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Review Article

Herbal Therapeutics for Oral Mucosal Ulcerations: From Phytoconstituents to Buccal and Mucoadhesive Drug Delivery System

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ABSTRACT

Oral ulcers, most frequently recurrent aphthous stomatitis (RAS), are painful inflammatory lesions of the oral mucosa. The exact etiology and pathogenesis are not fully understood; local trauma, microbial factors, immune responses, nutritional deficiencies and systemic diseases are considered to be involved. Conventional management relies on topical corticosteroids, analgesics, antiseptics and other symptomatic therapies, but prolonged use and recurrences have generated interest in herbal alternatives. Several medicinal plants and natural products, including *Jasminum grandiflorum*, *Psidium guajava*, *Matricaria chamomilla*, *Centella asiatica*, *Calendula officinalis*, *Phyllanthus emblica*, clove, myrrh, *Myrtus communis*, pomegranate and *Tridax procumbens*, have shown beneficial effects in experimental or clinical studies. These agents have been reported to reduce ulcer size and pain, promote wound closure, exert antimicrobial activity and modulate inflammatory pathways. More recently, research has focused on mucoadhesive buccal delivery systems such as patches, films, gels and other retentive formulations. Such systems can prolong contact with the ulcerated mucosa, provide controlled drug release, improve local therapeutic efficacy and improve patient compliance. However, further formulation studies, safety evaluation, animal studies and well-designed clinical trials are required to establish their potential as advanced therapies for oral ulcers.

INTRODUCTION

Mouth ulcers, also referred to as oral or mucosal ulcers, are localized lesions that develop on the mucous membrane of the oral cavity. They may appear as single or multiple sores and are commonly characterized by a red, yellowish, or whitish appearance. Depending on their location and severity, these lesions can cause considerable discomfort, particularly during eating, drinking, speaking, or brushing the teeth. Mouth ulcers may develop at different sites within the oral cavity, including the gums, tongue, palate, inner surface of the cheeks, and inner lips.[1]

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Oral ulcers are among the common problems affecting the mouth and may occur due to a variety of factors. In many cases, they are temporary and do not indicate a serious underlying disorder. However, their development has been associated with several nutritional, physiological, infectious, and environmental factors. Nutritional deficiencies, particularly deficiencies of iron and vitamins such as vitamin B12 and vitamin C, may contribute to ulcer formation. Other possible contributing factors include inadequate oral hygiene, infections, psychological stress, indigestion, accidental or mechanical trauma, food sensitivity, hormonal changes, and certain skin or systemic disorders (Table 1). The pain and irritation associated with these lesions can interfere with normal daily activities and may affect the quality of life of affected individuals.[1]

Among the different types of oral ulcers, recurrent aphthous stomatitis (RAS) is one of the most frequently encountered conditions involving the oral mucosa. It is estimated to affect approximately 20% of the general population, although its prevalence may vary among different populations and age groups.[2-4] RAS is characterized by the repeated development of painful, well-defined ulcers within the oral cavity. The lesions may recur over an extended period, with some individuals experiencing episodes for several years.[4]

The development of RAS is associated with a complex immune-mediated inflammatory process. One of the important mechanisms involves a T-cell-mediated immune response within the oral mucosa. During this response, inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) are released and contribute to local tissue inflammation. Increased inflammatory activity can subsequently promote the activation of cytotoxic CD8+ T cells, which may contribute to damage and destruction of the oral epithelial cells.[5] Despite considerable research into the mechanisms involved in RAS, its exact etiology has not yet been completely established. A combination of genetic, immunological, nutritional, hormonal, psychological, and local factors has been suggested to influence the onset and recurrence of the condition.[3]

Because recurrent oral ulcers can cause repeated pain and interfere with eating and other routine activities, effective and convenient local treatment approaches remain important. This has encouraged interest in therapeutic approaches that can provide prolonged contact with the affected oral mucosa and potentially improve local healing and symptom relief.

Table 1: Causes of Oral Ulcers

Sr. No.	Causes
1	Genetic predisposition
2	Hormonal imbalance
3	Infectious agents
4	Smoking cessation
5	Trauma
6	Allergies
7	Hematological deficiencies
8	Immunological factors
9	Nutritional deficiencies
10	Physical or mental stress

There are three clinical variants of RAS, distinguished by the size, number, and duration of the lesions.

Minor aphthous ulcers are the most common form, typically presenting with one to five lesions, each 3-10 mm in size, round or oval, with a gray/yellow base and erythematous edges. They often affect non-keratinized mucosa, cause significant pain, and usually heal within 7-10 days (Fig. 1).[3,4] ***Major aphthous ulcers*** are larger (1-3 cm), deeper, and take longer to heal (2-6 weeks). They commonly affect the labial mucosa, soft palate, and tonsillar surfaces, account for 10% of RAS cases, and may leave scars (Fig. 2).[3,4] ***Herpetiform ulcers*** involve a much higher number of smaller lesions (1-3 mm), with up to 100 ulcers at once that can merge into larger lesions. They primarily affect non-keratinized,

non-adherent mucosal surfaces and typically heal within 7-10 days (Fig. 3).[3,4]



Fig. 1: Minor aphthous ulcer[1]



Fig. 2: Major aphthous ulcer[1]



Fig. 3: Herpetiform ulcer[1]

CONVENTIONAL MANAGEMENT OF RAS

The main objectives in managing RAS are to relieve pain, promote faster healing, and reduce the frequency of recurrence.[6] Both topical and systemic therapies are available; however, treatment selection can be difficult because the exact cause is often unknown or multifactorial, and evidence supporting many treatments is limited.[6,7] Some marketed treatments may cause adverse effects such as irritation, allergic reactions, staining of the teeth or tongue, dry mouth, unpleasant taste, and altered taste sensation.[1] Management should begin with identifying and avoiding triggers such as spicy, acidic, salty, hard or abrasive foods, carbonated or alcoholic drinks, and oral-care products containing sodium lauryl sulfate (SLS), together with correction of nutritional deficiencies and stress reduction.[8]

Topical treatment. Topical therapy is generally preferred as the first approach because the medication acts directly at the ulcer site while limiting systemic exposure. Chlorhexidine (0.2%) or triclosan may be used as mouth rinses or gels, and preparations containing diclofenac and hyaluronic acid may reduce pain and improve healing in minor RAS.[9,10] Amlexanox 5% has anti-inflammatory and immunomodulatory properties and has been reported to reduce pain, redness, ulcer size and healing time.[11,12] Tetracycline, doxycycline and minocycline have been used for their antimicrobial activity and their inhibition of metalloproteinases and collagenases.[13] Topical corticosteroids such as triamcinolone acetonide, fluocinolone acetonide and clobetasol propionate are commonly used to control inflammation, reduce pain and promote healing.[14] Topical 1% lidocaine provides temporary symptomatic relief,[15] and hyaluronic acid forms a protective layer over the ulcer and supports tissue repair.[16]

Systemic treatment. Systemic therapy may be considered when topical treatment is insufficient or when ulcers are severe, recurrent or numerous. Levamisole has been investigated as an immunomodulatory agent, with earlier studies reporting fewer ulcers and improved symptoms.[7,17,18] Systemic corticosteroids such as prednisolone may be used for severe or persistent cases but should be limited because of adverse effects.[7,19] Correction of deficiencies with vitamin B12, iron and zinc may be beneficial, and vitamin B12 supplementation has been reported to improve ulcer frequency, duration and pain.[20]

Limitations of existing approaches. Topical corticosteroids may produce local side effects and do not always prevent recurrence; anaesthetics mainly give short-term pain relief without improving healing; and prolonged antibiotic use may disturb the normal oral flora. Systemic corticosteroids and immunomodulators can be effective, but their systemic adverse effects make prolonged use less suitable, particularly for children and pregnant women. In addition, conventional mouthwashes, powders and gels are poorly retained at the ulcer site because saliva, swallowing and oral movements quickly remove them. Treatments that remain at the affected site for longer while providing safe and sustained action are therefore needed.[21]

HERBAL THERAPEUTICS FOR RAS

In recent years, medicinal plants and natural products have received increasing attention for the management of oral ulcers, including RAS. This interest is mainly associated with the wide range of biological activities shown by plant-derived compounds. Many herbal constituents have demonstrated anti-inflammatory, antioxidant, antimicrobial, analgesic, and wound-healing properties, which may help in reducing pain and

inflammation and supporting the natural healing of ulcers. Several natural agents, including licorice, aloe vera, curcumin, quercetin, and astragalus, have been investigated for their possible benefits in RAS management.[21,22]

Despite these promising findings, herbal therapy still faces certain challenges. Differences in plant composition, variation in active constituents, appropriate dose selection, stability, and lack of adequate clinical studies can affect the consistency and reliability of herbal preparations. An additional advantage of herbal therapy is the possibility of combining plant-derived compounds with suitable local drug-delivery systems. Buccal and mucoadhesive formulations can help keep the herbal preparation in contact with the affected mucosa for a longer duration, which may improve local action and reduce the rapid removal caused by saliva. Thus, incorporating herbal agents into such delivery systems may offer a promising direction for developing safer and more effective approaches for the management of RAS.[21] The medicinal plants considered in this review are listed in Table 2 along with their photographs.

Table 2: Medicinal Plants Used in Oral Ulcerations

Sr. No.	Plant	Family	Part used	Phytoconstituents	Relevant pharmacological activity
1	*Jasminum grandiflorum*[23,24] 	Oleaceae	Leaves, flowers	Ursolic acid, oleacein, oleoside dimethyl ester	Anti-inflammatory, antiulcer, antioxidant[23]
2	*Psidium guajava*[24] 	Myrtaceae	Leaves	Essential oil, flavonoids, carotenoids, polyphenolic substances, pentacyclic triterpenoids, esters, aldehydes	Antioxidant, antimicrobial, anti-inflammatory
3	*Calendula officinalis*[25] 	Asteraceae	Leaves, flowers	Flavonoids, triterpenoids, carotenoids, essential oils, saponins, phenolic compounds	Anti-inflammatory, antioxidant, antimicrobial, wound-healing
4	*Centella asiatica*[26,27] 	Apiaceae	Whole plant / aerial parts	Asiaticoside, madecassoside, asiatic acid, madecassic acid	Wound healing, anti-inflammatory, antioxidant, antimicrobial

Sr. No.	Plant	Family	Part used	Phytoconstituents	Relevant pharmacological activity
5	*Matricaria chamomilla*[28,29] 	Asteraceae	Flowers / flower heads	α-Bisabolol, bisabolol oxides A and B, bisabolone oxide A, chamazulene, β-farnesene	Anti-inflammatory, antioxidant, antibacterial, antifungal, analgesic, antipyretic, anti-allergic; traditionally used for mouth diseases and canker sores
6	*Phyllanthus emblica*[30] 	Phyllanthaceae	Fruit	Vitamin C (ascorbic acid), tannins, gallic acid, ellagic acid, flavonoids, emblicanin A and B, chebulagic acid	Antioxidant, anti-inflammatory, antimicrobial, analgesic, immunomodulatory, wound-healing
7	*Syzygium aromaticum*[31,32] 	Myrtaceae	Dried flower buds	Eugenol, eugenyl acetate, β-caryophyllene, α-humulene	Antioxidant, antimicrobial, anti-inflammatory, analgesic, antifungal, antiseptic, wound-healing
8	*Commiphora myrrha*[33,34] 	Burseraceae	Oleo-gum resin	Sesquiterpenes, monoterpenes, diterpenes, triterpenes and steroids	Anti-inflammatory, antimicrobial, antioxidant, analgesic, antiseptic, wound-healing; traditionally used for mouth ulcers, gingivitis, oral mucosal irritation and toothache
9	*Myrtus communis*[35,36] 	Myrtaceae	Leaves	Essential oils, alkaloids, flavonoids, phenolics, coumarins, saponosides, tannins, quinones	Analgesic, anti-inflammatory, antiseptic and wound-healing effects
10	*Punica granatum*[37-39]	Lythraceae	Fruit / peel and flowers	Polyphenolics, flavonoids, anthocyanosides, alkaloids, lignans and triterpenes	Anti-inflammatory, antioxidant, antimicrobial and wound-healing
11	*Tridax procumbens*[40]	Asteraceae	Leaves, aerial parts, flowers and whole plant	Flavonoids, terpenoids, essential oils, saponins	Antimicrobial, antioxidant, anti-inflammatory and wound-healing

Phytoconstituents and Potential Mechanisms Relevant to Oral Ulcers

Medicinal plants contain a variety of phytoconstituents that may contribute to the management of oral ulcers. Their possible therapeutic effects can be broadly related to anti-inflammatory, antioxidant, antimicrobial, analgesic, and wound-healing activities. These actions may work together to support recovery of the damaged oral mucosa.[23-40]

Anti-inflammatory activity. Plant-derived compounds may help reduce excessive inflammation at the ulcer site, which can consequently decrease swelling, irritation, and pain.

Antioxidant activity. Antioxidant constituents may help neutralize reactive oxygen species and reduce oxidative stress, thereby creating a more favorable environment for tissue repair.

Antimicrobial activity. Certain phytoconstituents possess antimicrobial properties and may help control microorganisms that can contribute to or complicate oral lesions.

Analgesic activity. Some herbal constituents may provide pain-relieving effects and help reduce the discomfort associated with oral ulcers.

Wound-healing activity. Herbal compounds may support tissue repair by influencing processes such as cell migration, collagen formation, and regeneration of damaged mucosal tissue.[23-40]

Conceptual pathway: Medicinal plant → Phytoconstituents → Biological activity → Reduced inflammation, oxidative stress and microbial burden + enhanced tissue repair → Possible improvement in ulcer symptoms and healing.

It is important to note that the presence of a particular phytoconstituent or demonstration of a pharmacological activity does not necessarily confirm clinical effectiveness against RAS. The activity of a plant preparation may vary depending on the plant species, plant part used, extraction procedure, concentration, and formulation. Therefore, proper standardization of herbal materials is important for obtaining consistent results and for their further development into formulations.[23-40]

FROM PHYTOCONSTITUENTS TO BUCCAL AND MUCOADHESIVE DRUG DELIVERY

Although a plant extract may possess useful biological properties, conventional preparations may not remain in contact with the ulcerated area for an adequate period, because saliva, swallowing, and movement of the cheeks and tongue quickly remove them. Mucoadhesive systems are designed to overcome this problem by increasing the residence time of the formulation on the mucosal surface.[41-43] For oral-ulcer management, prolonged contact may allow a standardized herbal extract or selected phytoconstituent to remain at the affected site for longer and, depending on the design, to be released in a controlled manner, reducing the need for frequent application. The major advantage is thus improved local retention and prolonged exposure rather than increased systemic absorption.[41-43]

Rationale: Herbal extract → Standardization of phytoconstituents → Suitable dosage form → Mucoadhesion → Increased residence time → Controlled/local release → Prolonged opportunity for local therapeutic action.

Buccal and Mucoadhesive Drug Delivery Systems

Buccal drug delivery involves administering a drug through the buccal mucosa, the inner lining of the cheek, which is easily accessible and can be used for local or systemic delivery. In systemic therapy, it may reduce exposure to gastrointestinal degradation and hepatic first-pass metabolism. For oral ulcers, the formulation can be placed close to the affected area, and mucoadhesive systems attach to the mucosa to prolong residence time and provide sustained or controlled release.[43] The main reasons for developing such systems are controlled and localized drug release, protection of susceptible drugs from degradation, prolonged effect and improved contact with the absorbing mucosa.[44] Their advantages include easy administration and termination of therapy, extended release, avoidance of first-pass metabolism and gastric instability, and flexibility in dosage-form design.[45] Their limitations include unsuitability for drugs that are unstable, bitter, strongly odorous or irritating, suitability only for relatively small doses, and loss of adhesion due to eating, drinking and continuous saliva flow.[46]

Three sites of delivery are recognized in the oral cavity: sublingual (ventral surface of the tongue and floor of the mouth), buccal (lining of the cheek) and local delivery for oral conditions such as ulcers, fungal infections and periodontal disease. These sites differ greatly in anatomy, permeability and ability to retain a delivery system.[47,48]

Structure of the Buccal Mucosa

The buccal mucosa is composed of the oral epithelium, the lamina propria and the submucosa (Fig. 4). The *oral epithelium* is the first line of protection against mechanical, chemical and microbial challenges and is made up mainly of keratinocytes in a stratified squamous arrangement. It may be keratinized (stratum basale, spinosum, granulosum and corneum) or non-keratinized, in which the granular and corneal layers are not clearly developed.[49] The *lamina propria* is the connective tissue layer beneath the epithelium, containing blood vessels, nerves, fibroblasts, macrophages, mast cells, and collagen and elastic fibres, with a superficial papillary and a deeper reticular layer.[49] The *submucosa* connects the mucosa to the underlying tissues and may contain adipose tissue, minor salivary glands, lymphoid tissue and muscle; it is absent in areas such as the attached gingiva and hard palate, where a mucoperiosteum is formed.[49]

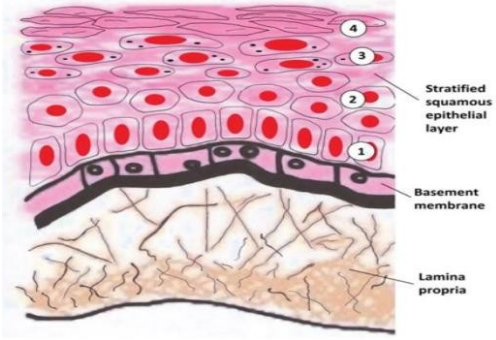


Fig. 4: Buccal mucosa structure[50]

Mucus is a translucent, viscous secretion forming a continuous layer, reported to be about 50 to 450 µm thick in humans, over the epithelium.[51] It consists mainly of water, mucins, lipids, mineral salts and proteins, and mucins interact with polymers of mucoadhesive systems to form the adhesive interface.[51,52] Drugs cross the buccal epithelium by the transcellular and paracellular pathways, with transport considered to occur predominantly by the paracellular route through lipid-containing intercellular regions.[53]

Mucoadhesion

Mucoadhesion is generally described in two stages (Fig. 5).[54] In the *contact stage*, the formulation contacts the mucosal surface and spreads and swells in the presence of moisture, increasing contact with the mucus layer. In the *consolidation stage*, moisture hydrates the mucoadhesive material, increasing polymer mobility so that chains can interact with mucus; hydrogen bonding and van der Waals forces strengthen adhesion. Although the complete mechanism is not fully established, it is explained as a sequence of wetting and swelling of the polymer, interpenetration of polymer and mucus chains, and formation of interfacial bonds.[55]

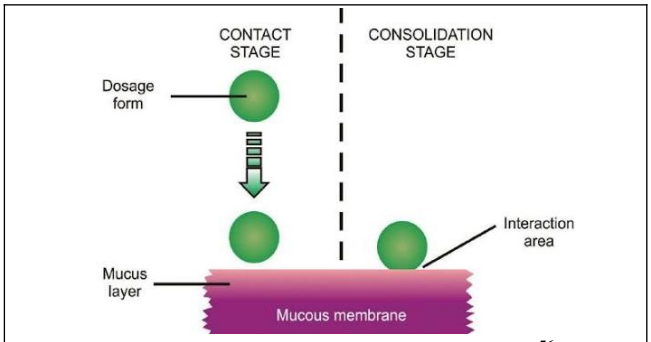


Fig. 5: Steps involved in mucoadhesion[56]

Buccal Dosage Forms

Buccal dosage forms can be matrix-type, in which drug and polymer form a single matrix that may release drug in one or more directions, or reservoir-type, in which the drug is held in a separate compartment with an impermeable backing layer that directs release towards the mucosa and reduces loss into the oral cavity.[57] ***Solid forms*** include buccal tablets, usually prepared by direct compression for local or systemic use;[58] bioadhesive micro- and nanoparticles, which provide a large surface area for close contact with mucus and can be given as suspensions or in pastes and ointments;[59,60] bioadhesive wafers, multilayer systems investigated mainly for periodontal delivery;[61] and bioadhesive lozenges, which dissolve gradually to prolong contact and can deliver antimicrobials, corticosteroids, anaesthetics and antifungals.[62] ***Semi-solid forms*** include adhesive gels, for example cross-linked polyacrylic acid polymers, which spread over the mucosa and support

sustained release,[63] and buccal patches/films, thin flexible systems with a backing layer, a drug layer and a mucoadhesive surface that direct release towards the mucosa.[64] ***Liquid forms*** include viscous liquids that act as protective coatings or vehicles; an example is Oralin, an aerosol-based system for buccal insulin delivery.[65]

MARKETED HERBAL FORMULATIONS FOR ORAL ULCERS

HiOra-SG Gel (Himalaya Wellness Company; oral gel) contains jasmine (*Jasminum grandiflorum*), licorice (*Glycyrrhiza glabra*), Triphala and spreading hogweed (*Boerhavia diffusa*), and is indicated for mouth ulcers.[66] **Tuliq Gel** (Aushadhi Wellness Pvt. Ltd., Rajkot, Gujarat, India; 15 g tube) contains liquid extracts of khadir (*Acacia catechu*) 4.50%, dadi fruit (*Punica granatum*) 4.50%, yashtimadhu root (*Glycyrrhiza glabra*) 3.00%, haldi rhizome (*Curcuma longa*) 3.00% and amalaki fruit (*Emblica officinalis*) 1.50%, with menthol (*Mentha* species) 0.25% and clove flower bud oil (*Syzygium aromaticum*) 0.10%, and is marketed for mouth ulcers and associated pain, swelling, itching and burning.[67] **OroBen Oral Gel** (Aboca S.p.A., Italy) contains Resinox FP, a plant-based complex of polysaccharides from *Aloe vera* and marshmallow, flavonoids from chamomile (*Matricaria chamomilla*) and resins from myrrh (*Commiphora myrrha*), along with liquorice extract, sodium alginate, peppermint oil and other excipients, and is marketed for mouth ulcers, RAS and inflamed gums.[68] **Mora-X Mouth Ulcer Gel** (Wheezal Homoeo Pharma, Dehradun, India; 12 g) contains *Calendula officinalis*, *Hamamelis virginiana*, *Plantago major* and *Foeniculum vulgare*, and is marketed for mouth ulcers and oral discomfort.[69] **Kin Care Mouth Gel** (Laboratorios KIN S.A.; 15 mL) contains hyaluronic acid (0.2%), *Aloe vera* and *Centella asiatica*, and is marketed for the care of irritated or damaged oral tissues.[70]



Fig. 6: HiOra-SG Gel



Fig. 7: Tuliq Gel



Fig. 8: OroBen Oral Gel



Fig. 9: Mora-X Mouth Ulcer Gel



Fig. 10: Kin Care Mouth Gel[71]

RECENT STUDIES

Randomized, double-blind, placebo-controlled trials have evaluated mucoadhesive patches containing cinnamaldehyde (Molania et al., 2022),[72] mucoadhesive tablets containing caffeic acid in 47 patients (Salehi et al., 2024)[73] and atorvastatin tablets in 44 patients (Molania et al., 2023)[74] in minor RAS, generally reporting reduced pain and lesion size, although ulcer-size differences were not consistently significant with caffeic acid. A randomized trial of 204 participants found a greater reduction in ulcer size with a *Psidium guajava* herbal gel than with no treatment (Mansoor et al., 2025).[75] Formulation studies include bilayer mucoadhesive films releasing triamcinolone acetonide (Alhallak et al., 2023),[76] 3D-printed buccal patches giving unidirectional release of dexamethasone acetate (Chen et al., 2023),[77] and an *in vitro* study of an amla (*Phyllanthus emblica*) bark and fruit extract patch with promising wound-closure activity (Jairam et al., 2025).[78] A recent review of randomized trials over the past decade also noted promising outcomes but a need for stronger clinical evidence (D'Amario et al., 2025).[79] Most of these studies call for larger clinical trials and long-term safety evaluation.

RESEARCH GAP AND FUTURE PERSPECTIVES

Although several medicinal plants and herbal preparations show potential in oral ulcers and RAS, the

evidence remains heterogeneous. Differences in plant material, extraction methods, formulation, dosage, treatment duration and outcome assessment make comparison difficult, and systematic reviews have identified limitations in design, reporting and risk of bias.[80,81] The specific phytoconstituents responsible for the anti-inflammatory, antioxidant, antimicrobial and wound-healing effects of individual plants also need identification and standardization, and the relationship between composition, mechanism and clinical efficacy requires further study.[27,82] Moreover, the integration of standardized herbal extracts or individual phytoconstituents into optimized mucoadhesive systems specifically for oral ulcers remains comparatively underexplored.

Future research should therefore include well-designed, adequately powered randomized controlled trials; standardization of plant material, extraction methods and phytochemical composition using advanced analytical techniques; and development of mucoadhesive gels, films, patches, tablets and lozenges using polymers such as chitosan, carbomers, HPMC, sodium carboxymethylcellulose and natural gums.[41,42] Nanocarriers such as nanoparticles, nanoemulsions and phytosomes may improve the solubility, stability and local availability of poorly soluble phytoconstituents, but require in-vitro, ex-vivo, in-vivo and clinical evaluation. Dose optimization, toxicity, stability, formulation quality and patient acceptability should also be addressed.[27,41,42,80-82]

CONCLUSION

Herbal therapeutics provide a promising area for investigation in the management of oral mucosal ulcers because selected medicinal plants contain phytoconstituents with reported anti-inflammatory, antioxidant, antimicrobial, analgesic and wound-healing activities. The eleven plants reviewed here represent a range of traditional and experimentally investigated candidates, but the strength of evidence is not uniform across them. The therapeutic potential of these plants should therefore be linked to standardized phytochemical composition and clearly defined mechanisms rather than to their traditional use alone. A major formulation challenge is the short residence time of conventional oral preparations. Buccal and mucoadhesive systems offer a rational strategy for increasing local contact and potentially providing prolonged or controlled release. The overall research direction can be summarized as: medicinal plants → standardized phytoconstituents → demonstrated pharmacological activity → suitable buccal/mucoadhesive formulation → prolonged local contact → preclinical and clinical validation. Further research is required to establish safety, standardization, formulation performance and clinical efficacy before these approaches can be considered established therapies for recurrent oral ulcers.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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