

# Herbal Gel Formulations From Medicinal Plants: A Review Of Antimicrobial And Anti-Inflammatory Activity For Treatment Of Mouth Ulcers

Avani Upadhyay<sup>1</sup>, Miritunjay Singh<sup>2</sup>, Akash Deep Kumar<sup>2</sup>, Hiloni Bhavsar<sup>2</sup> and Indrani Bhattacharya<sup>3\*</sup>

<sup>1,2</sup>Student, Department of Life Sciences, Parul Institute of Applied Sciences, Faculty of Applied Sciences, Parul University, Vadodara 391760, Gujarat, India.

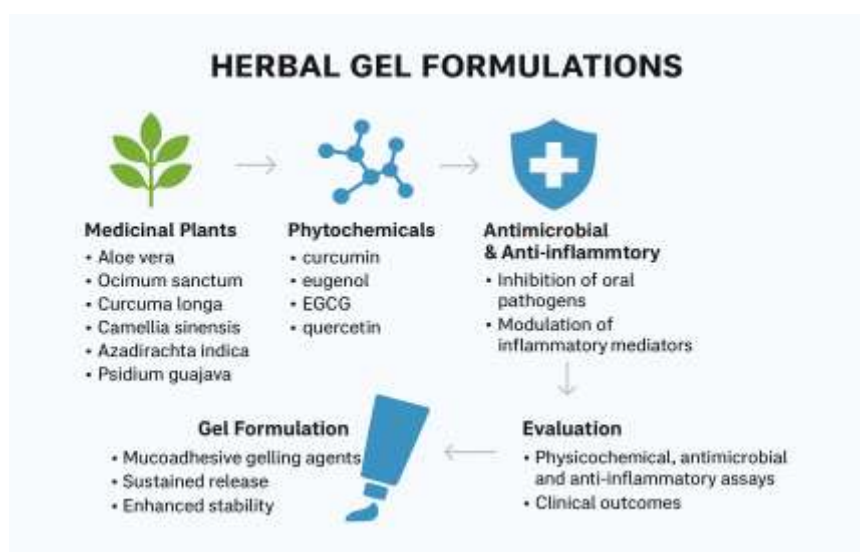
<sup>3\*</sup>Assistant Professor, Department of Life Sciences, Parul Institute of Applied Sciences, Faculty of Applied Sciences, Parul University, Vadodara 391760, Gujarat, India.

## ABSTRACT

One of the most prevalent conditions affecting the oral mucosa, mouth ulcers are frequently linked to discomfort, inflammation, microbial colonization, and a reduced quality of life. While they offer short-term respite, traditional treatment options like corticosteroids and antiseptics can have negative side effects and low patient compliance. Herbal gel formulations have become viable substitutes in recent years because of their dual antimicrobial and anti-inflammatory qualities, localized drug delivery, and biocompatibility. Medicinal plants like *Aloe vera*, *Ocimum sanctum*, *Curcuma longa*, *Camellia sinensis*, *Azadirachta indica*, and *Psidium guajava* are highlighted in this review because they contain phytochemicals that can inhibit *Streptococcus* species and other important oral pathogens. They can also modulate inflammatory mediators like nitric oxide, cyclooxygenase, TNF- $\alpha$ , IL-1 $\beta$ , and IL-6.

These plants' therapeutic potential to lessen ulcer severity and speed mucosal healing is supported by data from *in vitro*, *ex vivo*, *in vivo*, and clinical studies. Additionally, improved patient acceptability, stability, and sustained release are made possible by advancements in formulation techniques that use mucoadhesive gelling agents (Carbopol, HPMC, and chitosan). The effectiveness of these gels is further supported by evaluation parameters that include stability, antimicrobial, anti-inflammatory, physicochemical, and clinical results. All things considered, herbal gel formulations offer a therapeutic strategy for the treatment of mouth ulcers that is secure, efficient, and patient-friendly. To determine their place in mainstream oral healthcare, future studies concentrating on standardization, innovative delivery methods, synergistic plant combinations, and extensive clinical trials will be crucial.

## GRAPHICAL ABSTRACT



**Keywords:** Herbal gels, medicinal plants, mouth ulcers, antimicrobial, anti-inflammatory, phytochemicals.

## 1. INTRODUCTION

Mouth ulcers, also known as canker sores or aphthous stomatitis, are among the most prevalent oral cavity lesions that can affect individuals of all ages. They are distinguished by painful, round or oval sores on the cheeks, lips, tongue, or mucosal lining of the mouth. Despite not being life-threatening, they severely impair everyday functions like speaking, swallowing, and eating, which lowers the patient's quality of life. Ulcers frequently recur, and their episodes are frequently brought on by stress, malnutrition, hormonal changes, trauma, and microbial infections. (Scully & Porter, 2008; Belenguer-Guallar et al., 2014; Preeti et al., 2011)

Traditional methods of treating mouth ulcers include immunomodulatory drugs, topical corticosteroids, antiseptic rinses, and anesthetics. These treatments may reduce pain and inflammation temporarily, but they frequently have drawbacks like side effects, irritation of the mucosa, a high rate of recurrence, and ineffectiveness over the long run. (Altenburg et al., 2014;) Additionally, the increasing issue of antibiotic resistance has fueled the hunt for safer and more environmentally friendly substitutes. (Ventola, 2015)

Herbal medicine has drawn more attention recently as a potentially effective treatment for oral ulcers. Bioactive substances with antimicrobial, anti-inflammatory, antioxidant, and wound-healing qualities, including flavonoids, alkaloids, tannins, terpenoids, and phenolic acids, are abundant in medicinal plants. (Tapsell et al., 2006; Newman & Cragg, 2016) Herbal extracts are generally thought to be safer, more affordable, and more widely available than synthetic drugs. Many of the plant-based treatments used for oral illnesses in traditional medical systems, such as Ayurveda, Unani, and Chinese medicine, are now being scientifically validated by recent research. (Pandey et al., 2013; Chen et al., 2015)

Treating oral ulcers has shown particular promise when using herbal gels as a drug delivery system. Compared to other dosage forms, gels offer a number of benefits, including localized delivery at the ulcer site, mucoadhesion, which guarantees a longer retention period on the oral mucosa, controlled and sustained release of active compounds, and enhanced patient compliance because of their pleasant texture and ease of application. (Pundir et al., 2014; Shojaei, 1998; Semalty et al., 2010)

To create stable, biocompatible gels that can include plant extracts, common gelling agents like carbopol, hydroxypropyl methylcellulose (HPMC), and sodium carboxymethylcellulose (NaCMC) are frequently used. (Desai & Kumar, 2004) Medicinal plants like Aloe vera, Tulsi (*Ocimum sanctum*), Green tea (*Camellia sinensis*), Tea tree (*Melaleuca alternifolia*), Bhringraj (*Eclipta alba*), and Guava (*Psidium guajava*) have been extensively explored in gel formulations for their ability to inhibit microbial pathogens and reduce inflammation in the oral cavity. (Upadhye et al., 2021; Garala & Rabara, 2022; Sahu et al., 2020; Gupta et al., 2017)

Pharmaceutical parameters (pH, viscosity, spreadability, mucoadhesion, and stability) and biological activities (antimicrobial activity against oral pathogens like *Streptococcus mutans*, *Candida albicans*, and *Staphylococcus aureus*, as well as anti-inflammatory effects through inhibition of COX enzymes, cytokines, and oxidative stress markers) are commonly assessed in research on these formulations. (Jain et al., 2018; Sharma et al., 2014; Rajeshkumar et al., 2019; Singh et al., 2020) All of these studies show that using herbal gels to treat mouth ulcers is a safe and efficient substitute for synthetic medications.

This review offers a thorough analysis of herbal gel formulations made from therapeutic plants that may be used to treat mouth ulcers. It identifies current issues and potential paths forward in this developing field, talks about formulation strategies and evaluation methods, and highlights the phytochemicals that have antimicrobial and anti-inflammatory properties.



**Figure 1: Representative image of a mouth ulcer**

## **2. MEDICINAL PLANTS FOR TREATING MOUTH ULCER**

The potential of medicinal plants as treatments for oral health is being thoroughly studied because they are abundant in bioactive phytochemicals such as flavonoids, tannins, terpenoids, and alkaloids. The antimicrobial, anti-inflammatory, antioxidant, and wound-healing qualities of these substances can be used to treat mouth

ulcers. Compared to synthetic drugs, plant-derived extracts are usually safer, less expensive, and better tolerated over time. (Zou, 2022)

One of the most researched plants for the treatment of oral ulcers is Aloe vera (*Aloe barbadensis*). Anthraquinones, polysaccharides, and flavonoids found in its gel hasten wound healing, lower inflammation, and calm irritated mucous membranes. According to clinical research, aloe vera speeds up the healing process for aphthous ulcers and lessens pain and burning feelings. (Zou, 2022; Giroh et al., 2019)

Another intriguing medicinal plant is tulsi (*Ocimum sanctum*), commonly referred to as "Holy Basil." Eugenol, ursolic acid, and flavonoids—all of which have potent antimicrobial and immunomodulatory qualities—are abundant in it. Research has demonstrated that Tulsi extracts dramatically reduce oral pathogens like *Staphylococcus aureus* and *Streptococcus mutans*. (Pai et al., 2022; Agarwal et al., 2010; Yamani et al., 2016)

There are other plants that have been shown to inhibit microbial growth, suppress inflammatory mediators like COX-2 and TNF- $\alpha$ , and promote tissue regeneration, including green tea (*Camellia sinensis*), tea tree (*Melaleuca alternifolia*), bhringraj (*Eclipta alba*), guava (*Psidium guajava*), neem (*Azadirachta indica*), and turmeric (*Curcuma longa*). For instance, guava tannins have antimicrobial and wound-healing properties, turmeric's curcumin has strong anti-inflammatory properties, and green tea's catechins are strong antioxidants.

All of these plants work together to promote mucosal repair, inhibit oral pathogens, reduce inflammation by downregulating cytokines, and provide antioxidant protection against oxidative stress. Medicinal plants are great candidates to be included in herbal gel formulations for the treatment of mouth ulcers because of their multifactorial therapeutic profile.

#### Relevant Phytochemicals for Mouth Ulcers:

- Flavonoids lessen inflammation and oxidative stress by scavenging free radicals.
- Tannins have antimicrobial properties, lessen pain, and create protective layers on mucosal tissue.
- Because of their antimicrobial properties, alkaloids and terpenoids combat oral pathogens.
- Saponins aid in the healing and regeneration of tissue.

**Table 1: Commonly used medicinal plants to treat mouth ulcers.**

Plant (scientific name)	Key phytochemicals	Pharmacological Activities	References
Aloe vera ( <i>Aloe barbadensis</i> )	Anthraquinone, polysaccharides, flavonoids	Anti-inflammatory, wound healing, soothing mucosa	Zou, 2022; Giroh et al., 2019
Tulsi ( <i>Ocimum sanctum</i> )	Eugenol, ursolic acid, flavonoids	Antimicrobial, antioxidant, immunomodulatory	Pai et al., 2022; Agarwal et al., 2010; Yamani et al., 2016
Green Tea ( <i>Camellia sinensis</i> )	Catechins (EGCG), polyphenols	Antioxidant, antimicrobial, reduces oral inflammation	Chatterjee et al., 2012
Tea tree ( <i>Melaleuca alternifolia</i> )	Terpinen-4-ol, cineole	Antibacterial, antifungal	Carson et al., 2012
Bhringraj ( <i>Eclipta alba</i> )	Wedelolactone, flavonoids, coumestans	Anti-inflammatory, antioxidant, tissue regeneration	Singh et al., 2011
Guava ( <i>Psidium guajava</i> )	Quercetin, tannins, flavonoids	Antimicrobial, analgesic, wound healing	Jalary et al., 1999
Neem ( <i>Azadirachta indica</i> )	Azadirachtin, nimbin, quercetin	Antibacterial, antifungal, anti-inflammatory	Subapriya & Nagini, 2005
Turmeric ( <i>Curcuma longa</i> )	Curcumin, demethoxycurcumin	Anti-inflammatory, antioxidant, wound healing	Hewlings & Kalman, 2017

### 3. ANTIMICROBIAL ACTIVITIES

Mouth ulcer severity and persistence are significantly influenced by microbial colonization. *Streptococcus mutans*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans* are common pathogens that cause pain, delayed healing, and secondary infections. (Agarwal et al., 2010)

### 3.1 Bacterial Involvement in Mouth Ulcers

While stress, nutritional deficiencies, trauma, or viral infection are the main causes of mouth ulcers, subsequent bacterial infections frequently exacerbate the condition and slow its healing. Oral ulcer etiology and persistence have been linked to a number of bacterial species.

#### **Species of *Streptococcus* (*S. oralis*, *S. mitis*, and *S. sanguinis*):**

Although these Gram-positive cocci are a natural component of oral flora, they have the ability to infiltrate ulcerated mucosa, leading to inflammation and subsequent infection. (Han & Wang, 2015)

Damaged mucosal tissue is often colonized by the Gram-positive bacterium *Staphylococcus aureus*, which exacerbates inflammation and slows down the healing process. (Rivera et al., 2022)

***Helicobacter pylori*:** This Gram-negative spiral bacterium is frequently associated with stomach ulcers, but it has also been found in oral lesions, which may indicate that it plays a part in recurrent aphthous stomatitis. (Karaca et al., 2008)

*Fusobacterium nucleatum* is a Gram-negative anaerobic rod that causes necrotic oral infections and has good adhesion characteristics. It has the ability to infiltrate epithelial cells, causing tissue injury and inflammation. (Groeger et al., 2022; Chen et al., 2022)

Gram-negative anaerobic bacteria called *Porphyromonas* and *Prevotella* species have been linked to periodontal disorders and have been observed in mouth ulcers that are infected or do not heal. (Han & Wang, 2015)

All things considered, these bacterial species exacerbate the clinical course of mouth ulcers by contributing to tissue necrosis, secondary infection, and delayed epithelial regeneration.

### 3.2 Antimicrobial Activities of Medicinal plants

Aloe vera gel can help prevent bacterial and fungal superinfections of oral ulcers because it has been shown to inhibit the growth of *Staphylococcus aureus* and *Candida albicans*. (Giroh et al., 2019)

Tulsi, or *Ocimum sanctum*, exhibits broad-spectrum antibacterial activity. Particularly good at preventing *S. mutans* and *S. aureus*, which are connected to dental cavities and oral infections, are eugenol and ursolic acid. (Pai et al., 2022; Yamani et al., 2016)

By breaking down bacterial cell walls, blocking glucosyltransferase enzymes, and stopping *S. mutans* from forming biofilms, the catechins in *Camellia sinensis* (green tea), particularly EGCG, exhibit strong antimicrobial properties. Green tea is a promising treatment for gastric and oral ulcers because EGCG has also been demonstrated to inhibit *H. pylori* growth and lower its virulence factors. (Chatterjee et al., 2012)

Terpinen-4-ol, which is found in tea tree oil (*Melaleuca alternifolia*), is very effective against a variety of oral pathogens. Its mechanism involves the disruption of membranes, the release of intracellular contents, and the inhibition of fungal growth, specifically that of *Candida* species. (Carson et al., 2006)

Compounds like azadirachtin and nimbin are responsible for the strong antimicrobial activity of neem (*Azadirachta indica*) against oral pathogens. Additionally, neem extracts exhibit *H. pylori* inhibitory activity, which may aid in lowering ulcer recurrence linked to microbial infection. (Subapriya & Nagini, 2005)

**Collectively, these studies confirm that plant-derived phytochemicals act via multiple antimicrobial mechanisms:**

- Disrupting microbial cell membranes.
- Inhibiting enzymes involved in bacterial metabolism.
- Preventing adhesion and biofilm formation.
- Reducing fungal and bacterial proliferation in oral mucosa.

## 4. ANTI-INFLAMMATORY EVIDENCE

One of the main characteristics of mouth ulcers is inflammation, which manifests as pain, redness, swelling, and a delayed healing period. The fundamental process entails the release of pro-inflammatory mediators that harm oral mucosa and prolong ulceration, including cyclooxygenase-2 (COX-2), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), and reactive oxygen species (ROS). (Scully & Porter, 2008) Because medicinal plants contain bioactive phytochemicals with potent anti-inflammatory and antioxidant qualities, they offer a natural way to alter these pathways.

One of the most researched plants in this area is *Curcuma longa*, or turmeric. Its active ingredient, curcumin, reduces inflammation and speeds up mucosal repair by downregulating the COX-2, TNF- $\alpha$ , and NF- $\kappa$ B signaling pathways. Turmeric extracts have been shown in clinical and experimental studies to lessen oral ulcer models' pain and lesion size. (Hewlings & Kalman, 2017)

Polysaccharides and flavonoids found in Aloe vera promote epithelial regeneration and inhibit inflammatory cytokines. In patients with recurrent aphthous stomatitis, topical aloe gel has been demonstrated to dramatically reduce erythema and pain. (Giroh et al., 2019)

The catechins in green tea (*Camellia sinensis*), particularly EGCG, neutralize ROS and lower lipid peroxidation, making them strong antioxidants. Additionally, they inhibit the production of pro-inflammatory cytokines, which speeds up the healing of mucosal lesions. [Chatterjee et al., 2012]

Eugenol and ursolic acid, which are found in *Ocimum sanctum* (tulsi), are substances that have potent immunomodulatory effects. Tulsi extracts reduce the production of prostaglandin and leukotrienes by inhibiting the enzymes cyclooxygenase and lipoxygenase, which lessens oral tissue pain and swelling. (Agarwal et al., 2010)

Neem (*Azadirachta indica*) has long been used to treat gum and oral diseases because its extracts have anti-inflammatory properties that prevent neutrophil infiltration and reduce inflammatory mediators. (Subapriya & Nagini, 2005)

Another powerful anti-inflammatory plant is *Psidium guajava*, or guava, whose tannins and quercetin function as free radical scavengers to lessen tissue damage during ulcerative episodes. (Jaiarj et al., 1999)

The use of medicinal plants to treat oral ulcers is generally well supported by the anti-inflammatory data. They are promising substances to include in herbal gel formulations because of their dual capacity to reduce inflammatory mediators and strengthen antioxidant defense.

#### 4.1 Mechanistic Evidence

It has been demonstrated that certain phytochemicals, including quercetin (from *Psidium guajava*), eugenol (from *Ocimum sanctum*), curcumin (from *Curcuma longa*), and catechins (from *Camellia sinensis*),

- By blocking inducible nitric oxide synthase (iNOS), you can reduce the production of NO.
- Reduce the production of prostaglandins and leukotrienes by downregulating the COX-2 and LOX enzymes.
- Reduce mucosal edema and pain by inhibiting pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , and IL-6).
- Stop the transcription of inflammatory genes by blocking NF- $\kappa$ B signaling. (Hewlings & Kalman, 2017; Chatterjee et al., 2012)

#### 4.2 Experimental Models

In vitro: RAW264.7 murine macrophage assays are frequently employed to quantify the release of cytokines and NO. In these models, plant extracts like green tea and turmeric dramatically lower the NO and TNF- $\alpha$  produced by lipopolysaccharide (LPS). (Subapriya & Nagini, 2005)

Ex vivo: Cytokine ELISA from inflammatory mucosal tissues shows reduced levels of IL-1 $\beta$  and IL-6 after treatment with Aloe vera and tulsi extracts.

In vivo: Herbal extracts have been shown to decrease inflammatory mediator expression in mucosal tissues, decrease erythema, and speed wound closure in animal ulcer models. (Pai et al., 2022)

#### 4.3 Clinical Evidence

These results are corroborated by numerous clinical trials. For instance, in patients with recurrent aphthous stomatitis, Aloe vera gel dramatically decreased erythema, pain scores, and healing time (Giroh et al., 2019). By altering COX-2 and TNF- $\alpha$  levels, turmeric gel has been demonstrated to lessen ulcer size and inflammatory symptoms. In patients with ulcerative lesions, green tea mouthwashes reduced oral mucosal inflammation and pain scores. (Chatterjee et al., 2012)

### 5. FORMULATION STRATEGIES

For the best bioadhesion, drug release, stability, and patient compliance, plant extracts, gelling agents, and excipients must be carefully chosen when creating herbal gels for oral ulcers. Gels offer localized delivery in contrast to traditional dosage forms, guaranteeing extended contact with the oral mucosa and improved therapeutic effect.

#### 5.1 Selection of Herbal Extracts

To optimize phytochemical yield, extracts are usually made with aqueous, ethanolic, or hydroalcoholic solvents. Because of their antimicrobial and anti-inflammatory properties, plants like Aloe vera, *Ocimum sanctum*, *Curcuma longa*, *Camellia sinensis*, *Azadirachta indica*, and *Psidium guajava* are commonly used to treat mouth ulcers. (Subapriya & Nagini, 2005; Chatterjee et al., 2012)

#### 5.2 Choice of Gelling Agents

The perfect gelling agent should be stable in the oral environment, biocompatible, non-irritating, and mucoadhesive. Typical polymers include:

- Good mucoadhesion and viscosity are provided by carbopol 934/940.
- Film formation and spreadability are enhanced by hydroxypropyl methylcellulose (HPMC).
- Sodium alginate provides sustained release and bioadhesion.

- Chitosan improves drug penetration and is biodegradable.

### 5.3 Incorporation of Extracts into Gel Base

In order to ensure that the phytochemicals are evenly distributed, the extracts are typically mixed into the hydrated gel base by mechanical stirring. Co-solvents, such as glycerin and propylene glycol, are occasionally added to increase solubility and stop active compounds from precipitating.

### 5.4 Optimization Strategies

The following criteria are used to optimize the formula:

- To make it compatible with the oral mucosa, adjust the pH between 6.5 and 7.0.
- Spreadability and viscosity for simple application.
- Bioadhesion to extend retention at the site of ulceration.
- Mechanisms for controlled release to guarantee a long-lasting therapeutic effect.

### 5.5 Advantages of Herbal Gels

- Targeted medication administration at the ulcer site.
- Fewer systemic adverse effects in contrast to synthetic medications.
- Continuous phytochemical release.
- Increased patient compliance as a result of the simple application.

## 6. EVALUATION OF GEL

To guarantee quality, stability, bioactivity, and patient compliance, herbal gels must be evaluated. Physicochemical, antimicrobial, anti-inflammatory, stability, and clinical evaluations are examples of standard evaluation parameters.

### 6.1 Physicochemical Evaluation

According to Patel et al. (2012), herbal gels are evaluated for appearance, homogeneity, and pH (which should be kept between 6.5 and 7.0 to avoid irritating mucosal tissue). Spreadability and extrudability determine ease of application, while viscometers are used to test viscosity and rheology. (Nandini et al., 2016) Uniform drug content guarantees that phytochemicals are distributed consistently throughout the formulation. (Dash et al., 2014)

### 6.2 Bioadhesion Studies

Ex vivo buccal mucosa models (goat, sheep, or bovine tissue) are used to assess mucoadhesive strength. Greater adhesion increases therapeutic action by enabling longer retention on the ulcer site. (Kumar et al., 2013)

### 6.3 In Vitro Release Studies

Phytochemical release from gels into simulated saliva medium is frequently studied using dialysis membrane assays or Franz diffusion cells. (Singh et al., 2011)

### 6.4 Antimicrobial Testing

Agar diffusion assays, minimum inhibitory concentration (MIC) tests, and biofilm inhibition studies are used to assess antimicrobial activity against common oral pathogens, including *Helicobacter pylori*, *Staphylococcus aureus*, *Streptococcus mutans*, and *Candida albicans*. (Carson et al., 2006; Chatterjee et al., 2012)

### 6.5 Anti-Inflammatory Assays

In vitro: RBC membrane stabilization, protein denaturation assay, and RAW264.7 macrophage cytokine assays (IL-1 $\beta$ , TNF- $\alpha$ , and IL-6). (Subapriya & Nagini, 2005)

Ex vivo: Plant-based gel-treated inflammatory oral tissues were subjected to cytokine ELISA.

In vivo: Rodent ulcer models show reduction in lesion size, erythema, and pain after treatment with Aloe vera and turmeric gels. (Hewlings & Kalman, 2017)

### 6.6 Stability Studies

To assess physical appearance, viscosity, pH, and phytochemical content over time, ICH guidelines call for accelerated stability testing (40 °C  $\pm$  2 °C, 75% RH for 3–6 months). (Dash et al., 2014)

### 6.7 Clinical Evaluation

Clinical trials evaluate:

- Ulcer healing period.
- The Visual Analogue Scale (VAS) is used to calculate pain reduction scores.
- Decrease in erythema and ulcer size.
- Acceptability by patients (taste, comfort, and application ease). (Giroh et al., 2019; Scully & Porter, 2008)

## 7. CONCLUSION AND FUTURE ASPECTS

Mouth ulcers are a frequent oral mucosal illness that significantly affects daily activities such as speaking, eating, and overall quality of life. Conventional treatment methods only provide temporary comfort and are usually associated with adverse effects. Herbal gel compositions have emerged as a safe, effective, and patient-friendly

alternative due to their antibacterial, anti-inflammatory, and wound-healing properties. Aloe vera, *Ocimum sanctum*, *Curcuma longa*, *Camellia sinensis*, *Azadirachta indica*, and *Psidium guajava* are among the medicinal plants that contain phytochemicals that can inhibit *Streptococcus* species and other significant oral pathogens while altering inflammatory mediators such as cyclooxygenase, nitric oxide, TNF- $\alpha$ , IL-1 $\beta$ , and IL-6. Formulation advances using mucoadhesive substances including Carbopol, HPMC, and chitosan have improved mucosal retention, gel stability, and extended release. Their therapeutic potential is validated by a thorough examination that includes stability, antimicrobial, anti-inflammatory, physicochemical, and clinical tests.

A number of areas merit more investigation in the future. Because variations in phytochemical composition can change the effectiveness of treatments, standardization of plant extracts is essential. New strategies including phytosomes, delivery methods based on nanotechnology, and bioadhesive smart polymers may improve solubility, bioavailability, and site-specific action even further. Combining several medicinal plants in a synergistic composition may increase therapeutic efficacy while reducing microbial resistance. Furthermore, to validate preclinical results and make herbal gels a common treatment choice, extensive clinical trials following established methods are required. Achieving worldwide acceptability will require bridging the gap between contemporary pharmaceutical breakthroughs and traditional medicine.

In conclusion, herbal gel compositions provide a novel therapeutic approach for the successful treatment of mouth ulcers by bridging the gap between traditional knowledge and contemporary research. These formulations have the potential to revolutionize oral healthcare with further study, improvement, and clinical validation.

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