Universidad Europea

GRADUATION PROJECT

Degree in Dentistry

DIFFERENTIAL DIAGNOSIS AND MANAGEMENT OF CHRONIC ORAL ULCERS

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ABSTRACT

Introduction: Chronic oral ulcers represented a frequent clinical condition in dental practice, often associated with pain and impaired quality of life. Their multifactorial etiology and variable response to treatment made their management challenging. **Objective:** This review aimed to analyze and compare the effectiveness of topical and systemic therapies for the management of chronic oral ulcers. **Materials and methods:** A literature review was conducted using scientific databases, including PubMed and MEDLINE, selecting articles published between 2016 and 2026. Inclusion and exclusion criteria were applied to identify and analyze 10 studies evaluating various therapeutic approaches in human subjects. **Results:** Both topical and systemic treatments demonstrated clinical benefits, including reduced pain, smaller ulcer size, faster healing, and reduced recurrence. Topical therapies such as corticosteroids, bioadhesive gels, statin-based formulations, growth factor combinations, and natural compounds showed significant effectiveness with minimal adverse effects and were associated with faster local symptom relief. Novel approaches such as low-level laser therapy and photobiomodulation also improved healing outcomes and patient comfort. In contrast, systemic therapies, including immunomodulatory drugs, were mainly effective in severe or refractory cases by targeting underlying inflammatory mechanisms but were associated with potential adverse effects and recurrence after treatment discontinuation. **Conclusions:** Topical therapies appeared to be the most appropriate first-line treatment for most cases of chronic oral ulcers, given their efficacy and safety profile, whereas systemic treatments should be reserved for severe or systemic conditions. A personalized approach based on disease severity and patient characteristics was essential to optimize clinical outcomes.

KEYWORDS

Dentistry, chronic oral ulcers, topical therapy, systemic therapy, treatment effectiveness

RESUMEN

Introducción: Las úlceras orales crónicas son una patología frecuente en odontología, generalmente asociada a dolor y a una disminución de la calidad de vida. Su etiología multifactorial y su respuesta variable al tratamiento hacen que su manejo resulte complicado. **Objetivo:** Comparar la eficacia de los tratamientos tópicos y sistémicos en el manejo de las úlceras orales crónicas. **Material y método:** Se realizó una revisión bibliográfica en bases de datos científicas como PubMed y Medline, incluyendo artículos publicados entre 2016 y 2026. Tras aplicar los criterios de inclusión y exclusión, se seleccionaron diez estudios centrados en terapias aplicadas a humanos. **Resultados:** Ambos tipos de tratamiento mostraron beneficios clínicos, incluyendo la reducción del dolor, la disminución del tamaño de las lesiones, la aceleración de la cicatrización y una menor recurrencia. Los tratamientos tópicos, como corticosteroides, geles bioadhesivos, estatinas, factores de crecimiento y compuestos naturales, destacaron por su eficacia y mínimos efectos adversos, proporcionando un alivio rápido de los síntomas locales. Además, técnicas emergentes como la terapia láser de baja intensidad y la fotobiomodulación mejoraron los resultados de cicatrización. Por otro lado, los tratamientos sistémicos, como los inmunomoduladores, resultaron más útiles en casos severos o refractarios al actuar sobre la inflamación subyacente, aunque presentaron más efectos adversos y posibles recaídas tras su suspensión. **Conclusiones:** Los tratamientos tópicos constituyen la primera opción terapéutica en la mayoría de los casos por su eficacia y seguridad, mientras que los tratamientos sistémicos deben reservarse para casos graves. Un enfoque individualizado es clave para optimizar los resultados clínicos.

PALABRAS CLAVE

Odontología, úlceras orales crónicas, tratamiento tópico, tratamiento sistémico, eficacia del tratamiento

Abbreviations

BS: Behçet Syndrome

CHX: Chlorhexidine

COX-2: Cyclooxygenase 2

HIV: Human immunodeficiency Virus

HSV: Herpes Simplex Virus

LLLT: Low-Level Laser Therapy

OSCC: Oral Squamous Cell Carcinoma

PDE-4: Phosphodiesterase-4

RAS: Recurrent Aphthous Stomatitis

RAU: Recurrent Aphthous Ulcer

Rb-bFGF: Recombinant bovine basic Fibroblast Growth Factor

ROU: Recurrent Oral Ulcer

SLS: Sodium Lauryl Sulfate

TA: Triamcinolone Acetonide

TB: Tuberculosis

TGO: Triester Glycerol Oxide

VAS: Visual Analog Scale

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1. INTRODUCTION

1.1 Background and Relevance of Chronic Oral Ulcers

Ulcers are common in the oral cavity and among the most frequent diseases affecting the oral mucosa, leading to pain and difficulty with mastication, speech, and brushing (1,2). Recurrent oral ulcer (ROU) is a common and painful oral condition that affects not only the oral mucosa but also the patient's quality of life, necessitating multidisciplinary management (3). Ulceration results from a wide range of systemic and local causes, making the diagnosis challenging. Getting enough sleep, eating fruits and vegetables, taking vitamin supplements, and maintaining a moist oral environment are essential for preventing and delaying the onset of recurrent aphthous ulcers (RAU) (4).

1.1.1 Definition and clinical significance

An oral ulcer is described as a total loss or defect of the epithelium that results in a crateriform appearance (5,6) (Figure 1). It is usually coated with a fibrinous membrane and is clinically characterized by a whitish lesion surrounded by an erythematous halo (7).

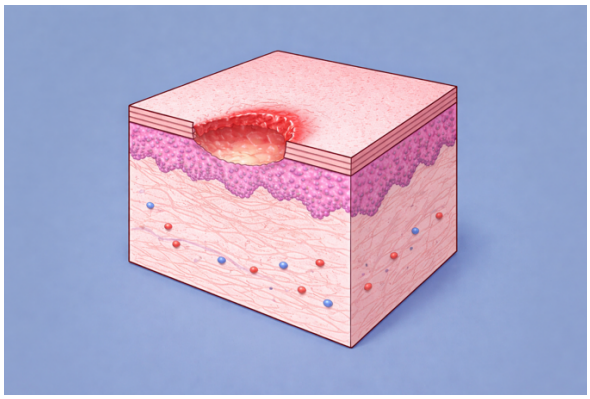


Figure 1. Schematic representation of epithelial ulceration. AI-generated illustration created with ChatGPT (OpenAI, DALL·E), 2026, based on prompt created by the author.

This desquamation produces pain, erythema, heat, discomfort during chewing or eating, swelling, and irritation from spicy, salty, or sour foods (1,5,7).

The duration of symptoms is key to differentiating between acute and chronic oral ulcers: if an ulcer lasts 2 weeks or longer, it is considered chronic; otherwise, it is considered acute (7). Acute ulcers are temporary and usually resolve on their own within two weeks, whereas chronic

ulcers last longer and may indicate a more serious underlying condition (8). On the other hand, recurrent ulcers show a pattern of recurrence with periods of healing in between episodes (7). Ulcers can be solitary (one ulcerative lesion) or multiple (two or more ulcerative lesions) (7). They are mostly located on the buccal mucosa, inner side of the lips, the lateral border of the tongue, or the posterior part of the palate due to infectious diseases such as tuberculosis (9,10).

1.1.2 Diagnostic challenges and need for differential diagnosis

Diagnosis of an ulcer may be challenging due to various factors, features, and the wide range of diseases that can cause ulceration; for that reason, a differential diagnosis is important to arrive at a final diagnosis (11). Diseases that produce erosion and ulceration should be considered in the differential diagnosis of chronic oral ulcer. Also, our patients' medical history is an important tool that may help us in diagnosis, as some oral ulcers are associated with systemic diseases such as tuberculosis, diabetes, Behçet syndrome, or gastrointestinal and infectious diseases (7,9). The dentist should also verify the use of drugs, medications, chemotherapy, or radiotherapy, as they can contribute to oral ulceration (8,12).

1.2 Diagnostic approach

Diagnosis of chronic oral ulcers is difficult in most cases (6,10). But an accurate diagnosis is fundamental to subsequent appropriate treatment (7). Most of the diagnoses are based on clinical criteria and the patient's history (7). For infectious diseases like syphilis that present with an ulcerative lesion, serological tests, complete blood test, and creatinine must be done to diagnose the sexually transmitted disease and properly treat it (13). One diagnostic approach to help clinicians is first to establish whether the lesion follows an acute, chronic, or recurrent pattern (7). For example, the diagnosis of necrotizing ulcerative gingivitis is based on three symptoms: painful, bleeding gums; ulceration; and necrosis of the interdental papilla (7).

When clinical history and intraoral examination fail to establish a diagnosis of oral ulcers, a biopsy should be considered (6). There are three situations in which a biopsy is indicated:

1. Ulceration with an unclear etiology that persists for over two weeks without showing signs of healing
2. Ulcer of probably known etiology that, even after two weeks of treatment, is unresponsive
3. Persistent ulcer two weeks after removal of the triggering factor (14).

However, before performing the biopsy, a blood test should be performed to rule out contraindications (6). This blood test can provide diagnostic insights by including a complete blood count, serology for sexually transmitted infections, and blood sugar levels (6). Hyperglycemia can predispose to fungal infections, while oral ulcers may result from fungal infections or HIV (6). Serology for syphilis and HIV helps rule out ulcers associated with these infections (6). If the blood test didn't help with the diagnosis and there are no contraindications, a biopsy should be considered; when ulcers are present in multiple sites and exhibit different characteristics, several biopsies should be performed (6). A positive biopsy will indicate oral squamous cell carcinoma, bullous disease, eosinophilic ulcer, lymphoid hematopoietic malignancies (like leukaemia), granulomatous inflammation (due to infection like tuberculosis and syphilis or will indicate Crohn's disease) or other disease where a negative biopsy will require patient's medical history and further examination like CT scans to detect tuberculosis or urine tests to detect diabetes for example (6).

The microbiological Tzanck smear test is a useful tool for diagnosing herpesvirus, fungal, and bacterial infections (14). Histological examination is essential; it reveals specific features of chronic oral ulcers: epithelial hyperplasia and a large number of plasma cells in the connective tissue of the oral mucosa (15).

1.3 Etiology, clinical features, and management

Its etiology is broad and varies from minor trauma to tumors, infectious to inflammatory diseases, and from allergic to autoimmune diseases (8,16). Several factors can cause it, and it can present with similar or different clinical features depending on its etiology.

1.3.1 Main etiology and clinical characteristics

Chronic oral ulcers can be:

- Traumatic (thermal, electrical, chemical, mechanical) (17)
- Infectious (Herpes Simplex Virus: HSV, syphilis, tuberculosis: TB, HIV, Candida) (17)
- Inflammatory (Behçet's syndrome, Crohn's disease, ulcerative colitis, inflammation of minor salivary glands) (18,19)
- Immune-mediated (recurrent aphthous stomatitis, RAU, erythema multiforme, lichen planus, pemphigus vulgaris, celiac disease) (20)
- Neoplastic (oral squamous cell carcinoma: OSCC)

- Nutritional (lack of iron, vitamin B, C, or folate) (20)
- Due to stress or allergies to certain foods or toothpastes with ingredients like sodium lauryl sulfate (SLS) (8,20)
- Iatrogenic: due to medications; various medicines are known to cause oral lesions as an adverse effect, like chemotherapy, or also a few cases have been reported involving antidepressants (Amitriptyline and Fluoxetine) (21).

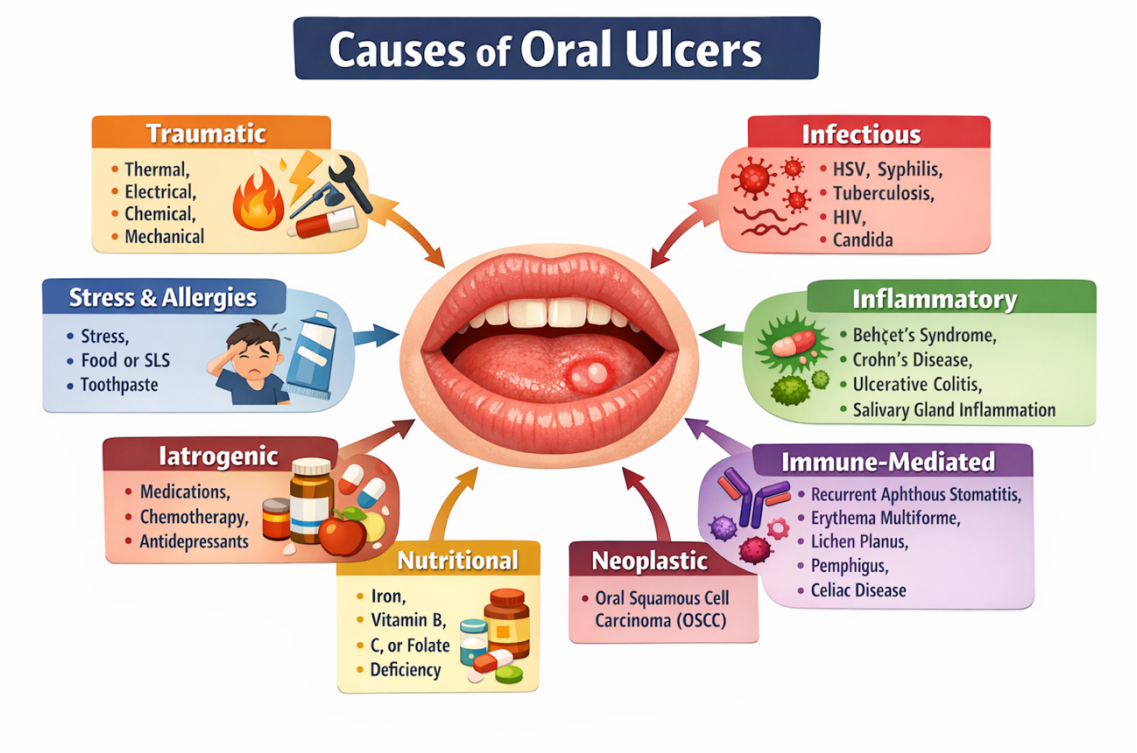


Figure 2. Scheme illustrating the causes of oral ulcers. AI-generated illustration created with ChatGPT (OpenAI, DALL·E), 2026, based on prompt created by the author.

Clinical characteristics for recurrent aphthous stomatitis (RAS) are round, well-defined, with an erythematous halo and central yellowish-grey pseudo membrane accompanied by burning sensations lasting from 2 to 48 hours before ulcer apparition (7). They are primarily located on the soft-tissue mucosa of the oral cavity and lack keratinization in the buccal and labial soft tissues (7). The features of HSV vary from gingivitis to painful ulcers (7). HIV's ulcer is characterized as necrotic ulcers, which cause dysphagia and are typically located on the buccal and pharyngeal sites, while tuberculosis causes ulcerative mouth sores and is commonly located on the tongue, gingiva, floor of the mouth, palate, lips, and buccal soft tissues (7). Primary syphilis presents a chancre at the infected site, secondary syphilis presents regional lymphadenopathy with snail tract ulcer, and tertiary syphilis presents gumma with neurological

complications (13,22,23). As these characteristics can vary, the differential diagnosis is an important tool for distinguishing the disease we are facing.

1.3.2 Management and therapeutic options

While most oral ulcers are generally harmless and heal on their own, they can be hard to manage due to their unresponsiveness (24). Oral ulcer prevention includes gentle brushing with a soft toothbrush and avoiding gum irritation (14). Generally, oral ulcers heal on their own within 2 weeks; if not, they can be more serious and may indicate an underlying disease that requires treatment (25).

Depending on disease severity, therapeutic options may vary, but treatment is usually topical or systemic (14). Treatment of oral ulcers mainly consists of topical and/or systemic glucocorticoids (anti-inflammatory), colchicine (anti-inflammatory), antibiotics, and apremilast (inhibitor of inflammatory cytokines) (14,20). But many other treatments exist. Management of RAS relies on symptom severity, recurrence, ulcer diameter, and ulcer count (20). Topical antibiotics, such as tetracycline mouth rinses, have been shown to decrease healing time and pain; however, their use is limited due to reported cases of oral candidiasis and allergic reactions (20). Topical anti-inflammatory and antiseptic agents help prevent overinfection and improve oral hygiene (14). Indeed, most oral mucosal ulcerations are managed according to three principles: anti-inflammation and antiseptic (chlorhexidine, povidone-iodine), pain relief (lidocaine gel, chamomile compound), and promotion of healing (patch, paste, gel) (4). Non-pharmaceutical interventions, such as laser therapy and photobiomodulation, can also be used, and even natural compounds like curcumin and sumac have shown positive results (26–29). Dietary habits are important determinants in the onset and course of recurrent oral ulcers (3). Oral nutritional supplements, as well as antioxidants and proteins, facilitate the healing process (3). Nutritional deficiencies have been described as etiological factors for RAS; deficiencies in iron, folic acid, zinc, vitamins B1, B2, B6, and B12, calcium, and vitamin C, as well as neutropenia, could influence the pathogenesis of RAS (14,20). A plant-based diet helps reduce inflammation and oxidative stress; it is well known for its benefits on oral health due to its high content of antioxidant and anti-inflammatory biomarkers (3). Studies show that specific foods, such as high nut intake, could reduce the risk of ROU (3). Also, a high intake of plant-based foods, such as grains and fruits, may be advantageous for the prevention and treatment of ROU (3). Excessive consumption of red and processed meat, as well as dairy products and eggs, may

increase the risk of oral disease by promoting oxidative stress and inflammatory responses due to their high levels of cholesterol and fat (3).

The management of chronic oral ulcers also includes avoiding non-irritating foods and trigger foods, such as spicy, salty, acidic, and hot foods and drinks; alcohol; carbonated beverages; hard and crunchy foods; and toothpaste containing sodium lauryl sulfate, which can irritate and aggravate the tissues (3,18).

1.4 Justification

Chronic oral ulcers are a common, painful condition with a significant impact on patients' quality of life. Although most oral ulcers are benign and tend to resolve spontaneously, their management can be challenging due to frequent recurrence and variable treatment response. Depending on disease severity, therapeutic approaches may differ; however, management primarily relies on topical or systemic treatments. Despite the wide range of available options, there is no clear consensus regarding the most effective approach. The variability in clinical presentation and patient response further complicates treatment selection. Therefore, a systematized review is justified to critically analyze and compare the effectiveness of topical and systemic therapies to support evidence-based clinical decision-making.

2. OBJECTIVE

To compare the effectiveness of topical treatment compared to systemic treatment in chronic oral ulcer.

3. MATERIAL AND METHODS

To conduct this literature review, we performed an in-depth bibliographic search across multiple sources, including the CRAI Dulce Cachón library and reliable databases such as PubMed and Medline Complete. The two main sources used for this review were PubMed and the CRAI Dulce Cachón library.

Key terms included: oral ulcer, therapy, topical treatment, systemic treatment, ulcer management, corticosteroids, and effectiveness.

The advanced research terms used in the databases were: “chronic oral ulcer” OR “oral ulceration” AND “treatment of oral ulcer” OR “management of oral ulcer” AND “recurrent oral ulcer” AND “recurrent aphthous stomatitis” OR “recurrent aphthous ulcers” AND “treatment alternative chronic oral ulcer” AND “topical treatment chronic oral ulcer” AND “systemic treatment chronic oral ulcer” AND “steroid treatment oral ulcers”.

Out of 4263 articles, a few were chosen for this review with the use of a few filters like “articles from the last 10 years”, “English language”, and “integral text”. The articles were selected using the inclusion and exclusion criteria listed in Table 1 below.

The PICO research question (Participant, Intervention, Comparison, Outcomes) formulated to define the objective of this study is as follows: In patients with chronic oral ulcers (P), does systemic therapy (I) provide better ulcer healing and pain control (O) compared with topical therapy (C)?

By clearly defining this question as our guiding objective, we can select and analyze relevant literature more precisely, helping us better understand the topic.

Table 1: Inclusion and exclusion criteria

Inclusion criteria	**Exclusion criteria**
Scientific articles published between 2016-2026	Scientific articles published before 2016
English written articles	Articles written in non-English languages
Articles from reliable sources like Pubmed, Medline…	Articles from unreliable sources
Relevant information about chronic oral ulcer	Irrelevant information or no information about chronic oral ulcer
Articles on humans	Articles on animals
Integral text	Non-integral text

4. RESULTS

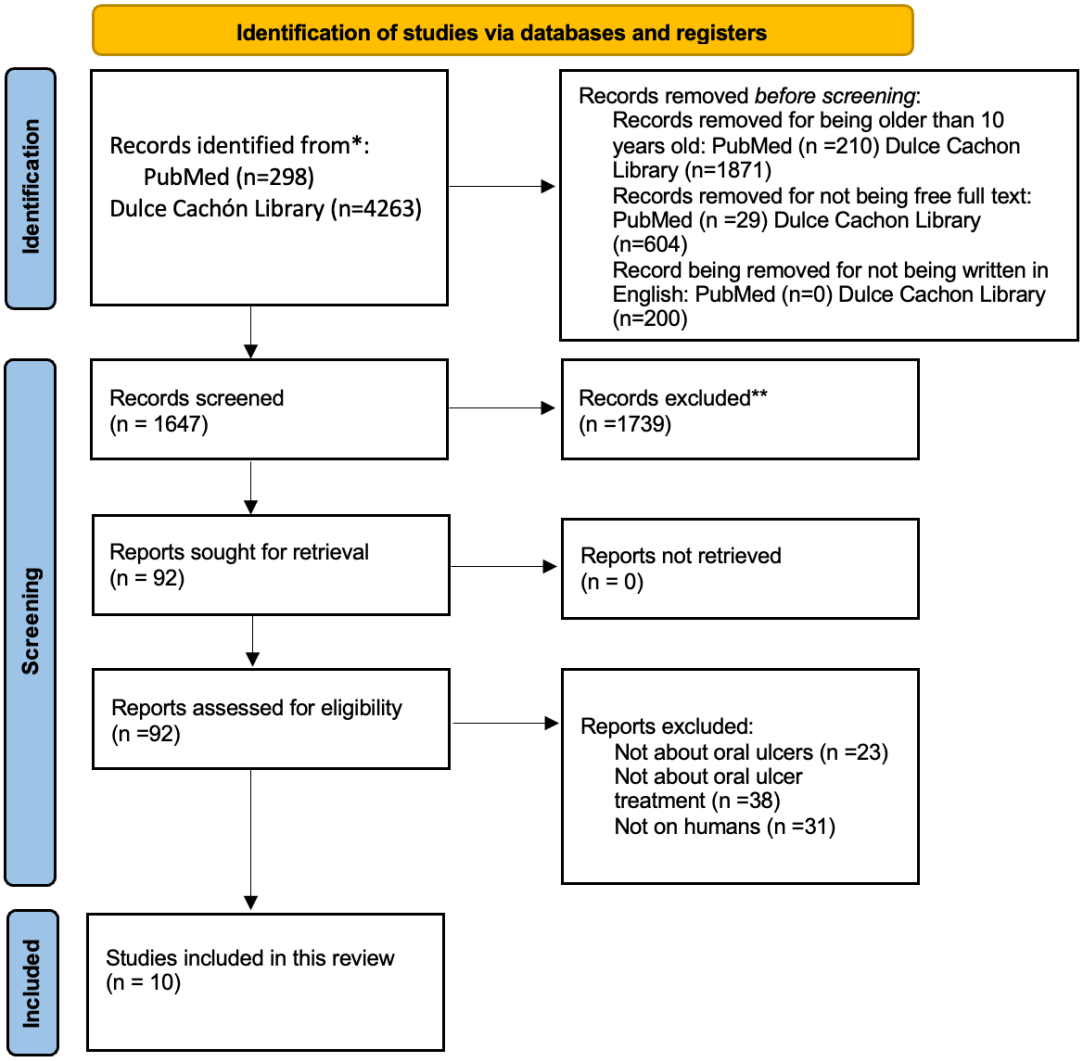


Figure 3. Prisma flow chart of the included studies in this review

Table 2: Table summarizing the 10 studies on the treatment and management of oral ulcers

	Year and author	Country	Type of study	Sample size (n)	Age range	Objective	Summary of the study	Outcomes
1	2022, Y. Deng et al. (30)	China	Randomized controlled clinical trial	125	44-53	Evaluation of the efficacy and safety of thalidomide using low doses and high doses in maintenance treatment of RAS (recurrent aphthous stomatitis).	All patients first received short-term prednisolone (15mg/day for 1 week) to control active ulcers. They were then given either 25mg/day (low-dose) or 50mg/day (high-dose) thalidomide (immunosuppressive and anti-inflammatory) for maintenance during 4 or 8 weeks.	Both high and low doses reduced ulcer number, incidence and pain equally after 4 and 8 weeks. Symptoms returned 4 weeks after stopping the treatment. The 25mg/day dose was safer and prolonged the ulcer free period.
2	2017, D. Ofluoglu et al. (31)	Turkey	Randomized, double-blind, placebo-controlled clinical trial	160	18-65	To compare and determine the efficacy of Triester Glycerol Oxide (TGO) gel with triamcinolone acetonide (TA) pomade and a placebo in the treatment of minor RAS.	3 groups were made in this study: - TA group - TGO group - placebo group They were followed over a period of 6 days. The pain was recorded as well as ulcer size.	TGO significantly reduced pain and ulcer size while accelerating healing, unlike TA which showed minimal benefit over placebo. TGO was more effective and better tolerated.
3	2021, G. Hatemi et al. (32)	Turkey, Switzerland, Japan, South	Randomized clinical trial	207	≥ 18	To assess whether Apremilast is effective and safe for treating oral ulcers in Behçet	This phase 3 study focuses on adult patients with active BS which were given a placebo or 30mg oral apremilast twice daily for 12 weeks,	Apremilast significantly reduced oral ulcer number, pain, disease activity and improved quality of life by week 12, with sustained benefits up to 64

		Korea, France, USA				syndrome (BS) up to 64 weeks.	then during the extension phase, all patients received apremilast until week 64 ending with a 4-week post-treatment follow-up. Oral ulcer number, pain, disease activity and quality of life were all assessed during the study.	weeks. Symptoms reappeared within 4 weeks after stopping treatment. It was well-tolerated long-term.
4	2023, T. Molania et al. (33)	Iran	Double-blind clinical trial	44	20-40	To evaluate whether Atorvastatin can decrease symptoms and healing time of minor recurrent aphthous ulcers (RAU).	Patients were divided into 2 groups: - Atorvastatin group (22patients) - Placebo group (22 patients) They all received 3 mucoadhesive tablets daily (morning, noon, night) as topical treatment. Examination was made at day 0,3,5,7 to control the inflammatory halo diameter. Pain was recorded after each meal.	There was a significant pain reduction from day 3-6 in the atorvastatin group as well as a faster decrease in inflammatory halo diameter. Smaller ulcers in shorter healing time were observed by days 3,5 and 7 in the atorvastatin group.
5	2024, C. Haishan et al. (34)	China	Randomized clinical trial	96	≥ 18	To determine whether adding recombinant bovine basic fibroblast growth factor (rb-bFGF) to standard chlorhexidine rinses improves the clinical outcome of recurrent oral ulcers (ROU), influences inflammatory and immune markers and decrease recurrence rate.	Patients were divided into 2 groups: - Chlorhexidine + rb-bFGF group (48 patients) - Chlorhexidine alone (48 patients) Therapeutic effectiveness, symptoms improvement, and the 3-months recurrence rate were compared between the two groups. Serum inflammatory and immune markers were assessed in both groups before and after treatment.	CHX+ rb-bFGF group showed a higher effectiveness rate (95,83%) than control (81,25%), with faster pain relief, longer pain-free period, fewer and smaller ulcers and quicker return to normal eating. Inflammatory markers decreased more significantly in the experimental group and recurrence was also lower over 3 months (8,33% vs 29,17%), with improved immune response.

6	2024, Z. Rezvani et al. (29)	Iran	Randomized clinical trial	60	18-40	To evaluate and compare the clinical efficacy of Rhus coriara (sumac) gel versus triamcinolone acetonide (TA) paste versus placebo in treating minor aphthous lesions.	Patients were divided into 3 groups and received: - Sumac adhesive gel group - Triadent oral paste (triamcinolone) group - Placebo group All the patients presented with minor aphthous ulcers. Healing time, ulcer size and pain were recorded.	The sumac group had the fastest healing time (4,35 days), while the Triadent group had the longest (7,8 days). Sumac significantly reduced lesion size and pain from day 3 to 7 compared to Triadent and placebo. Pain scores were similar between Triadent and placebo, but still, sumac was the most effective treatment.
7	2023, S. Alsahaf et al. (35)	UK	Randomized clinical trial	106	18-65	To evaluate and compare the effectiveness of topical betamethasone, systemic colchicine and combined therapy and determine the optimal treatment duration for reducing disease severity.	The patients were divided into 3 groups: - Betamethasone mouthwash group - Colchicine tablets - Combined therapy (betamethasone + colchicine) All the patients suffered from RAS and the evaluation was made every 3 months for one year. Ulcer severity score (USS) was recorded.	All three treatments reduced USS by 30% at 3 months and 50% at 12 months, with major improvements seen by 3-6 months. Betamethasone showed the greatest reduction at 12 months and the best overall results, while combination therapy was not superior to steroids alone. Colchicine was effective but caused adverse effects such as gastric pain, neuropathy and alopecia.
8	2026, M. El Mansy et al. (26)	Egypt	Randomized clinical trial	30	6-14	To compare the clinical effectiveness of low-level laser therapy (LLLT), lidocaine and with chlorhexidine (CHX) gel in reducing pain and accelerating healing of traumatic oral ulcers in pediatric patients.	The patients were divided into 3 groups: - LLLT group (10 patients) - lidocaine gel group (10 patients) - Chlorhexidine mouthwash group (10 patients) All children presented traumatic oral ulcers. Ulcer size was measured with	The laser group showed the fastest ulcer size reduction and shortest healing time, with significant differences at days 5 and 7 compared to lidocaine and CHX. It also had the lowest pain scores at all evaluated times points and the highest parental satisfaction.

							a periodontal probe; pain intensity was assessed using Visual Analog Scale (VAS) and parental satisfaction was also evaluated.	
9	2022, V. Ramezani et al. (28)	Iran	Randomized clinical trial	37	18-75	To determine whether curcumin therapy can decrease the severity and pain of oral mucositis in patients undergoing radiotherapy.	The patients were divided into 3 groups: - Curcumin mouthwash - Sinacurcumin soft gel - Placebo mouthwash The patients were told to do the mouthwash for 1 minute, 3 times daily during radiotherapy. Evaluation was made at baseline, and every week for up to 3 weeks.	Both topical curcumin treatments significantly reduced mucositis severity, burning sensation, and pain during the first 3 weeks compared to placebo. VAS pain scores were lower in the curcumin group. By the end of the study, over 33% of the mouthwash group and 15% of the soft gel group remained ulcer-free, while all the placebo patients developed mucositis.
10	2025, M. Khalil et al. (27)	Syria	Randomized clinical trial	45	<45 and >45	To evaluate if preconditioning with photobiomodulation (laser light therapy) using specific diode lasers before first-time chemotherapy prevents oral mucositis and xerostomia and improves patients' quality of life.	The patients were divided into 3 groups: - Group 1: basic oral care instructions before undergoing chemotherapy - Group 2: basic oral care instructions + photobiomodulation using a 650 nm diode laser intra orally - Group 3: basic oral care instructions + photobiomodulation using a 650 nm diode laser intra orally and a 980 nm extra orally diode laser	After 1 week, 73,3% of patients in group 2 and 80% of patients in group 3 did not develop oral mucositis, while 100% of patients in group 1 did. After 2 weeks, 80% and 86,7% of the laser groups 2 and 3 remained free of mucositis where 93,3% in the control group 1 developed it. Mucositis severity was significantly lower in the laser groups, with no ulcerative cases, and quality of life and xerostomia scores were better.

							The 45 patients were assessed for presence and severity of oral mucositis, quality of life and xerostomia after 1 week and after 2 weeks.	

5. DISCUSSION

Chronic oral ulcers, particularly recurrent aphthous stomatitis (RAS) and ulcerations associated with systemic diseases such as Behçet syndrome, represent a significant clinical challenge due to their recurrent nature, associated pain, and impact on patients' quality of life. Oral ulcers are very painful, so most treatments are symptomatic rather than preventive, as the etiology is often unknown. The studies included in the result table highlight a wide range of therapeutic approaches, including systemic medications targeting the underlying inflammatory process and several topical agents that act locally on the mucosa, focusing on inflammation, pain control, and mucosal healing in patients with various conditions. The objective of this review was to analyze and compare the effectiveness of topical and systemic therapies in the management of chronic oral ulcers, based on evidence from the selected clinical studies. Since many therapeutic options are available on the market, comparing their effectiveness is essential to selecting the most appropriate therapy. The ten studies included in the present review evaluated a variety of therapeutic approaches, including corticosteroids, antiseptics, immunomodulatory drugs, anesthetics, regenerative agents, plant-based compounds, and other novel topical products available in multiple formulations. This wide range of options can make choosing the most suitable treatment complex and sometimes challenging for clinicians. Also, the appropriate treatment approach must be chosen based on the severity of the lesion, the patient's medical history, the number and size of ulcers, and the patient's tolerance to the treatment (31).

4.1 General interpretation of the findings

The studies included in this review suggest that both topical and systemic treatments can improve chronic oral ulcer symptoms, but topical therapies appear effective with fewer systemic risks. Although most studies reported improvements in pain reduction, ulcer size, healing time, and recurrence frequency, the mechanisms and magnitudes of improvement vary by therapeutic approach. Topical treatments were frequently associated with faster local symptom relief, while systemic therapies tended to target underlying inflammatory pathways, particularly in patients with more severe or recurrent disease. Overall, both systemic and topical therapies demonstrated clinical benefits in reducing the number of ulcers, pain intensity, and healing time. However, the mechanism of action, indications, and safety profiles differed significantly between these approaches.

4.2 Effectiveness of topical treatment

In contrast to systemic treatments, topical therapies act locally on the oral mucosa and are usually considered first-line treatment for mild to moderate oral ulcerations (26,30,32). These therapies aim to reduce inflammation, control pain, promote healing, and protect the ulcer surface from further irritation.

Commonly used topical therapies include corticosteroids, chlorhexidine, and lidocaine (26). However, the effectiveness of topical corticosteroids may vary by formulation. Triamcinolone acetonide (TA) is a topical corticosteroid; it is the most common agent prescribed in Turkey, and Triester Glycerol Oxide (TGO) is a topical bio-adhesive gel; it adheres to the mucosa thanks to the formation of a lipid layer that shields against mechanical trauma and aids in reducing inflammation (31). In a randomized, placebo-controlled trial by Duygu Ofluoglu et al. (2017) including 160 patients, the authors compared the efficacy of TGO gel, TA pomade, and placebo in the treatment of minor RAS (31). The results showed that TGO gel significantly reduced pain (at days 2, 4, and 6) and ulcer size (at days 4 and 6), while accelerating healing, whereas TA demonstrated minimal benefit over placebo (31). TGO was more effective and well-tolerated, suggesting it is a better first-line topical treatment for minor RAS than corticosteroids (31). Also, no important side effects were reported (31). These findings question the common belief that topical corticosteroids are always more effective than other topical treatments. They also suggest that bioadhesive protective formulations may significantly help manage and protect oral ulcers, thanks to their mechanical barrier properties.

More recent studies have explored the potential of alternative pharmacological agents in topical form. T. Molania et al. (2023) investigated the utilization of atorvastatin mucoadhesive tablets for the treatment of minor recurrent aphthous ulcers (RAU) (33). Atorvastatin tablets have anti-inflammatory, analgesic, and tissue regeneration properties (33). Their double-blind clinical trial included 44 patients and demonstrated that topical atorvastatin significantly reduced pain from days three to six and accelerated healing compared with placebo (33). The inflammatory halo surrounding the ulcer also decreased more rapidly in the atorvastatin group, showing us its anti-inflammatory mechanism (33). Also, smaller ulcers with shorter healing times were observed on days 3, 5, and 7 in the atorvastatin-treated patients (33). No side effects were reported during the study period, suggesting that this treatment may offer a safe and effective alternative for ulcer management (33). These findings highlight the anti-inflammatory, analgesic, and tissue-healing properties of statins when applied locally (33). It is a recent and efficient method for

managing minor RAU, thanks to its protective coating that covers the lesion. Other benefits of this medicine include preventing secondary ulcer infections and eliminating the need for antibiotics or antifungal treatments (33).

Another innovative topical strategy was evaluated by C. Haishan et al. (2024), who investigated the addition of recombinant bovine basic fibroblast growth factor (rb-bFGF) to chlorhexidine (CHX) mouthwash therapy (34). Rb-bFGF is a lab-made protein that accelerates mucosal healing, reduces inflammation, and improves tissue regeneration. In this randomized clinical trial involving 96 patients, the combination therapy demonstrated a higher overall effectiveness rate (95,83%) than CHX alone (81,25%) (34). Patients receiving rb-bFGF also experienced faster pain relief, longer pain-free intervals, fewer and smaller ulcers, improved immune response (greater decrease in IL-2, IL-6, IL-8, and TNF-α, indicators of inflammation), and quicker return to normal eating (34). Furthermore, the recurrence rate was significantly lower (8,33%) in the combined treatment group than in the control group (29,17%) over a 3-month follow-up (34). Adding rb-bFGF gel to CHX rinsing improves symptom relief, speeds healing, strengthens immune response, reduces inflammation, and significantly lowers the rate of ulcer recurrence compared with rinsing alone (34). This study demonstrates that the combined use of CHX mouthwash and rb-bFGF gel improves clinical outcomes in patients presenting recurrent oral ulcers (ROU) (34). The treatment was associated with reduced levels of inflammatory factors, enhanced immune function, and a lower recurrence rate (34). These findings suggest that this therapeutic approach is clinically effective and may be recommended for wider use (34). It's a modern and promising therapy, especially when combined with chlorhexidine. It has the advantage of targeting healing rather than just symptoms.

Rezvani et al. (2024) evaluated the clinical efficacy of two topical treatments for RAS: triamcinolone acetonide (Triadent oral paste), a corticosteroid, and Rhus Coriaria (sumac adhesive gel), a plant-based topical formulation derived from a medicinal plant with anti-inflammatory, antioxidant, and antimicrobial properties (29). In this randomized clinical trial involving 60 patients, participants were divided into three groups that received Triadent paste, sumac gel, or placebo (29). The results demonstrated that the healing time was longer in the Triadent group (7.8 days) compared with the sumac group (4.35 days) (29). Also, a significant reduction in lesion size was observed in the sumac group on the third, fifth, and seventh days compared with the Triadent and placebo groups (29). Additionally, a significant decrease in pain score from the third to the seventh day was reported in the sumac group, whereas pain scores

did not differ significantly between the placebo and Triadent groups at any time during the study period (29). These findings indicate that sumac gel results in a faster healing time, significant size reduction, and a lower pain score, making sumac the most effective treatment in patients with RAS (29). Sumac gel is an interesting natural option for treating RAS due to its multiple beneficial properties.

M. El Mansy et al. (2026) compared low-level laser therapy (LLLT) with lidocaine gel and chlorhexidine mouthwash for the management of traumatic oral ulcers in children (26). The randomized clinical trial included 30 pediatric patients aged 6-14 years (26). The results showed faster ulcer size reduction and shorter healing time in the LLLT group, with a significant difference observed on days 5 and 7 of treatment, followed by the lidocaine and chlorhexidine groups (26). The lowest visual analog scale (VAS) pain score was recorded in the LLLT group immediately, and at days 2, 5, and 7 (26). Also, the highest parental satisfaction was observed in the laser therapy group, and no significant adverse effects were recorded (26). In contrast, lidocaine gel mainly provided temporary pain relief without significantly accelerating the healing process (26). These findings suggest that LLLT therapy may be an effective non-pharmacological option for managing traumatic oral ulcers, particularly in pediatric patients where systemic medication may not be desirable.

V. Ramezani et al. (2022) examined the effectiveness of curcumin in reducing oral mucositis severity in patients with head and neck cancer undergoing radiotherapy (28). In this randomized clinical trial, 37 patients were divided into three groups: curcumin mouthwash, Sinacurcumin soft gel, and placebo mouthwash (28). Curcumin's mechanism of action consists of increasing noradrenaline levels in the frontal lobe and hippocampus of the brain, which results in a reduction of pain (28). Also, curcumin can affect opioid receptors, having effects on pain and relief of superficial pain (28). Moreover, curcumin has been shown to inhibit chemical mediators of inflammation, such as cyclooxygenase 2 (COX-2), thereby reducing prostaglandin synthesis (which mediates inflammation and fever) and attenuating the inflammatory process (28). The results demonstrated that both curcumin-treated groups significantly reduced mucositis severity and the associated burning pain during the first 3 weeks compared with the placebo group (28). The VAS pain scores were lower in the curcumin groups (28). At the end of the study, more than 33% of patients using curcumin mouthwash and 15% of patients using Sinacurcumin soft gel remained ulcer-free, whereas all patients in the placebo group developed oral mucositis (28). No adverse effects were reported using curcumin; even at high doses, it is not toxic (28). These findings highlight the potential role of natural anti-inflammatory compounds, such as

curcumin, in the management of ulcerative oral conditions, particularly those associated with cancer therapy.

M. Khalil et al. (2025) evaluated the preventive and therapeutic effects of photobiomodulation using diode lasers for oral mucositis in patients undergoing chemotherapy (27). In this randomized clinical trial involving 45 patients, participants were divided into three groups receiving: oral care alone (group 1), oral care with a 650nm (intraoral) diode laser (group 2), or oral care with combined 650nm (intraoral) and 980nm (extraoral) diode laser treatment (group 3) (27). Photobiomodulation is a laser light therapy, and it was performed before receiving the first chemotherapy treatment (27). The results showed that after one week, most patients (73.3% in group 2 and 80% in group 3) receiving photobiomodulation did not develop oral mucositis, whereas 100% of patients receiving oral care alone did (27). After two weeks, most of the laser group's patients (80% in group 2 and 86,7% in group 3) remained mucositis-free, while 93,3% of the control group developed it (27). Patients receiving photobiomodulation experienced significantly lower mucositis severity (absence of ulcerative mucositis), improved quality of life, and reduced xerostomia symptoms compared with the control group (27). No side effects from the diode laser treatment were reported (27). These findings suggest that photobiomodulation therapy may represent a promising supportive treatment for managing oral ulcerative conditions associated with cancer therapy.

4.3 Effectiveness of systemic treatment

Systemic therapies are generally reserved for severe, recurrent, or refractory cases of oral ulceration that do not respond adequately to topical treatment. These therapies typically act by modulating the immune response or reducing systemic inflammation.

One systemic approach was evaluated by Y. Deng et al. (2022), who investigated the efficacy of thalidomide as a maintenance therapy for recurrent aphthous stomatitis in 125 patients (30). Thalidomide is an immunomodulatory drug that suppresses the exaggerated immune response responsible for tissue destruction in severe inflammatory ulcers, such as major RAS or Behçet-type lesions. In this randomized clinical trial, participants initially received short-term prednisolone to control active ulcers before being assigned to low-dose (25mg/day) or high-dose (50mg/day) thalidomide therapy (30). Clinical findings showed that both regimens were similarly effective in reducing ulcer numbers, incidence, and pain intensity after four and eight weeks of treatment (30). The authors reported that the lower dose demonstrated a better safety profile, with fewer adverse effect events, while maintaining comparable clinical effectiveness

and being more suitable as a maintenance approach for RAS (30). Furthermore, the 25mg/day regimen was associated with a longer ulcer-free recurrence interval (30). However, when the drug was discontinued for 4 weeks, lesions reappeared, suggesting that the therapeutic effect of thalidomide is mainly suppressive rather than curative, and it also indicates that continuous low-dose therapy may be necessary to maintain remission (30). Despite its efficacy, thalidomide use remains limited due to its potentially serious side effects, particularly at higher doses (30). These include teratogenicity, thromboembolic events, and peripheral neuropathy, which require strict monitoring and careful patient selection (30). For this reason, it can be considered as a last-line treatment reserved for severe or refractory cases of RAS but may be excessive for simple aphthous ulcers.

Similarly, systemic immunomodulation was evaluated in the multicentre randomized clinical trial conducted by G. Hatemi et al. (2021), which investigated the efficacy of apremilast for Behçet syndrome ulcer-related (32). Apremilast is an oral medication that inhibits the enzyme phosphodiesterase-4 (PDE-4) (32). Inhibiting this enzyme increases the level of a molecule called cAMP inside cells, which helps regulate inflammation (32). As a result, it decreases the production of inflammatory substances and promotes anti-inflammatory effects in the body (32). This international study included 207 adult patients and demonstrated that oral apremilast significantly reduced ulcer count, pain intensity, and disease activity, and improved patients' quality of life by week 12 (32). These benefits persisted during the extension phase up to 64 weeks, indicating sustained therapeutic efficacy (32).
Nevertheless, consistent with the findings of Y. Deng et al., ulcer recurrence was observed after cessation of treatment (30,32). These results suggest that systemic treatments may provide effective disease control but may not eliminate the underlying predisposition to ulcer recurrence. Also, the most common side effects observed were diarrhea, nausea, headache, and upper respiratory infection; however, apremilast was well tolerated in the long-term treatment of oral ulcers in Behçet syndrome (32).

Taken together, these findings support the use of systemic therapies in patients with severe or systemic disease manifestations. However, their use may be limited by potential adverse effects and the need for long-term administration (30). Drugs such as thalidomide, due to their significant risks stated above, necessitate strict monitoring of the patients.

4.4 Comparison between topical and systemic approaches

When comparing topical and systemic treatments, several important observations emerge across the included studies. Topical therapies demonstrated strong effectiveness in reducing pain and accelerating ulcer healing. Studies such as T. Molania et al. (2023), C. Haishan et al. (2024), Z. Rezvani et al. (2024), and D. Ofluoglu et al. (2017) showed that locally applied treatments, including atorvastatin tablets, growth factor formulations, protective gels, and triester glycerol oxide gel, significantly improved clinical outcomes without systemic side effects (29,31,33,34).

Similarly, S. Alsahaf et al. (2023) reported that topical betamethasone mouthwash significantly reduced the ulcer severity score when compared with a systemic therapy, indicating that topical anti-inflammatory agents can effectively control disease symptoms (35). This study investigated the effectiveness of topical betamethasone mouthwash compared with systemic colchicine (an anti-inflammatory) therapy in patients with recurrent oral ulcers (35). In this randomized clinical trial conducted in the United Kingdom, involving 106 patients, three treatment groups were evaluated: betamethasone mouthwash, colchicine tablets, and a combination of both treatments (35). Betamethasone, being a corticosteroid, suppresses inflammation, while colchicine, despite also treating inflammation, is also an immunosuppressor (35). The results demonstrated that the three treatments reduced the ulcer severity score (USS) by 30% in the first three months and by 50% after twelve months, indicating similar efficacy (35). The major improvements were observed by 3-6 months, with little additional benefit after 9 months (35). However, the largest reduction in USS after 12 months of treatment was achieved by the betamethasone group, suggesting it is the most effective regimen (35). Although colchicine also showed beneficial effects, the combined therapy did not demonstrate superior results compared with topical steroid therapy alone (35). In total, 86% of participants improved clinically by the end of the study, and betamethasone alone showed the best overall results (35). These findings indicate that topical corticosteroids may provide considerable symptom relief without the need for systemic medication in many cases. Also, some participants reported adverse effects like gastric pain, neuropathy, and alopecia, occurring only with colchicine (35). This study supports the use of topical anti-inflammatory therapy as an effective first-line approach for recurrent aphthous stomatitis.

Other studies explored non-pharmacological or natural treatment options. M. El Mansy et al. (2026) demonstrated that low-level laser therapy accelerated healing and reduced pain in traumatic oral ulcers, particularly in pediatric patients (26). Likewise, V. Ramazani et al. (2022)

showed that curcumin mouthwash reduced the severity of mucositis and burning pain in patients undergoing radiotherapy (28). Similarly, M. Khalil et al. (2025) showed that photobiomodulation decreased mucositis severity in patients undergoing chemotherapy, prevented oral mucositis and xerostomia, and improved patients' quality of life (27).

In contrast, systemic treatments such as those evaluated by Y. Deng et al. (2022) and G. Hatemi et al. (2021) were primarily used for severe or systemic forms of disease (30,32). While these medications significantly reduced ulcer recurrence and disease activity, their effects often diminished after treatment discontinuation.

Overall, the comparison suggests that topical therapies provide effective symptom control with fewer adverse effects, whereas systemic treatments may be necessary for more severe or systemic conditions.

4.5 Limitations of the included studies

Despite the valuable information provided by the included studies, several limitations should be considered when interpreting the findings.

First, there was considerable heterogeneity among the studies in patient populations, ulcer types, treatment protocols, and outcome measures. Some studies focused on recurrent aphthous stomatitis, while others investigated traumatic ulcers, treatment-related mucositis, or Behçet-syndrome related oral ulcers. This variability makes direct comparison between treatments more difficult.

Second, sample sizes varied significantly across the studies. Some trials included relatively small numbers of participants, such as the study by El Mansy et al. (2026), which may limit the generalizability of the results (26).

Third, the duration of follow-up differed between studies. While some trials evaluated short-term healing outcomes, others assessed longer-term recurrence rates. More long-term studies are needed to determine whether these treatments provide lasting benefits.

Also, in the study by V. Ramezani et al. (2022), only a limited number of screened patients completed the study because of the COVID-19 pandemic (28). Other factors not taken into account in this study included the radiation site and dose, which are important determinants of the severity of oral mucositis (28).

Finally, differences in treatment method, including pharmacological agents, herbal compounds, and laser therapies, make it challenging to determine which intervention is better than another.

Future research should aim to conduct larger randomized controlled trials with standardized outcome measures to allow more accurate comparisons between treatments.

4.6 Implications for clinical practice

The findings from the reviewed studies have several important implications for clinical practice. First, topical therapies remain the most appropriate first-line treatment for most chronic oral ulcer cases. Treatments such as corticosteroids, mouthwashes, protective pastes, growth factor formulations, and statin-based topical tablets have shown significant effectiveness in reducing pain and promoting healing.

In addition, newer treatment approaches such as low-level laser therapy and photobiomodulation appear promising for improving healing and reducing inflammation, particularly in patients with therapy-induced mucositis. These non-invasive approaches may be especially useful for pediatric patients or individuals who cannot tolerate systemic medications.

Natural compounds such as curcumin also represent potential alternative therapies due to their anti-inflammatory and antioxidant properties. Their low risk of side effects makes them interesting options for complementary treatment in patients undergoing cancer therapy.

Systemic therapies should be reserved for severe, persistent, or systemic forms of ulcerative disease, such as those associated with Behçet syndrome. In these cases, medications like thalidomide or apremilast may provide effective long-term disease control, although careful monitoring is required.

Discussion with the doctor or dentist is important for raising patients' awareness of the side effects of each treatment.

Overall, clinicians should adopt a personalized treatment strategy that considers the severity of the ulcers, the underlying cause, and the patient's overall health.

6. CONCLUSIONS

1. Systemic treatments such as thalidomide and apremilast showed strong efficacy in reducing ulcer frequency and disease activity, particularly in severe and systemic conditions such as Behçet syndrome. However, their use is often limited by potential adverse effects, the need for careful monitoring, and symptom recurrence after treatment discontinuation.

2. In contrast, topical treatments demonstrated consistent effectiveness in managing local symptoms, particularly pain and ulcer healing, while presenting a more favorable safety profile.

3. Conventional therapies such as topical corticosteroids remain widely used, but several innovative approaches, including atorvastatin mucoadhesive tablets, growth-factor-based formulations, curcumin, and protective pastes, have shown promising results.

4. Additionally, non-pharmacological therapies such as low-level laser therapy and photobiomodulation have emerged as effective alternatives, particularly in specific populations such as pediatric or oncologic patients.

5. Overall, the evidence suggests that topical treatments should be considered the first-line approach for most cases of chronic oral ulcers due to their efficacy, safety, and ease of use. Systemic therapies should be reserved for severe, recurrent, or treatment-resistant cases, or when ulcers are associated with systemic diseases.

6. The management of chronic oral ulcers also involves avoiding foods and drinks that are irritating or triggering, such as spicy, salty, acidic, and hot items; alcohol; carbonated beverages; hard or crunchy foods; and toothpaste containing sodium lauryl sulfate (SLS), which can aggravate the tissues. Integrating natural therapies and proper oral care may offer a sustainable approach to minimizing ulcer recurrence.

7. Despite these findings, several limitations were identified, including heterogeneity among studies, variability in sample sizes, and differences in outcome measures and follow-up durations. These factors highlight the need for further large-scale, well-

designed randomized controlled trials directly comparing topical and systemic treatments using standardized evaluation criteria.

8. In conclusion, the management of chronic oral ulcers should be individualized, considering disease severity, underlying etiology, and patient-specific factors. Advances in topical therapies and emerging treatment modalities offer promising perspectives for improving patient outcomes while minimizing systemic risks.

7. SUSTAINABILITY

Sustainability means creating long-term, effective, and responsible ways to manage health problems, in our case, chronic oral cancer, while considering three dimensions: social, economic, and environmental. The goal is to improve patients' health now, without creating bigger problems or higher costs in the future.

A sustainable approach to chronic oral cancer should focus on prevention, early detection, and responsible clinical practice that benefits patients, the healthcare system, and the environment. From a social perspective, awareness of risk factors such as tobacco, alcohol consumption, HPV and HIV infection, tuberculosis, syphilis, and poor oral hygiene should be increased. Early detection can help reduce the occurrence of disease. Routine oral check-ups and screenings should be included in every dental service, particularly for vulnerable groups such as the elderly or populations with limited access to healthcare. Additionally, education about oral hygiene, diet, and lifestyle can help prevent disease and minimize complications.

From an economic perspective, investments should be made in preventive education, early diagnosis technologies, and minimally invasive treatments to help reduce the high cost of cancer treatment.

From an environmental perspective, adopting digital workflows, reducing single-use materials, and choosing eco-friendly materials or products minimizes waste generated by cancer diagnosis and treatment. Also, encouraging an anti-inflammatory, antioxidant-rich diet will improve systemic health and, therefore, environmental sustainability. A holistic and sustainable approach improves patient health, supports early diagnosis, and reduces long-term social, financial, and environmental burdens associated with managing chronic oral cancer.

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9. ANNEXES