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Herbal Therapeutics for Oral Ulcers: Bridging Tradition and Modern Care

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Abstract

Recurrent aphthous stomatitis (RAS) and traumatic oral ulcers are painful lesions that significantly impair oral function and quality of life, arising from multifactorial causes including immune dysregulation, microbial imbalance, trauma, and nutritional or systemic factors. Herbal agents such as papaya (*Carica papaya*), Tulsi (*Ocimum sanctum*), Aloe vera, honey, and clove (*Syzygium aromaticum*) exhibit anti-inflammatory, antimicrobial, antioxidant, and wound-healing properties, supporting mucosal repair and reducing recurrence. Incorporation of these herbal agents into mucoadhesive systems, including gels, oral disintegrating strips, and lozenges, enables localized, sustained therapy with improved patient compliance, safety, and efficacy. Compared to conventional corticosteroid- or amlexanox-based treatments, herbal formulations offer a biocompatible, patient-friendly, and holistic approach. Future studies should focus on optimizing formulation strategies, standardizing phytochemical profiles, and conducting clinical validation to bridge traditional knowledge with modern pharmaceutical science, advancing effective and sustainable oral ulcer management.

Keywords: *Oral ulcers, recurrent aphthous stomatitis,* Carica papaya, Ocimum sanctum, *Aloe vera, honey, clove, oral wound healing*

1. Introduction

Oral aphthous ulcers (OAU), also known as recurrent aphthous stomatitis (RAS), are among the most common oral mucosal lesions, affecting approximately 20–25% of the global population [2]. These painful ulcers, which may vary from shallow to deep lesions, disrupt essential oral functions such as eating, speaking, and swallowing, significantly impairing quality of life. The etiology of OAU is multifactorial, involving trauma, infections, immune dysregulation, genetic predisposition, nutritional deficiencies, and environmental triggers [1,3]. Conventional therapies, including topical corticosteroids, amlexanox, and photodynamic therapy, provide symptomatic relief but are often limited by short retention in the oral cavity, recurrence, and potential side effects [4,5]. Recently, herbal and natural agents — such as papaya (*Carica papaya*), Tulsi (*Ocimum sanctum*), Aloe vera, honey, and clove (*Syzygium aromaticum*) — have gained attention for their anti-inflammatory, antioxidant, antimicrobial, and wound-healing properties [4–31]. Incorporating these agents into novel delivery systems, including mucoadhesive oral disintegrating strips, fast-dissolving films, gels, and lozenges, allows localized, sustained treatment, minimizing systemic exposure while enhancing therapeutic efficacy [11–15,18,19]

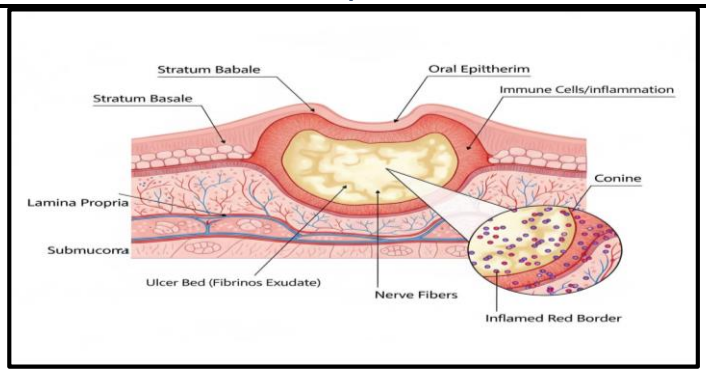
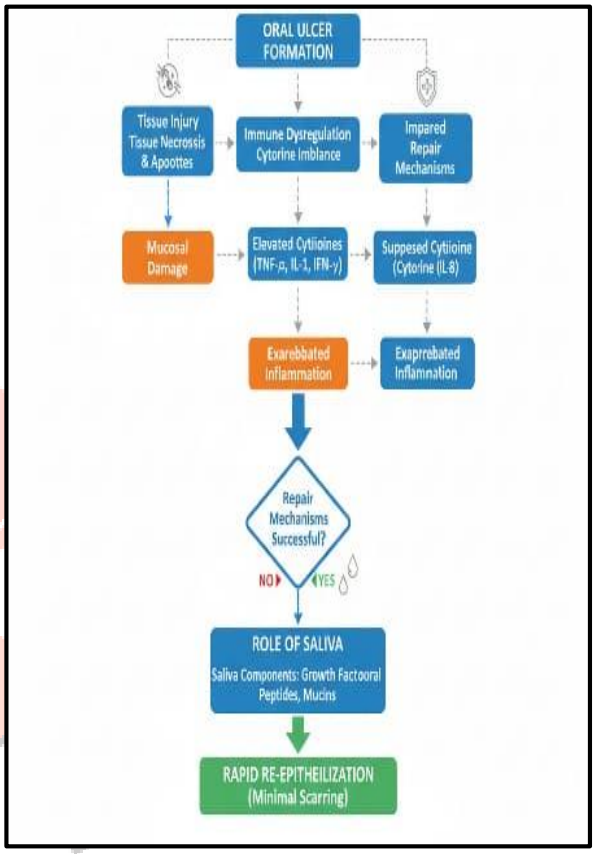


Fig 1.1: oral ophthous ulcer

2. Etiology and Pathophysiology:



Oral ulcers arise from a complex interplay of tissue injury, immune dysregulation, and impaired repair mechanisms. Tissue necrosis and apoptosis contribute to mucosal damage, while imbalances in cytokines — including elevated TNF-α, IL-1, IFN-γ, and suppressed IL-8 — exacerbate inflammation [1,2]. Saliva plays a critical role in healing by providing growth factors, antimicrobial peptides, and mucins, which promote rapid re-epithelialization with minimal scarring compared to skin [2].

Several additional factors influence the development and recurrence of oral ulcers, as summarized in Table: 2.1

- **Nutritional deficiencies:** Adequate levels of iron, folic acid, and vitamin B12 are essential for tissue repair [3].
- **Systemic diseases:** Conditions such as Behçet's disease, Crohn's disease, MAGIC syndrome, and HIV infection increase susceptibility to recurrent ulcers [3].
- **External factors:** Ultraviolet exposure, NSAID or aspirin use, stress, and hormonal fluctuations can trigger exacerbate ulcer formation [1,3].

Table 2.1: causes and contributing factors of oral ulcers

Category	Examples / Details
Pathogenic Stimuli	Trauma, infections, autoimmune diseases, chemical/thermal injuries
Cytokine Imbalance	Elevated TNF-α, IL-1, IFN-γ; suppressed IL-8
Genetic Predisposition	Variations in immune response and tissue repair
Nutritional Deficiency	Iron, folic acid, vitamin B12
External Factors	UV exposure, aspirin/NSAID use, stress, menstruation
Systemic Diseases	Behçet's disease, Crohn's disease, MAGIC syndrome, HIV

This comprehensive overview underscores that oral ulcer development is multifactorial, involving molecular, systemic, and environmental factors, which must be considered when designing effective therapeutic interventions [1–3].

3. Classification of Oral Ulcers

Oral aphthous ulcers can be classified into three major types based on size, number, depth, healing time, and potential for scarring (Table 2). Understanding these distinctions is important for diagnosis and selecting appropriate therapeutic strategies.

Table 3.1: classification of oral ulcers

Type	Features	Healing Time	Scarring
Minor Aphthous Ulcer	<4 mm, shallow, few lesions	10–14 days	None
Major Aphthous Ulcer	>10 mm, deep, may cluster	Up to 6 weeks	Possible
Herpetiform Ulcer	Numerous small ulcers (10–100), irregular distribution	1–2 weeks (variable)	Possible

These classifications highlight the variability in clinical presentation and healing patterns of oral ulcers, which is crucial for tailoring treatment approaches [3].

4. Healing Mechanism

Oral ulcer healing is a dynamic process that occurs in overlapping but distinct phases: **hemostasis, inflammation, proliferation,** and **maturation/remodeling**. The oral mucosa demonstrates unique regenerative capacity due to its rich vascularization, continuous cell turnover, and the protective role of saliva.

- **Hemostasis:**

Immediately after tissue injury, platelet aggregation and fibrin clot formation limit blood loss and establish a provisional matrix. Platelet-derived growth factors (PDGFs) initiate cellular recruitment, attracting immune and progenitor cells to the wound site [2].

- **Inflammation:**

Neutrophils and macrophages infiltrate the lesion to remove debris and microbial contaminants. Pro-inflammatory cytokines such as TNF-α, IL-1, and IFN-γ coordinate immune signaling, while IL-8 mediates neutrophil chemotaxis. Controlled inflammation is essential for proper repair; however, excessive cytokine activity can delay epithelial regeneration and increase tissue damage [1,2].

- **Proliferation:**

During this phase, fibroblasts synthesize extracellular matrix components, while keratinocytes proliferate and migrate to restore epithelial continuity. Angiogenesis ensures adequate perfusion and nutrient supply to the regenerating tissue. Saliva contributes antimicrobial peptides, mucins, and growth factors that accelerate epithelial migration and minimize scarring [2].

- **Maturation and Remodeling:**

Collagen fibers are reorganized to strengthen the repaired tissue, vascular structures mature, and the keratinized epithelium restores mucosal integrity. The oral mucosa typically heals faster and with less fibrosis than skin, primarily due to its high vascularity and continuous exposure to salivary growth factors [2,3].

Herbal agents such as **papaya** (rich in papain and chymopapain), **Tulsi** (containing antioxidants and anti-inflammatory phytoconstituents), **Aloe vera** (polysaccharides and glycoproteins), and **honey** (bioactive peptides and enzymes) support these healing mechanisms. They promote cellular regeneration, modulate inflammation, enhance collagen synthesis, and reduce microbial colonization, collectively accelerating mucosal repair [4–27].

5. Microbiota and External Influences

The oral microbiome plays a crucial role in the pathogenesis and recurrence of oral ulcers. Dysbiosis — an imbalance between commensal and pathogenic microorganisms — can exacerbate mucosal inflammation and delay healing. Key bacterial species associated with ulcerative lesions include *Streptococcus oralis*, *S. mitis*, *Prevotella* spp., and *Acinetobacter johnsonii* [3]. In some cases, viral pathogens such as cytomegalovirus (CMV) have also been implicated in triggering recurrent episodes [3].

External factors significantly influence ulcer initiation and progression:

- **Trauma:** Sharp teeth, dental procedures, or ill-fitting prostheses can directly damage the mucosa, initiating or worsening ulcerative lesions.
- **Chemical and environmental exposures:** Use of NSAIDs, aspirin, and consumption of spicy or acidic foods may induce mucosal irritation. UV radiation and oxidative stress further compromise epithelial integrity [1,3].
- **Immune and systemic factors:** Autoimmune disorders, hormonal fluctuations, and nutritional deficiencies can impair local immunity and delay tissue regeneration [3].

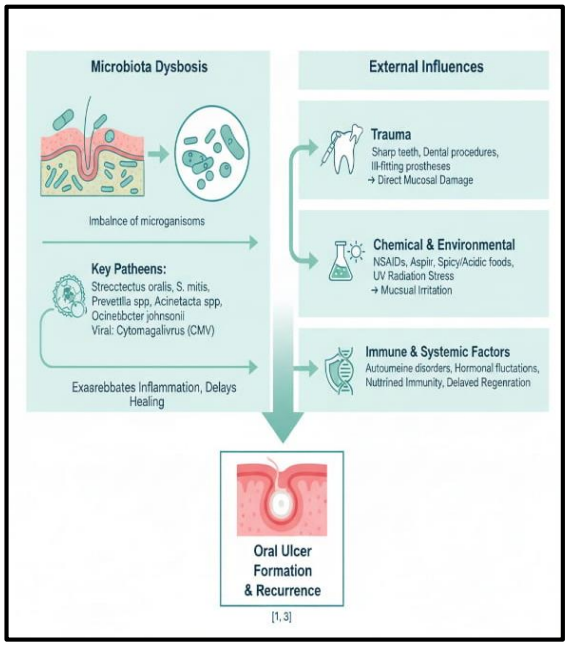


Fig 5.1: microbiota and external influences

Herbal agents can beneficially modulate the oral microenvironment. Extracts of **papaya** and **clove** have demonstrated antimicrobial activity against *Streptococcus mutans*, *Staphylococcus aureus*, and *Candida albicans*, thereby reducing secondary infections [7,8,28,29]. **Tulsi**, through its strong antioxidant potential, neutralizes reactive oxygen species and minimizes oxidative stress, while **honey** exhibits both antimicrobial and prebiotic effects, supporting a balanced oral microbiota and faster mucosal recovery [16,22,25].

Collectively, maintaining microbial balance and mitigating external insults are vital components of effective oral ulcer management, and herbal therapeutics offer a promising adjunctive strategy in achieving this balance.

6. Diagnosis

Diagnosis of oral ulcers is based on a thorough patient history, detailed clinical examination, and the exclusion of systemic or autoimmune conditions. Evaluation should encompass inspection of all oral mucosal sites, including the lips, tongue, buccal mucosa, gingiva, soft palate, and oropharyngeal region [3]. Key diagnostic considerations include ulcer morphology, number, recurrence pattern, pain intensity, and associated systemic symptoms. Laboratory tests—such as complete blood count, vitamin B12 or folate levels, and screening for celiac or autoimmune disorders—may be warranted to identify underlying etiologies [3].

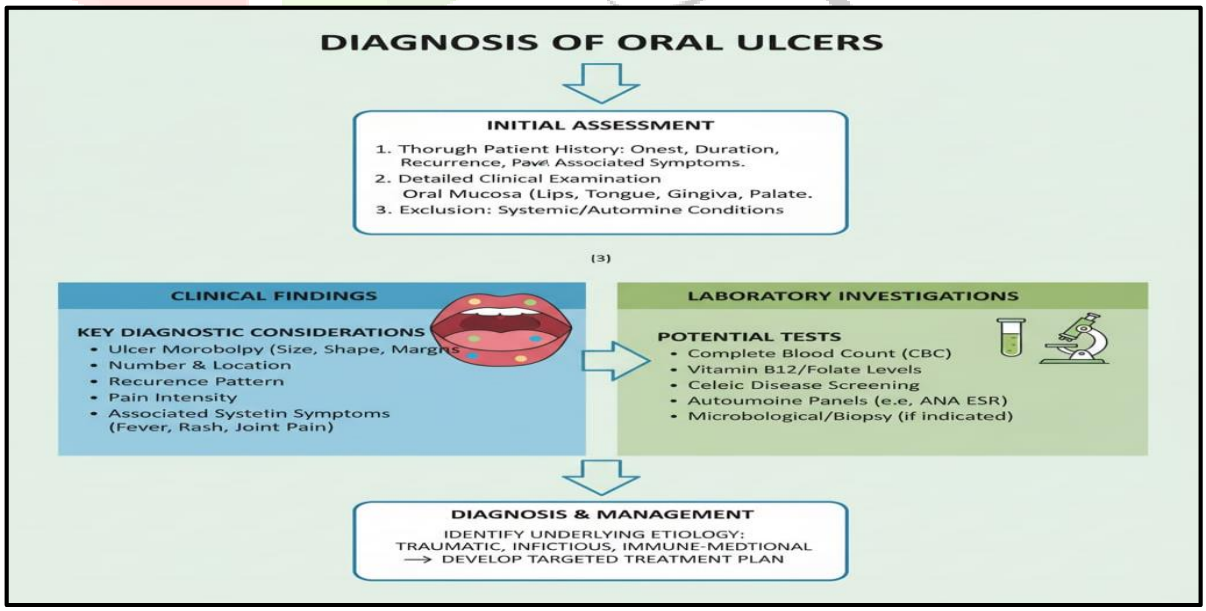


Fig 6.1: diagnosis of oral ulcer

7. Herbal Agents for Oral Ulcers

Several herbal agents have demonstrated significant therapeutic potential in oral ulcer management through anti-inflammatory, antioxidant, antimicrobial, and tissue-regenerative mechanisms. Their integration into novel formulations enhances local bioavailability, accelerates healing, and minimizes recurrence.

7.1 Papaya (*Carica papaya*): Nature's Regenerative Enzyme

Papaya fruit and leaf extracts promote ulcer healing via anti-inflammatory, antioxidant, proteolytic, and antimicrobial effects. Enzymes such as papain and chymopapain facilitate debridement and tissue regeneration, while flavonoids, saponins, and vitamin C stimulate collagen synthesis [4–6]. Papaya also demonstrates broad-spectrum antibacterial and antifungal activity against *Streptococcus mutans*, *Staphylococcus aureus*, and *Candida albicans* [7,8]. Additionally, its amino acid and micronutrient profile supports mucosal repair, with traditional evidence reinforcing its safety and efficacy [9,10].

7.2 Tulsi (*Ocimum sanctum*): The Queen of Herbs

Tulsi exhibits a synergistic combination of anti-inflammatory, antimicrobial, anti-ulcerogenic, and wound-healing activities. Herbal lozenges and gummies containing Tulsi maintain prolonged contact with ulcerated tissues, enhancing mucosal recovery [11,12]. Fast-dissolving films incorporating Tulsi and *Glycyrrhiza glabra* improve localized delivery and therapeutic response [13]. Topical Tulsi paste has alleviated burning sensations in oral submucous fibrosis [14], while Tulsi–Aloe vera–Neem gels demonstrate potent antimicrobial and anti-inflammatory efficacy [15]. Tulsi's strong antioxidant and cytoprotective activity further promotes oral tissue integrity [16,17].

7.3 Aloe Vera: Soothing and Restorative

Aloe vera effectively reduces ulcer size, inflammation, and pain. Clinical studies report therapeutic outcomes comparable to triamcinolone acetonide and amlexanox [18–21]. Its bioactive polysaccharides and glycoproteins stimulate fibroblast proliferation and collagen deposition, accelerating mucosal re-epithelialization and ensuring a soothing, non-irritant profile [18].

7.4 Honey: Sweet Relief and Healing

Topical application of honey significantly reduces ulcer size, erythema, and pain duration, achieving results comparable to corticosteroid therapy [22–24]. Pediatric and clinical studies confirm its safety, palatability, and superior healing rates [25]. Thyme-infused honey enhances analgesic and antimicrobial effects [26], while preclinical studies validate epithelial regeneration and non-toxic mucosal healing [27].

7.5 Clove (*Syzygium aromaticum*): Eugenol-Powered Mucosal Protection

Clove, rich in the bioactive compound eugenol, provides potent antimicrobial, anti-inflammatory, and wound-healing properties. Clove-based mouthwash has been shown to reduce the severity and duration of radiation-induced oral mucositis [28]. Collagen sponges incorporating clove oil accelerated ulcer healing in diabetic models [29]. Clovinol, a polyphenol-rich extract, exhibited over 97% protection against experimental ulcers with excellent safety margins [30], while eugenol displayed pronounced mucosal and gastroprotective activity [31].

Collectively, these herbal agents offer a safe, multifaceted, and evidence-based approach for promoting oral mucosal repair and preventing ulcer recurrence.

Conclusion:

Oral ulcers, including recurrent aphthous stomatitis, are common and recurrent lesions with multifactorial etiology, involving immune dysregulation, microbial imbalance, and impaired mucosal regeneration. Herbal agents such as papaya (*Carica papaya*), Tulsi (*Ocimum sanctum*), Aloe vera, honey, and clove (*Syzygium aromaticum*) demonstrate complementary pharmacological actions, including anti-inflammatory, antimicrobial, antioxidant, and wound-healing effects. Incorporating these natural agents into advanced mucoadhesive systems — such as gels, oral disintegrating strips, and lozenges — enables localized, sustained therapy with enhanced safety, patient compliance, and therapeutic efficacy. Compared to conventional corticosteroid- or amlexanox-based treatments, herbal formulations offer holistic, biocompatible healing with minimal adverse effects. Future research should focus on optimizing formulation strategies, standardizing phytochemical profiles, and validating clinical efficacy through randomized controlled trials, thereby bridging traditional knowledge with modern pharmaceutical science to develop effective, sustainable, and patient-centered solutions for oral ulcer management.

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