ADVANCES IN HERBAL MOUTH ULCER GELS: DEGLYCYRRHIZINATED LICORICE AS A KEY BIOACTIVE

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Abstract

Mouth ulcers, particularly recurrent aphthous stomatitis, are among the most prevalent oral mucosal disorders affecting individuals of all age groups. These lesions are characterized by pain, inflammation, and delayed healing, significantly impacting quality of life. Conventional management strategies primarily involve topical corticosteroids, antiseptics, and local anesthetics, which provide symptomatic relief but may cause adverse effects upon prolonged use. In response to growing concerns regarding safety and long-term tolerability, herbal-based formulations have emerged as promising alternatives. Among various herbal actives, Deglycyrrhizinated Licorice (DGL), derived from Glycyrrhiza glabra, has gained attention due to its potent anti-ulcer, anti-inflammatory, antioxidant, and mucosal protective properties without the mineralocorticoid side effects associated with glycyrrhizin. This review critically examines recent advances in herbal mouth ulcer gel formulations, emphasizing DGL as a key bioactive ingredient. The paper discusses the pathophysiology of mouth ulcers, the rationale for gel-based delivery systems, pharmacological mechanisms of DGL, formulation considerations, safety aspects, and future research prospects. The review aims to provide a scientific foundation for the development of safe, effective, and steroid-free herbal mouth ulcer gels.

Keywords: Deglycyrrhizinated licorice; DGL; Mouth ulcer gel; Aphthous stomatitis; Herbal formulation; Oral mucosal healing.

1. INTRODUCTION

Oral mucosal health plays a critical role in maintaining overall well-being, yet it is frequently compromised by conditions such as mouth ulcers. Mouth ulcers, also known as aphthous ulcers or aphthous stomatitis, are painful lesions that occur on the non-keratinized mucosal surfaces of the oral cavity. Epidemiological studies suggest that a significant proportion of the global population experiences mouth ulcers at least once in their lifetime, with recurrence being common in susceptible individuals.

The etiology of mouth ulcers is multifactorial and includes local trauma, nutritional deficiencies, stress, immune dysregulation, hormonal changes, and microbial imbalance. Despite extensive research, the precise pathogenesis remains incompletely understood. Conventional treatment modalities focus on reducing pain, inflammation, and secondary infection; however, these approaches are largely symptomatic.

Topical corticosteroids are considered the mainstay of therapy for severe or recurrent ulcers, but their prolonged use may lead to mucosal thinning, opportunistic infections, and altered oral microbiota. Consequently, there is increasing interest in herbal and natural therapeutic agents that offer comparable efficacy with improved safety profiles. Herbal mouth ulcer gels represent a patient-friendly, non-invasive, and localized drug delivery approach. Among herbal bioactives, Deglycyrrhizinated Licorice (DGL) has emerged as a promising candidate due to its well-documented gastroprotective and mucosal healing properties.

2. ORAL ULCERS

Overview

Oral ulcers are common lesions observed within the oral cavity and may arise from various causes, including traumatic, infective, aphthous, drug-induced, ulceration associated with dermatoses, systemic diseases, and malignancy. When ulcers present with typical clinical features, diagnosis may be straightforward. However, in many cases, establishing an exact diagnosis is challenging, and histopathological examination may be required.

Figure 01: Mouth ulcer

Treatment of Drug-Induced Oral Ulceration

Topical corticosteroids are generally ineffective in the treatment of drug-induced oral ulcers. If ulcerations fail to improve after 1–2 weeks of topical steroid therapy and there are no clinical signs suggestive of malignancy, drug exposure should be carefully reviewed. When a medication is suspected as the causative factor, communication with the prescribing physician is essential to discuss possible drug substitution or dose reduction. Following cessation, replacement, or dose reduction of the suspected drug, oral ulcerations typically improve within 1–2 weeks. Confirmation of drug causality ideally requires re-challenge; however, this is often difficult and ethically challenging.

3. CASE PRESENTATIONS

Case 1

A 76-year-old woman presented with ulceration on the left lateral margin of the tongue. Her medical history included rheumatoid arthritis, diabetes mellitus, hypertension, and anemia. She had been receiving indomethacin (75 mg/day) for the management of rheumatoid arthritis–related pain. Clinical examination revealed a solitary ulcer measuring 20 × 14 mm on the left tongue margin, with no induration (Fig. 1). The ulcer surface was flat and clean, without bleeding, and the margins were slightly elevated. Despite clinical suspicion of a benign ulcer, no improvement was observed following topical corticosteroid therapy. Denture-related trauma was excluded. After consultation with her physician, indomethacin was discontinued. Complete re-epithelialization of the lesion was observed within two weeks.

Figure 02: Indomethacin-induced oral ulceration

Case 2

A 71-year-old man presented with ulceration of the floor of the mouth and had a six-year history of rheumatoid arthritis (RA). His medical history also included hypertension, prostatic hyperplasia, and cardiac disease. He had been treated with methotrexate (MTX) at a dose of 8 mg/week. Oral examination revealed an ulcer measuring 22 × 18 mm on the left floor of the mouth, with a flat, clean surface and no induration or bleeding (Fig. 2). The lesion did not respond to topical corticosteroid therapy. Denture irritation was ruled out, and his physician was consulted. Following a reduction of MTX dosage from 8 mg/week to 2 mg/week, the ulcer showed marked improvement, with complete re-epithelialization.

Figure 03: Oral ulceration induced by low-dose methotrexate

Case 3

A 77-year-old woman was referred with a persistent oral ulcer. Her medical history included type 2 diabetes mellitus, and she had been treated with dipeptidyl peptidase-4 (DPP-4) inhibitors for 1.5 years. Clinical examination revealed a single ulcer measuring 10 × 7 mm on the left labial mucosa (Fig. 3). The ulcer surface was flat and clean, with no bleeding or induration, and the margins were slightly raised. The lesion did not improve despite topical corticosteroid therapy, suggesting a possible drug-induced etiology.

Case 4

An 82-year-old woman presented with multiple oral ulcerations. She had been receiving alendronate therapy for osteoporosis for five years. Several irregularly shaped ulcers were observed on the lower lip, soft palate, and upper and lower gingiva (Fig. 4). The lesions were covered with pseudomembrane. Although autoimmune bullous disease was initially suspected, serological investigations were negative. After consultation with her physician, alendronate therapy was discontinued. Complete epithelialization occurred within seven days. Further history revealed that the patient had been sucking the tablets instead of swallowing them, resulting in direct mucosal injury.

Figure 04: Oral ulcerations induced by incorrect administration of alendronate

Case 5

A 77-year-old man presented with multiple painful oral ulcers. His medical history included heart disease and atrial fibrillation, and he was receiving multiple medications. Following a change in medication to nicorandil, he developed multiple oral ulcerations. Clinical examination revealed irregularly shaped ulcers on the bilateral buccal mucosa and lateral margins of the tongue (Fig. 5). The ulcer surfaces were covered with pseudomembrane, and no induration was present. After consultation with his physician, nicorandil was replaced with an alternative medication. The oral lesions resolved within two weeks.

Figure 05: Oral ulcerations associated with nicorandil

Figure 06: Multiple ulcers on bilateral buccal mucosa and tongue margins

Herbal Mouth Ulcer Gels as Drug Delivery Systems

Gel-based formulations are particularly suitable for oral applications due to their ability to adhere to mucosal surfaces and provide sustained release of active ingredients. Herbal mouth ulcer gels offer several advantages, including localized action, reduced systemic exposure, ease of application, and improved patient compliance.

The incorporation of herbal extracts into gels allows for synergistic therapeutic effects, combining anti-inflammatory, analgesic, antimicrobial, and wound-healing activities. Furthermore, herbal gels are generally free from alcohol and harsh chemicals, making them suitable for sensitive oral tissues and long-term use.

Deglycyrrhizinated Licorice (DGL): Source and Characteristics

Licorice (Glycyrrhiza glabra) has been used for centuries in traditional medicine systems for its soothing and healing properties. However, the presence of glycyrrhizin in conventional licorice extracts may lead to adverse effects such as hypertension and electrolyte imbalance when used chronically. Deglycyrrhizinated Licorice (DGL) is produced by selectively removing glycyrrhizin while retaining beneficial flavonoids and chalcones.

DGL retains the therapeutic efficacy of licorice without associated systemic side effects, making it suitable for oral and mucosal applications. It is water-soluble, non-irritating, and exhibits excellent compatibility with common pharmaceutical and cosmetic excipients.

Licorice (Glycyrrhiza glabra) –
Botanical Name: Glycyrrhiza glabra Linn.

Family: Fabaceae (Leguminosae)

Common Names

- Licorice
- Mulethi / Yashtimadhu
- Sweet root

TABLE No.1: Licorice (Glycyrrhiza glabra) – Botanical Profile

Parameter	Details
Botanical Name	*Glycyrrhiza glabra* Linn.
Family	Fabaceae (Leguminosae)
Common Names	Licorice, Mulethi, Yashtimadhu
Plant Type	Perennial herb
Plant Height	1–1.5 m
Medicinal Part Used	Roots and rhizomes
Distribution	Southern Europe, Central Asia, Indian subcontinent
Traditional Uses	Mouth ulcers, sore throat, gastric ulcers, cough, wound healing

Major Phytoconstituents	Glycyrrhizin, flavonoids, liquiritin, chalcones, coumarins, polysaccharides
Limitations of Crude Extract	Hypertension, sodium retention on long-term use
Modified Form	Deglycyrrhizinated Licorice (DGL)
Key Advantage	Glycyrrhizin removed; safer for long-term oral use

Plant Description

Glycyrrhiza glabra is a perennial herbaceous plant native to Southern Europe, Central Asia, and parts of the Indian subcontinent. The plant grows up to 1–1.5 meters in height and is characterized by pinnate leaves, purple to pale blue flowers, and oblong pods. The roots and rhizomes are the medicinally active parts and are known for their characteristic sweet taste.

Traditional and Ethnomedicinal Uses

Licorice has been extensively used in traditional systems of medicine such as Ayurveda, Unani, and Traditional Chinese Medicine. Traditionally, it has been employed for the treatment of:

- Oral ulcers and sore throat
- Gastric ulcers and indigestion
- Respiratory conditions such as cough and bronchitis
- Inflammatory and infectious conditions
- Wound healing and mucosal protection
- Its demulcent and soothing properties make it particularly valuable in disorders involving mucosal irritation.

Figure 07: Licorice (Glycyrrhiza glabra)

The therapeutic activity of licorice is attributed to a wide range of bioactive compounds, including:

- Glycyrrhizin (triterpenoid saponin)
- Flavonoids (liquiritin, isoliquiritin, liquiritigenin)
- Chalcones
- Coumarins
- Polysaccharides
- Phenolic compounds

In Deglycyrrhizinated Licorice (DGL), glycyrrhizin is removed while preserving the beneficial flavonoids and polyphenols.

Pharmacological Activities

Licorice exhibits diverse pharmacological properties, including:

- Anti-ulcer activity
- Anti-inflammatory effects
- Antioxidant activity
- Antimicrobial action
- Immunomodulatory effects

- Mucoprotective and wound-healing properties

These activities support its application in oral and gastrointestinal mucosal disorders.

Limitations of Conventional Licorice Extract

Although licorice offers significant therapeutic benefits, prolonged use of conventional extracts containing glycyrrhizin may cause adverse effects such as sodium retention, hypertension, hypokalemia, and edema. These limitations restrict its long-term use, particularly in sensitive populations.

Deglycyrrhizinated Licorice (DGL)

Deglycyrrhizinated licorice is a modified form of licorice extract in which glycyrrhizin has been selectively removed. DGL retains the therapeutic efficacy of licorice while eliminating glycyrrhizin-related side effects. This makes DGL particularly suitable for oral mucosal applications, including mouth ulcer gels, lozenges, and oral rinses.

Mechanism of Action of DGL in Mouth Ulcers

The therapeutic efficacy of DGL in mouth ulcer management can be attributed to multiple mechanisms. DGL enhances mucosal defense by stimulating mucus secretion and promoting epithelial regeneration. Its anti-inflammatory action is mediated through the inhibition of pro-inflammatory mediators and suppression of oxidative stress.

DGL also exhibits antimicrobial activity against common oral pathogens, reducing the risk of secondary infection. Additionally, its antioxidant properties protect oral tissues from oxidative damage, thereby accelerating the healing process. These multifaceted mechanisms make DGL an ideal bioactive for mouth ulcer gel formulations.

Formulation Aspects of DGL-Based Mouth Ulcer Gel

The formulation of a Deglycyrrhizinated Licorice (DGL)-based mouth ulcer gel requires careful consideration of excipient selection, physicochemical compatibility, and patient acceptability. Since the oral mucosa is highly sensitive, the formulation must be non-irritating, mucoadhesive, and capable of delivering the active ingredient locally for an adequate duration.

Gel-based delivery systems are preferred for mouth ulcer treatment due to their ability to adhere to the ulcer surface, provide sustained release of bioactive compounds, and reduce systemic exposure. DGL, being water-soluble and stable within a slightly acidic to neutral pH range, is well suited for incorporation into aqueous gel formulations.

The choice of gelling agent plays a crucial role in determining the viscosity, clarity, and residence time of the gel. Carbopol 940, hydroxyethyl cellulose, and similar polymers are commonly employed due to their excellent mucoadhesive properties and compatibility with herbal extracts. The pH of the formulation should be maintained between 5.5 and 6.5 to ensure mucosal compatibility and optimal stability of DGL.

Humectants such as glycerin and propylene glycol are incorporated to maintain hydration of the ulcerated tissue and improve patient comfort. Preservatives must be carefully selected to ensure microbial stability while minimizing irritation. Flavoring agents and mild sweeteners may be added to mask the natural taste of herbal components and enhance patient compliance.

Overall, a well-designed DGL-based mouth ulcer gel should provide effective ulcer healing, pain relief, and protection of the oral mucosa while ensuring safety and ease of use.

TABLE No.2: Formulationof DGL-Based Mouth Ulcer Gel

SR. NO	INGREDIENTS	QTY.100
1	Dm Water	86.2
2	Sodium Gluconate	0.1
3	Allantoin	0.2
4	Deglycyrrhizinated Licorice	5

5	Carbopol 940	0.6
6	Sodium Benzoate	0.5
7	Potassium Sorbate	0.3
8	Glycerin	4
9	Propandiol	3
10	Menthol	0.1

TABLE No.3: Evaluation parameters for Deglycyrrhizinated Licorice-based mouth ulcer gel.

Evaluation Parameter	Method / Description	Significance
Appearance	Visual inspection	Ensures clarity, absence of lumps, and aesthetic acceptability
Color	Visual observation	Indicates formulation consistency
Odor	Sensory evaluation	Ensures patient acceptability
Homogeneity	Visual and tactile examination	Confirms uniform texture
pH	Digital pH meter	Oral mucosal compatibility (ideal: 5.5–6.5)
Viscosity	Brookfield viscometer	Determines flow behaviour and retention time
Spreadability	Glass slide method	Ease of application on ulcer surface
Extrudability	Tube press method	Ease of gel extrusion from tube
Drug Content Uniformity	UV/analytical method	Ensures uniform DGL distribution
In Vitro Drug Release	Franz diffusion cell	Evaluates release profi

3. CONCLUSION

Deglycyrrhizinated Licorice (DGL) has emerged as a promising bioactive for the management of mouth ulcers due to its anti-inflammatory, antioxidant, mucosal protective, and wound-healing properties. The development of DGL-based mouth ulcer gels combines the therapeutic benefits of herbal medicine with the advantages of gel-based drug delivery systems, including localized action, prolonged residence time, ease of application, and minimal systemic absorption. Formulation studies demonstrate that appropriate selection of gelling agents, pH adjustment, humectants, preservatives, and flavoring agents can produce a stable, mucoadhesive, and patient-friendly gel. Evaluation parameters such as viscosity, spreadability, drug content uniformity, in vitro release, and microbial safety confirm the quality and suitability of DGL gels for oral use. Compared to conventional steroid and anesthetic therapies, DGL-based gels provide a safer, natural, and steroid-free alternative for managing recurrent aphthous ulcers.

4. FUTURE SCOPE

Clinical Validation: Large-scale clinical trials are needed to establish the efficacy, safety, and optimal dosing of DGL-based gels in diverse patient populations.

Advanced Formulations: Incorporation of nanoparticles, liposomes, or mucoadhesive microspheres may enhance bioavailability, retention time, and sustained release of DGL.

Combination Therapy: DGL gels can be combined with complementary herbal actives such as Centella asiatica, Aloe vera, or curcumin to achieve synergistic effects on ulcer healing and pain relief.

Pediatric and Geriatric Applications: Development of flavor-masked, low-irritant formulations suitable for children and elderly patients.

Regulatory Standardization: Further research is required to standardize extract quality, ensure batch-to-batch consistency, and comply with regulatory guidelines for commercial herbal oral care products.

Multifunctional Oral Care Products: Integration of DGL gels into mouth rinses, lozenges, or sprays could

provide versatile, patient-friendly options for oral mucosal health.

Summary Statement:
DGL-based mouth ulcer gels represent a safe, effective, and modern herbal approach to oral ulcer management. With ongoing research, advanced formulation strategies, and clinical validation, these gels have the potential to become a mainstream, natural alternative to conventional therapies.

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