatory effect (15).

The potential therapeutic properties of pomegranate are wide-ranging and include treatment of

Table 1. Cochrane Risk of Bias Tool (*continued*)

Authors	Random sequence generation	Confounding variables	Incomplete outcome	Measurement of intervention	Selective outcome reporting	Total risk
Pedersen AML <i>et al.</i> (2019) (23)	+	+	+	+	+	Low risk
Aggour RL <i>et al.</i> (2020) (24)	+	±	+	+	+	Low risk
Dugourd PM <i>et al.</i> (2020) (25)	+	±	±	+	+	Unclear risk
Owlia MB <i>et al.</i> (2020) (26)	+	+	+	+	+	Low risk
Zeng Q <i>et al.</i> (2020) (27)	+	±	+	+	+	Low risk
Deng Y <i>et al.</i> (2022) (28)	+	±	+	±	+	Unclear risk
Hisham Abdelmonem Soliman <i>et al.</i> (2019) (29)	+	+	+	+	+	Low risk
Tahere Molania <i>et al.</i> (2022) (30)	+	+	+	+	+	Low risk
Ankita Chugh <i>et al.</i> (2022) (31)	+	±	±	±	±	Unclear risk
Esam Halboub <i>et al.</i> (2019) (32)	+	±	±	±	+	Unclear risk
Hemcle Shalma G <i>et al.</i> (2019) (33)	+	+	+	+	+	Low risk
Naglaa M. El-Wakeel <i>et al.</i> (2019) (34)	+	+	+	+	+	Low risk
Medhi Ansari <i>et al.</i> (2021) (35)	+	±	±	+	+	Low risk
Praveena Raman <i>et al.</i> (2020) (36)	+	±	±	+	±	Unclear risk
Ana Andabak Rogulj <i>et al.</i> (2021) (37)	+	+	+	+	+	Low risk
Anahita Ghorbani <i>et al.</i> (2020) (38)	+	+	+	+	+	Low risk
Ghadah Ali Al-Oudah <i>et al.</i> (2020) (39)	+	±	±	+	+	Low risk

inflammatory conditions, cancer, cardiovascular disease, diabetes and dental conditions (18).

Salvia officinalis (common Sage, culinary Sage) is an aromatic plant often used for different purposes, especially as a traditional medicine for treating several infectious diseases. Sage contains different compounds with influential characteristics. Ethanolic compounds of Sage have antibacterial activity. Also, the terpenoids available in leaves of Sage, such as ursolic acid, have an anti-inflammatory effect (21)

Aloe vera (AV – *Aloe barbadensis* Miller) is one amongst the natural herbal medicine which is used as an alternative therapy for RAS. The transparent gel derived

from *Aloe vera* leaves contains a series of natural components which has immunomodulators, anti-inflammatory, wound healing, antioxidant, anti-diabetic and anti-neoplastic to use it in management of minor RAS (33).

The positive healing effects of topical insulin on wound healing was proven early. Insulin has the ability to enhance healing by increasing the rate of re-epithelialization, angiogenesis and extracellular matrix secretion by keratinocytes, endothelial cells and fibroblasts (34).

Fenugreek's seeds have anti-inflammatory and analgesic effect which has been attributed to flavonoids, alkaloids and saponins. Also, the im-

Table 2. RAS treatment with lasers

Authors	Sample size	Test Group	Control Group	Results
Hussien G.H. Ghali <i>et al.</i> (2022) (8)	21 patients (3 groups, n=7)	Group 1 (940 nm for 3 minutes, 0.5 W, CW, exposure for 45s, then 15s gap and repeated twice, with a gap of 3 days between each visit)	Group 2 (10 mL aerosol solution (Anginovag spray), each 2-3 hours 3 days) Group 3 (motivation and follow up)	Better effect on reduction in pain, ulcer size and duration of the aphtous ulcer (test group)
Hasan Guney Yilmaz <i>et al.</i> (2017) (11)	40 patients (2 groups, n=20)	Test group: Er, Cr: YSGG laser (Waterlase MD, Biolase, Irvine, CA, USA) 600 µm diameter, 6mm lenght, 0.25 W 20s per surface without water)	Same Er, Cr: YSGG laser without laser emission	Better effect on pain relief and accelerate the healing (test group)
Xiao Huo <i>et al.</i> (2020) (12)	56 patients (2 groups, n=28)	Diode laser, 810 nm, 1.0 W, CW, irradiation time 20 s for 3 applications) once daily, 3 days.	Triamcinolone acetone 0.1% three times a day until the lesion was healed	Better effect on pain relief (test group)
Hisham Abdelmonem Soliman <i>et al.</i> (2019) (29)	20 patients (2 groups, n=10)	Diode laser 660 nm, 100-130 mW/cm, 40 sec/spot	Diluted sodium bicarbonate rinse 4 times/day	Better effect in reduction of healing time, pain and lesion size (test group)
Hisham Abdelmonem Soliman <i>et al.</i> (2019) (29)	20 patients (2 groups, n=10)	Diode laser 660nm, 100-130 mW/cm, 40sec/spot	Diluted sodium bicarbonate rinse 4 times/day	Better effect in reduction of healing time, pain and lesion size (test group)

Table 3. RAS treatment with membranes

Authors	Sample size	Test Group	Control Group	Results
Yanxiong Shao <i>et al.</i> (2019) (10)	72 patients (2 groups, n=36)	10 mm mucoadhesive film containing chitosan twice a day	A polyvinyl alcohol film	Promotes oral healing (test group)
Qian Du <i>et al.</i> (2018) (14)	59 patients (2 groups, n=30 and n=29)	Dried ginger rhizome membrane	Placebo membrane	Better effect on pain relief, healing time, reducing the EGF level in saliva, and has an inhibitory effect on TNF-α release (test group)
Chalapinyo Umpreecha <i>et al.</i> (2023) (22)	72 patients (3 groups, n=24)	0.1% CBD applied with a provided calibrated spoon to the ulcers 3 times/ day after meals for 7 days	0.1% triamcinolone acetone (TA), or placebo applied with a provided calibrated spoon to the ulcers 3 times/ day after meals for 7 days	Topical 0.1% CBD reduced ulcer size and accelerated ulcer healing without side effects (test group)
Tahere Molania <i>et al.</i> (2022) (30)	44 patients (2 groups, n=22)	10-mg cinnamaldehyde mucoadhesive tablets for seven days	Placebo for 7 days	Better effect in reduction of pain intensity (test group)

munomodulatory, anticholinesterase and cosmetic effects of the plant have further been reported (36).

Non-aromatic-very rich in steranes (NAVS) naph-talan is a transparent, earth mineral oil prepared by a complex set of separations and refining steps. NAVS is effective in the treatment of immune-mediated oral diseases (37). Different results of each gel are given in Table 6.

Tablets

Zinc is a mineral. It is called an “essential trace element“ because very small amounts of zinc are necessary for human health. Zinc citrate is used in toothpaste and mouthwash to prevent dental plaque formation and gingivitis (39). Treatment variations with zinc are given in Table 7.

Local antibiotics

Benzathine penicillin plays anti-inflammatory role via conjugation with interleukin (IL) IL-1B, IL-2, IL-5, and IL-13. Owlia MB *et al.* found out that using topical penicillin powders showed lower pain levels, smaller ulcer size, and earlier recovery after treatment. Therefore, due to the low side effects and significant improvement in symptoms in this clinical trial, they recommend topical penicillin powder as the first choice drug for treatment (26). Randomized clinical trial outcomes are presented in Table 8.

Systemic treatment

Supplements

Omega-3 polyunsaturated fatty acids have a potential anti-inflammatory effect and are inexpensive,

safe, and accessible dietary supplement. Studies have indicated the effect of omega-3 polyunsaturated fatty acids on the reduction of inflammatory biomarkers, cytokines, eicosanoids. In addition, eicosapentaenoic acid and docosahexaenoic acid are the two members of the omega-3 fatty acid family having anti-inflammatory and immunomodulatory characteristics (16). The results of the Hadian Z *et al.* study indicated that omega-3 supplements significantly improved the aphthous ulcer intensity and oral health-related quality of life in patients with recurrent aphthous stomatitis (Table 9).

Probiotics

Patients with RAS have an increased presence of proinflammatory cytokines such as TNF- α , IL-2 and IL-6, and aphthous like ulcers have been found to be associated with IgA deficiency (23). Probiotics modulate mucosal immune mechanism by reducing production of proinflammatory cytokines through actions on NFkB pathways, increasing production of anti-inflammatory cytokines and host defence peptides enhancing IgA defence, influencing dendritic cell maturation, and stimulating the activity of Treg lymphocytes (24). Three of the included studies (23-25) assessed different forms of probiotics as a treatment method of RAS, results are showed in Table 10.

Immunomodulators

At present, an increase in the levels of TNF- α that are secreted by lymphocyte infiltration in ulcers are considered to be one mechanism in the initiation

Table 4. RAS treatment with aerosols

Authors	Sample size	Test Group	Control Group	Results
Alberto Rodriguez-Archilla <i>et al.</i> (2017) (17)	125 patients (5 groups, n=25)	50 mg silver nitrate bars; 18% propolis in aerosol form; 5% rhubarb extract solution ; 5% extract of walnut bark solution	Flavoured distilled water	The fastest treatment with silver nitrate (test group)

Table 5. RAS treatment with mouth rinses

Authors	Sample size	Test Group	Control Group	Results
Samia A. Ibrahim MD <i>et al.</i> (2019) (1)	40 patients (2 groups, n=20)	Lactic acid 5% mouth wash 3 times daily for 1-2 weeks	Kenalog in Orabase (triamcinolone acetonide) twice daily	More reduction in the size, pain, and healing time (test group)
Narjes Akbari <i>et al.</i> (2020) (13)	70 patients (2 groups, n=35)	3ml of 5% hydroethanolic extract of licorice with diphenhydramine elixir (DSG) for three minutes four times a day	Diphenhydramine solution (DS)	DSG more effective in treating RAS than DS alone (test group)
Ankita Chugh <i>et al.</i> (2022) (31)	60 patients (2 groups, n=30)	0.5% minocycline mouth rinse prescribed along with vitamin supplement and topical anesthetic gel	Vitamin supplement and topical anesthetic alone	Better reduction in pain symptoms (test group)
Esam Halboub <i>et al.</i> (2019) (32)	58 patients (2 groups, n=38, n=20)	NAC 200 mg dissolved in 20 ml water and used for 30 sec	CHX digluconate 0.12% dissolved in 20 ml water and used for 30 sec	Better reduction in pain symptoms (test group)

of oral ulcers. Thalidomide was reported to regulate lymphocyte function and reduce the content of TNF- α (27). Despite thalidomide showing good efficacy, its use, especially large-dose application, is limited due

to the severity of potential adverse effects, such as embryo-fetal toxicity with teratogenicity, thromboembolic disease, and peripheral neuropathy (28). Randomized controlled clinical trials results showed in Table 11.

Table 6. RAS treatment with gels

Authors	Sample size	Test Group	Control Group	Results
Siti Rusdiana Puspa Dewi <i>et al.</i> (2020) (2)	30 patients (2 groups, n=15)	Gambier extract ointment for 7 days	Placebo ointment for 7 days	Effective in reducing the pain, the healing and the size of RAS (test group)
Enrica Giannammarino <i>et al.</i> (2019) (6)	48 patients (3 groups, n=16)	Group I: Dermovitamina aftaclin + oral instructions + Er, Cr: YSGG laser irradiation at first appointment; Group II: Dermovitamina aftaclin + oral instructions	Topical application of a placebo product two times a day + oral instructions	Both test groups showed better results, no significant difference between both groups.
Duygu Ofluoglu <i>et al.</i> (2017) (9)	160 patients (3 groups, n=53, n=56, n=51)	TA pomade (0.1% triamcinolon acetone); TGO gel (92.67% triester glycerol oxide)	Placebo gel (92.67% corn oil)	Better reduction in pain relieving, can accelerate ulcer healing (test group)
Seyed Javad Kia <i>et al.</i> (2020) (15)	58 patients (2 groups, n=28)	5% of Curcumin orabase three times a day for 10 days	0.1% of triamcinolone acetone orabase three times a day for 10 days	No differences between both orabases.
Sara Darakhshan <i>et al.</i> (2019) (18)	56 patients (2 groups, n=28)	Pomegranate peel extract (PPE) and distilled water, 0.5% carboxymethyl cellulose (CMC) 2% hydroxypropyl methylcellulose (HPMC), acorbic acid gel	Distilled water, 0.5% carboxymethyl cellulose (CMC) 2% hydroxypropyl methylcellulose (HPMC), acorbic acid gel with coloring agents	Effective in reducing the pain, ulcer size and healing duration of ulcers (test group)
Fatemeh Abbasi <i>et al.</i> (2023) (21)	60 patients (2 groups, n=30)	Salvian gel topically applied to aphthous ulcers three times a day using a swab as much as 1 cm, preferably after eating and mouth rinsing.	Triamcinolone acetone topically applied to aphthous ulcers three times a day using a swab as much as 1 cm, preferably	Better results in pain recovery and wound healing (test group)
Hemcle Shalma G <i>et al.</i> (2019) (33)	64 patients (2 groups, n=32)	Aloe vera gel 3 times a day for 10 days	5% Amlexanox oral paste 4 times a day for 10 days	Significant reduction in ulcer size and VAS score (test group)
Naglaa M. El-Wakeel <i>et al.</i> (2019) (34)	80 patients (2 groups, n=40)	Topical insulin-liposomal chitosan gel (20 U/g)	Topical placebo gel without insulin	Showed marked effectiveness in management of aphthous ulcers (test group)
Medhi Ansari <i>et al.</i> (2021) (35)	60 patients (2 groups, n=30)	Fenugreek buccoadhesive paste (FBP) three times daily for 10 days	Dexamethasone mouthwash three times daily for 10 days	FBP could improve the most symptoms of RAS (test group)
Praveena Raman <i>et al.</i> (2020) (36)	69 patients (2 groups, n=34, n=35)	Topical curcumin – “Curnext”: Curcuma longa 10 mg oral gel 2%	Topical triamcinolone acetone – “Ketacort”: triamcinolone acetone oral paste 0.1%	Effect in ulcer size, pain, healing and recurrence rate (test group)
Ana Andabak Rogulj <i>et al.</i> (2021) (37)	57 patients (2 groups, n=27, n=30)	NAVS	Betamethasone dipropionate	No differences
Ana Andabak Rogulj <i>et al.</i> (2021) (37)	57 patients (2 groups, n=27, n=30)	NAVS	Betamethasone dipropionate	No differences

DISCUSSION

Typically minor aphthous ulcer can spontaneously heal within 4-14 days. However, the lesions in oral cavity may trigger severe chewing, speaking, and swallowing difficulties, which seriously interfere

with the normal activities of patients in daily life (12). Since the etiology is still unknown, before starting any treatment it is necessary to check risk factors, systemic diseases and other conditions associated with RAS.

All current systemic or topical treatment methods are to relieve symptoms and accelerate healing (24).

Table 7. RAS treatment with tablets

Authors	Sample size	Test Group	Control Group	Results
Qingwen Guo <i>et al.</i> (2018) (5)	140 patients (2 groups, n=70)	Chinese medicine Kou-chang Xiaotong powder 3 times a day for 7 days	Placebo multi-vitamin B for 2 tablets a time and 3 times a day + cetylpyridinium chloride gargle is applied with 3 times a day.	Better effect in shortening time for pain disappearing, reduced ulcer area, better treatment efficiency and promoted recovery rate (test group)
Anahita Ghorbani <i>et al.</i> (2020) (38)	46 patients (2 groups, n=23)	Zinc sulfate mucoadhesive tablet for 7 days	Placebo without active ingredient of zinc sulfate for 7 days	Effective in recovery and reducing the pain and diameter of the aphthous lesion (test group)
Ghadah Ali Al-Oudah <i>et al.</i> (2020) (39)	52 patients (2 groups, n=28, n=24)	Zinc oral dispersible tablet 20mg once per day for 14 days	Oral placebo tablet 20mg daily for 14 days	Effective in healing of the major types aphthous ulceration (test group)

Table 8. RAS treatment with topical antibiotics

Authors	Sample size	Test Group	Control Group	Results
Owlia MB <i>et al.</i> (2020) (26)	45 patients (2 groups, n=23 and n=22)	Powder of penicillin: 600,000 IU of benzathine penicillin, 300,000 IU of penicillin - G potassium, and 300,000 IU of procaine	Powder of placebo	Statistically significant reduce in ulcer size and recovery after treatment in penicillin group

Table 9. RAS treatment with omega-3 supplements

Authors	Sample size	Test Group	Control Group	Results
Hadian Z <i>et al.</i> (2021) (16)	40 patients (2 groups, n=20)	Omega - 3 capsule (1000 mg)	Placebo capsule	After 3 months the average number, duration, site and severity score of ulcer were significantly reduces in the group of omega-3; After 6 months the size, mean pain intensity, ulcer-free period, average number, duration, site and severity score of ulcer were significantly reduces in the group of omega-3;

Table 10. RAS treatment with probiotics

Authors	Sample size	Test Group	Control Group	Results
Pedersen AML <i>et al.</i> (2019)23	20 patients (2 groups, n=10)	Probiotic lozenges with Lactobacillus Reuteri 5 x 10 ⁸ live bacteria per lozenge	Placebo lozenges	No statistically significant difference between two groups.
Aggour RL <i>et al.</i> (2020)24	120 patients (2 groups (adult and pediatric), 4 subgroups, n=30)	Adults: Lactobacillus acidophilus 1.5 billion, Bifidobacterium lactis 1.5 billion, insulin 0.13 g per lozenge; Pediatric: Lactobacillus acidophilus 0.5 billion, Bifidobacterium lactis 0.5 billion, insulin 0.13 g per lozenge;	Oracure oral gel	Adults: pain was statistically significantly reduced in probiotics group; Pediatric: statistically significant ulcer size reduction at day 5 and decrease in outbreak frequency within 6 months next to treatment in probiotics group.
Dugourd PM <i>et al.</i> (2020)25	19 patients (2 groups, n=9 and n=10)	Oral suspension Lactobacillus rhamnosus 1.5 billion	Placebo	No statistically significant difference were noted between two groups.

Table 11. RAS treatment with thalidomide

Authors	Sample size	Test Group	Control Group	Results
Zeng Q <i>et al.</i> (2020) (27)	51 patients (2 groups, n=29 and n=22)	Thalidomide 100 mg/d - 10 days; 50 mg/d - 10 days; 25 mg/d - 10 days;	Predisone 0,4 mg/kg - 15 days; 0,2 mg/kg - 15 days;	Statistically significantly reduced recurrence interval, pain, ulcer number and healing time in both groups compared to baseline, no statistically significant difference between groups.
Deng Y <i>et al.</i> (2022) (28)	113 patients (2 groups, (5 subgroups), n=23, n=24, n=21, n=22, n=23)	Prednisone 15 mg/d - 7 days + thalidomide 50 mg/d 4 weeks (High1) / 8 weeks (High2); Prednisone 15 mg/d - 7 days + thalidomide 25 mg/d 4 weeks (Low1) / 8 weeks (Low2);	Prednisone 15 mg/d - 7 days;	Statistically significant less incidence of ulcer, number and visual analog scale in the High2 and Low2 groups, compared to High1 and Low1. Statistically significant difference in the ulcer free days before and after treatment within each group.

A wide variety of topical therapies which includes avoiding certain foods, treatment with local anesthetics, protective bioadhesives, antiseptic or anti-inflammatory therapies, local antibiotics, and topical steroids or systemic agents have been suggested for the treatment of these ulcers over the years (8, 11).

CONCLUSION

Taken together this systemic review topical medications can promote the healing time of ulcers and relieve the pain, but most of the time can not

decrease the frequency of RAS relapse. However, for continuous RAS, treatment with systemic medication should be considered. One of the limitation of our systemic review was studies with different treatments methods compared with placebo and short follow up after treatment. Therefore, further studies are needed comparing different treatment methods in between and longer patients monitoring.

CONFLICT OF INTERESTS

All authors declare no conflict of interests.

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