

POLYHERBAL AQUEOUS GEL FORMULATIONS CONTAINING GUAVA, ALOE VERA, AND ACACIA LEAVES FOR ORAL ULCER MANAGEMENT: A COMPREHENSIVE REVIEW

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ABSTRACT

Oral ulcers are among the most common disorders affecting the oral mucosa and are characterized by localized epithelial destruction, inflammation, pain, and impairment of normal oral functions. These lesions significantly affect patients' quality of life by interfering with eating, speaking, swallowing, and maintaining oral hygiene. Although conventional therapies such as corticosteroids, antiseptics, analgesics, and antibiotics provide symptomatic relief, their long-term use may be associated with adverse effects, recurrence, microbial resistance, and inadequate healing. Consequently, there has been growing interest in herbal and polyherbal formulations as safer and more effective alternatives for oral ulcer management. Among medicinal plants, *Psidium guajava* (guava), *Aloe vera*, and *Acacia* species have received considerable attention owing to their extensive traditional use and scientifically validated pharmacological properties. These plants contain diverse phytoconstituents including flavonoids, tannins, polyphenols, polysaccharides, alkaloids, and terpenoids that exhibit antimicrobial, anti-inflammatory, antioxidant, analgesic, immunomodulatory, and wound-healing activities. The combination of these botanicals in an aqueous gel formulation offers a synergistic therapeutic approach by targeting multiple pathological mechanisms involved in ulcer development and healing. Aqueous gels further enhance therapeutic efficacy through prolonged mucosal retention, ease of application, improved patient compliance, and localized drug delivery. This review comprehensively discusses the etiology and pathophysiology of oral ulcers, limitations of conventional treatments, phytochemical and pharmacological profiles of guava, aloe vera, and acacia, scientific rationale for polyherbal combinations, formulation approaches, evaluation parameters, preclinical and clinical evidence, safety considerations, and future perspectives. The available evidence suggests that polyherbal aqueous gels containing guava, aloe vera, and acacia leaves represent a promising, cost-effective, and patient-friendly strategy for oral ulcer management.

Keywords: Oral ulcer; Recurrent aphthous stomatitis; Polyherbal gel; *Psidium guajava*; *Aloe vera*; *Acacia*; Herbal medicine; Wound healing; Anti-inflammatory activity; Antioxidant activity; Oral mucosa; Phytochemicals; Mucoadhesive gel; Oral healthcare; Natural therapeutics; Bioadhesive formulations; Medicinal plants; Ulcer healing; Phytopharmaceuticals; Oral drug delivery.

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1. INTRODUCTION

Oral ulcers are among the most frequently encountered lesions in oral medicine and dental practice. They are characterized by disruption of the oral epithelium accompanied by inflammation of the underlying connective tissue, resulting in pain, discomfort, and impaired oral function. Oral ulcers may occur as isolated lesions or as manifestations of local trauma, infections, autoimmune disorders, nutritional deficiencies, gastrointestinal diseases, hematological abnormalities, and systemic inflammatory conditions [1].

The oral mucosa serves as the primary protective barrier against physical, chemical, and microbial insults. Damage to this barrier initiates a cascade of inflammatory responses involving cytokine release, oxidative stress, and immune cell infiltration, ultimately leading to ulcer formation. Oral ulcers vary in size, duration, and severity, ranging from minor aphthous lesions that heal spontaneously within one to two weeks to major ulcers that persist for several weeks and often result in scarring.

Among oral ulcerative conditions, recurrent aphthous stomatitis (RAS) is the most prevalent. It affects approximately 5–25% of the global population and is characterized by recurrent episodes of painful ulceration on non-keratinized oral

mucosa [5]. The multifactorial etiology of RAS includes genetic predisposition, immune dysregulation, stress, nutritional deficiencies, hormonal fluctuations, and microbial factors.

Conventional treatment primarily aims to reduce pain, suppress inflammation, prevent secondary infection, and accelerate healing. Topical corticosteroids remain the gold standard for managing recurrent aphthous ulcers; however, prolonged use may predispose patients to opportunistic infections, mucosal atrophy, and local irritation. Similarly, antiseptics and antibiotics may alter normal oral microflora and contribute to antimicrobial resistance [2].

Growing awareness of the limitations associated with synthetic medications has stimulated interest in plant-based therapeutics. Medicinal plants have long been employed in traditional healthcare systems due to their efficacy, affordability, accessibility, and favorable safety profiles [9]. Herbal formulations often contain multiple bioactive compounds capable of exerting diverse pharmacological effects simultaneously.

Among medicinal plants, *Psidium guajava* (guava), *Aloe vera*, and *Acacia* species have emerged as promising candidates for oral ulcer management. These plants possess potent antimicrobial, anti-inflammatory, antioxidant, analgesic, and wound-healing properties that directly target the pathological processes involved in ulcer development and progression.

Polyherbal formulations, which combine multiple medicinal plants, are increasingly recognized for their synergistic therapeutic benefits. By integrating guava, aloe vera, and acacia into a single aqueous gel formulation, it becomes possible to achieve comprehensive management of oral ulcers through multiple mechanisms of action. Such formulations can improve therapeutic outcomes while minimizing adverse effects associated with synthetic medications.

This review critically examines the scientific evidence supporting the use of guava, aloe vera, and acacia leaves in polyherbal aqueous gel formulations for oral ulcer management.

2. EPIDEMIOLOGY AND BURDEN OF ORAL ULCERS

Oral ulcers represent a significant global healthcare challenge affecting individuals across all age groups and socioeconomic backgrounds. Their prevalence varies according to geographical location, ethnicity, dietary habits, systemic health conditions, and genetic predisposition.

Recurrent aphthous stomatitis is the most common form of oral ulceration. Epidemiological studies indicate that its prevalence ranges between 5% and 25% in the general population, with higher incidence observed among adolescents and young adults. Females are often more susceptible than males, possibly due to hormonal influences on immune regulation and inflammatory responses [3].

In developing countries, nutritional deficiencies remain important contributors to oral ulcer development. Deficiencies in iron, folic acid, zinc, vitamin B12, and other micronutrients have been associated with impaired epithelial integrity and delayed wound healing [15]. Furthermore, increasing psychological stress associated with modern lifestyles has been identified as a significant risk factor for recurrent ulceration.

The socioeconomic burden of oral ulcers extends beyond clinical symptoms. Frequent ulcer episodes contribute to reduced productivity, absenteeism, decreased nutritional intake, impaired social interactions, and diminished quality of life [4].

Table 01: Classification and Causes of Oral Ulcers

Type of Oral Ulcer	Common Causes	Clinical Characteristics
Recurrent aphthous ulcers	Immune dysfunction, stress, nutritional deficiency	Painful recurrent lesions
Traumatic ulcers	Mechanical injury, dental appliances	Localized ulceration
Infectious ulcers	Viral, bacterial, fungal infections	Associated with infection
Drug-induced ulcers	NSAIDs, chemotherapy agents	Medication-related lesions
Systemic disease-associated ulcers	Crohn's disease, Behçet's syndrome	Chronic recurrent ulcers

As shown in Table 01, oral ulcers arise from diverse etiological factors, necessitating multifaceted therapeutic approaches.

Table 02: Major Risk Factors Associated with Oral Ulcer Development

Risk Factor	Mechanism
Stress	Immune dysregulation
Nutritional deficiency	Impaired epithelial repair
Hormonal changes	Altered inflammatory response
Trauma	Direct mucosal injury

Genetic susceptibility	Increased inflammatory tendency
Microbial infection	Tissue damage and inflammation
Autoimmune disorders	Immune-mediated mucosal destruction

The factors summarized in Table 02 collectively contribute to ulcer initiation, progression, and recurrence.

3. Pathophysiology of Oral Ulcers

The development of oral ulcers is a complex process involving epithelial injury, inflammatory mediator release, oxidative stress, immune activation, and tissue destruction.

The initial stage begins with disruption of the mucosal epithelium due to trauma, infection, immune reactions, or chemical irritation. This disruption triggers activation of keratinocytes and resident immune cells, resulting in the production of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), and interferon-gamma (IFN- γ) [5].

These mediators promote recruitment of neutrophils, macrophages, and lymphocytes to the site of injury. Activated immune cells release reactive oxygen species (ROS), proteolytic enzymes, and additional inflammatory mediators that further damage surrounding tissues.

Oxidative stress plays a critical role in ulcer pathogenesis. Excessive ROS production causes lipid peroxidation, protein oxidation, DNA damage, and cellular apoptosis. These events compromise epithelial regeneration and delay wound healing.

During the healing phase, fibroblasts migrate into the ulcer bed and synthesize extracellular matrix components such as collagen and fibronectin. Simultaneously, angiogenesis restores blood supply to damaged tissues while epithelial cells proliferate and migrate to cover the wound surface [6].

The healing process may be impaired by persistent inflammation, microbial contamination, nutritional deficiencies, or systemic diseases. Therefore, effective oral ulcer management requires interventions capable of suppressing inflammation, controlling microbial growth, scavenging free radicals, and stimulating tissue regeneration [7].

4. Conventional Management and Limitations

Several therapeutic strategies have been employed for oral ulcer management. These interventions primarily aim to alleviate symptoms and promote healing rather than eliminate underlying causes.

Table 03: Conventional Therapeutic Agents Used in Oral Ulcer Management

Drug Class	Examples	Therapeutic Effect	Limitation
Corticosteroids	Triamcinolone, Dexamethasone	Anti-inflammatory	Candidiasis, recurrence
Antiseptics	Chlorhexidine	Antimicrobial	Tooth staining
Analgesics	Lidocaine, Benzocaine	Pain relief	Short duration
Antibiotics	Tetracycline	Infection control	Resistance development
Immunomodulators	Thalidomide	Severe ulcer management	Significant adverse effects

As indicated in Table 03, conventional therapies often provide symptomatic relief but may be associated with considerable limitations.

Corticosteroids remain the most widely prescribed agents for recurrent aphthous ulcers. They suppress inflammatory cytokine production and reduce immune-mediated tissue damage. However, prolonged administration may increase susceptibility to fungal infections and mucosal thinning [8].

Antiseptic mouthwashes such as chlorhexidine help reduce microbial colonization and secondary infections. Nevertheless, long-term use may cause tooth staining, taste disturbances, and mucosal irritation.

These limitations have stimulated the search for safer alternatives capable of providing comprehensive therapeutic benefits.

5. Polyherbal Approach in Oral Ulcer Therapy

The concept of polyherbalism is deeply rooted in traditional systems of medicine. Polyherbal formulations combine multiple medicinal plants to enhance therapeutic efficacy through synergistic interactions among their bioactive constituents [9].

Compared with single-herb preparations, polyherbal formulations offer several advantages:

- Multiple mechanisms of action
- Enhanced efficacy
- Reduced toxicity
- Improved patient outcomes

- Broader therapeutic spectrum

The therapeutic rationale for combining guava, aloe vera, and acacia is based on their complementary pharmacological activities. While guava provides potent antimicrobial and antioxidant effects, aloe vera promotes tissue regeneration and hydration, whereas acacia contributes astringent, antimicrobial, and anti-inflammatory actions.

The combination can simultaneously target microbial infection, oxidative stress, inflammation, pain, and delayed wound healing, making it particularly suitable for oral ulcer management.

6. PSIDIUM GUAJAVA (GUAVA): PHYTOCHEMISTRY AND PHARMACOLOGICAL ACTIVITIES

6.1 Botanical Description

Psidium guajava L., commonly known as guava, belongs to the family Myrtaceae and is widely cultivated throughout tropical and subtropical regions. Different parts of the plant, particularly the leaves, have been extensively used in traditional medicine for the treatment of gastrointestinal disorders, infections, wounds, and inflammatory conditions [10].

6.2 Phytochemical Composition

Guava leaves contain a diverse array of bioactive compounds responsible for their medicinal properties.

Table 04: Major Phytochemical Constituents of Guava Leaves

Phytochemical	Chemical Class	Biological Activity
Quercetin	Flavonoid	Anti-inflammatory
Kaempferol	Flavonoid	Antioxidant
Gallic acid	Phenolic acid	Antimicrobial
Catechin	Polyphenol	Wound healing
Tannins	Polyphenol	Astringent
Saponins	Glycoside	Antimicrobial
Terpenoids	Terpene compounds	Anti-inflammatory

As shown in **Table 04**, guava leaves contain numerous phytochemicals with therapeutic relevance to oral ulcer healing.

6.3 Anti-Inflammatory Activity

Quercetin is considered one of the principal anti-inflammatory compounds in guava leaves. It inhibits cyclooxygenase (COX) and lipoxygenase pathways, thereby reducing the synthesis of inflammatory mediators [10].

6.4 Antioxidant Activity

Guava leaves exhibit strong antioxidant activity due to their high polyphenol content. These compounds neutralize reactive oxygen species and protect tissues from oxidative damage.

Table 05: Pharmacological Activities of Guava Leaves Relevant to Oral Ulcer Management

Activity	Mechanism	Therapeutic Relevance
Antimicrobial	Inhibition of microbial growth	Prevents secondary infection
Anti-inflammatory	Cytokine suppression	Reduces inflammation
Antioxidant	Free radical scavenging	Accelerates healing
Analgesic	Modulation of pain mediators	Pain reduction
Wound healing	Enhanced collagen synthesis	Tissue repair

The activities summarized in **Table 05** support the therapeutic application of guava leaves in oral ulcer management [11].

7. ALOE VERA: PHYTOCHEMISTRY AND THERAPEUTIC POTENTIAL IN ORAL ULCER MANAGEMENT

7.1 Botanical Overview

Aloe vera (*Aloe barbadensis* Miller) is a perennial succulent plant belonging to the family Asphodelaceae. It has been widely utilized in traditional medicine systems for centuries owing to its remarkable wound-healing, anti-inflammatory, antimicrobial, and immunomodulatory properties. The plant is characterized by thick fleshy leaves containing a mucilaginous gel rich in bioactive compounds. The inner gel is the most therapeutically valuable portion and has been extensively investigated for oral healthcare applications.

The medicinal significance of *Aloe vera* arises from its ability to promote tissue regeneration while simultaneously reducing inflammation and microbial colonization. These properties make it particularly useful in managing oral ulcers, gingivitis, periodontal diseases, and oral mucositis.

Recent investigations have demonstrated that *Aloe vera* gel can significantly reduce ulcer size, alleviate pain, and accelerate epithelial regeneration. Its high water content also helps maintain a moist wound environment, which is essential for optimal healing.

7.2 Phytochemical Composition of *Aloe vera*

More than 200 biologically active constituents have been identified in *Aloe vera*. These compounds belong to various phytochemical classes including polysaccharides, anthraquinones, vitamins, enzymes, amino acids, minerals, and phenolic compounds.

Table 06: Major Bioactive Constituents of *Aloe vera* and Their Pharmacological Significance

Constituent	Chemical Class	Pharmacological Activity
Acemannan	Polysaccharide	Wound healing, immunomodulatory
Aloin	Anthraquinone	Antimicrobial
Aloe-emodin	Anthraquinone	Anti-inflammatory
Glucmannan	Polysaccharide	Fibroblast stimulation
Mannose-6-phosphate	Carbohydrate derivative	Tissue regeneration
Vitamin C	Antioxidant vitamin	Free radical scavenging
Vitamin E	Antioxidant vitamin	Membrane protection
Salicylic acid	Phenolic compound	Anti-inflammatory
Magnesium lactate	Mineral complex	Anti-pruritic activity

As shown in **Table 6**, *Aloe vera* contains numerous bioactive constituents that collectively contribute to its therapeutic efficacy in oral ulcer healing [12].

7.3 Anti-Inflammatory Activity

Inflammation is a central pathological feature of oral ulcers. Excessive production of inflammatory cytokines prolongs tissue damage and delays healing.

Aloe vera exerts potent anti-inflammatory effects through several mechanisms:

- Inhibition of cyclooxygenase pathways
- Suppression of prostaglandin synthesis
- Reduction of TNF- α production
- Downregulation of IL-1 β and IL-6
- Modulation of macrophage activity

These actions reduce tissue inflammation and create a favorable environment for healing.

Studies have shown that acemannan and aloe-emodin significantly decrease inflammatory cell infiltration in ulcerated tissues, thereby accelerating tissue repair.

7.4 Wound-Healing Activity

One of the most important properties of *Aloe vera* is its ability to promote wound healing. This activity is primarily attributed to glucmannan and acemannan, which stimulate fibroblast proliferation and collagen synthesis.

Fibroblasts play a critical role in wound healing by producing extracellular matrix proteins that provide structural support for tissue regeneration. Increased fibroblast activity leads to enhanced collagen deposition, angiogenesis, and epithelialization.

Furthermore, *Aloe vera* stimulates growth factor production, including:

- Transforming growth factor-beta (TGF- β)
- Vascular endothelial growth factor (VEGF)
- Fibroblast growth factor (FGF)
- These growth factors facilitate tissue repair and vascular regeneration.

7.5 Antioxidant Activity

Oxidative stress contributes significantly to ulcer pathogenesis and delayed healing. Reactive oxygen species damage cellular membranes, proteins, and DNA, thereby impairing tissue regeneration.

Aloe vera contains several antioxidant compounds, including:

- Vitamins C and E
- Flavonoids
- Polyphenols
- Glutathione peroxidase
- Superoxide dismutase
- These molecules neutralize free radicals and protect oral tissues from oxidative damage.

7.6 Antimicrobial Activity

Microbial colonization can aggravate oral ulcers and prolong healing. *Aloe vera* exhibits broad-spectrum antimicrobial activity against bacteria, fungi, and viruses [13].

Its antimicrobial effects are attributed to:

- Anthraquinones
- Saponins
- Phenolic compounds
- Salicylic acid

These constituents disrupt microbial cell membranes and inhibit microbial proliferation.

- Studies have demonstrated inhibitory activity against several oral pathogens including:
- *Streptococcus mutans*
- *Staphylococcus aureus*
- *Candida albicans*
- *Porphyromonas gingivalis*
- Such activity helps prevent secondary infections during ulcer healing.

Table 07: Therapeutic Activities of *Aloe vera* Relevant to Oral Ulcer Healing

Activity	Mechanism	Clinical Significance
Anti-inflammatory	Cytokine suppression	Reduced ulcer inflammation
Wound healing	Fibroblast stimulation	Faster tissue repair
Antioxidant	Free radical scavenging	Protection against oxidative stress
Antimicrobial	Inhibition of pathogens	Prevention of secondary infection
Immunomodulatory	Regulation of immune responses	Reduced recurrence
Analgesic	Modulation of inflammatory mediators	Pain reduction

The activities summarized in Table 07 demonstrate the multifaceted therapeutic potential of *Aloe vera* in oral ulcer management [14].

8. *Acacia* Species: Phytochemistry and Oral Healthcare Applications

8.1 Botanical Overview

The genus *Acacia* comprises more than 1,000 species distributed worldwide. Several species, particularly *Acacia nilotica* and *Acacia catechu*, have been widely utilized in traditional medicine for treating infections, wounds, inflammation, and oral diseases [15].

The medicinal value of *Acacia* species is largely attributed to their high content of tannins, flavonoids, catechins, and polyphenolic compounds.

Traditionally, *Acacia* extracts have been used as mouth rinses, gargles, and topical applications for oral ulcers, sore throat, gingivitis, and periodontal disorders.

8.2 Phytochemical Composition

Various phytochemicals contribute to the therapeutic effects of *Acacia* species.

Table 08: Major Phytochemical Constituents of *Acacia* Species

Constituent	Chemical Class	Pharmacological Activity
Catechin	Flavonoid	Antioxidant
Epicatechin	Flavonoid	Anti-inflammatory
Gallic acid	Phenolic acid	Antimicrobial
Tannins	Polyphenols	Astringent activity
Quercetin	Flavonoid	Antioxidant
Kaempferol	Flavonoid	Anti-inflammatory
Saponins	Glycosides	Antimicrobial
Terpenoids	Terpenes	Wound healing

As indicated in Table 08, *Acacia* species contain numerous bioactive constituents capable of supporting oral ulcer healing.

8.3 Astringent Activity

One of the distinguishing characteristics of *Acacia* is its high tannin content. Tannins possess strong astringent properties that promote contraction of damaged tissues and formation of a protective layer over ulcerated surfaces [16].

This protective barrier:

- Reduces pain
- Minimizes irritation
- Prevents microbial invasion
- Facilitates epithelial regeneration

Consequently, tannin-rich *Acacia* preparations have long been employed for oral wound care.

8.4 Anti-Inflammatory Activity

Inflammation contributes significantly to ulcer pain and tissue destruction. Flavonoids present in *Acacia* suppress inflammatory pathways by inhibiting cytokine release and reducing leukocyte migration [17].

Experimental studies have demonstrated reductions in:

- TNF- α
- IL-1 β
- Prostaglandins
- Nitric oxide

following administration of *Acacia* extracts.

8.5 Antioxidant Activity

Polyphenols and catechins present in *Acacia* possess strong antioxidant activity. These compounds neutralize reactive oxygen species and reduce oxidative damage within ulcerated tissues [18].

Antioxidant effects contribute to:

- Faster healing
- Reduced inflammation
- Enhanced collagen synthesis
- Improved epithelial regeneration

8.6 Antimicrobial Activity

Numerous studies have reported antimicrobial effects of *Acacia* extracts against oral pathogens.

These effects involve:

- Cell membrane disruption
- Enzyme inhibition
- Protein precipitation
- Biofilm suppression

Such activities are particularly beneficial in preventing secondary infections associated with oral ulcers [19].

Table 09: Pharmacological Properties of *Acacia* Relevant to Oral Healthcare

Pharmacological Property	Mechanism	Clinical Benefit
Astringent activity	Protein precipitation	Protective ulcer covering
Anti-inflammatory activity	Cytokine suppression	Reduced inflammation
Antioxidant activity	ROS scavenging	Enhanced healing
Antimicrobial activity	Pathogen inhibition	Infection prevention
Wound-healing activity	Collagen stimulation	Tissue regeneration
Analgesic activity	Reduction of inflammatory mediators	Pain relief

The activities shown in Table 09 support the therapeutic role of *Acacia* species in oral ulcer management [20].

9. Scientific Rationale for Combining Guava, Aloe Vera, and Acacia

Polyherbal formulations are based on the principle that combining medicinal plants can produce synergistic therapeutic effects superior to those obtained from individual herbs [21].

The combination of guava, aloe vera, and acacia is particularly attractive because each plant contributes distinct yet complementary pharmacological activities.

Guava primarily provides:

- Antimicrobial activity
- Antioxidant protection
- Anti-inflammatory effects

Aloe vera contributes:

- Tissue regeneration
- Moist wound environment
- Immunomodulation

Acacia contributes:

- Astringent activity
- Protective barrier formation
- Additional antimicrobial effects

Together, these plants target virtually all major pathological mechanisms involved in oral ulcer development and healing [22].

Table 10: Synergistic Therapeutic Mechanisms of Guava–Aloe Vera–Acacia Combination

Therapeutic Target	Guava	Aloe vera	Acacia
Antimicrobial activity	✓	✓	✓
Anti-inflammatory activity	✓	✓	✓
Antioxidant activity	✓	✓	✓
Wound healing	✓	✓✓	✓
Tissue regeneration	✓	✓✓✓	✓
Astringent effect	—	—	✓✓✓
Moisturization	—	✓✓✓	—
Pain reduction	✓	✓	✓

As demonstrated in Table 10, the three plants provide complementary therapeutic benefits that collectively support oral ulcer healing [23].

10. Development of Polyherbal Aqueous Gel Formulations

10.1 Advantages of Aqueous Gel Systems

Topical oral gels offer several advantages over mouthwashes and conventional dosage forms:

- Prolonged mucosal contact
- Localized drug delivery
- Reduced systemic exposure
- Enhanced patient compliance
- Controlled release of active compounds

These characteristics make gels particularly suitable for oral ulcer treatment [24].

10.2 Selection of Plant Material

The quality of herbal formulations depends heavily on the quality of plant materials used. Leaves selected for extraction should be:

- Disease free
- Properly authenticated
- Collected during appropriate seasons
- Adequately dried and stored

Standardization is essential to ensure batch-to-batch consistency [25].

10.3 Preparation of Aqueous Extracts

Aqueous extraction is preferred because:

- It is safe
- It avoids organic solvent residues
- It mimics traditional medicinal preparations
- It preserves hydrophilic phytochemicals

The general procedure includes:

1. Washing plant materials.
2. Shade drying.
3. Pulverization.
4. Aqueous extraction.
5. Filtration.
6. Concentration.
7. Storage under refrigerated conditions.

10.4 Selection of Gel Base

The gel base significantly influences formulation stability and performance.

Commonly used polymers include:

- Carbopol 934
- Carbopol 940
- Hydroxypropyl methylcellulose (HPMC)
- Sodium carboxymethyl cellulose
- Xanthan gum

Among these, Carbopol-based gels are widely preferred because of their excellent bioadhesive properties and favorable rheological characteristics [26].

10.5 Formulation Components

Table 11: Typical Composition of Polyherbal Aqueous Oral Gel

Ingredient	Function
Guava leaf extract	Antimicrobial and antioxidant
Aloe vera extract	Wound healing
Acacia leaf extract	Astringent and anti-inflammatory
Carbopol 934	Gelling agent
Glycerin	Humectant
Propylene glycol	Solubilizer
Methyl paraben	Preservative
Triethanolamine	pH adjustment
Purified water	Vehicle

The ingredients listed in Table 11 collectively contribute to formulation stability and therapeutic efficacy [27].

11. Evaluation Parameters of Polyherbal Aqueous Gel Formulations

The successful development of a polyherbal aqueous gel requires comprehensive evaluation to ensure quality, stability, safety, and therapeutic efficacy. Physicochemical characterization is essential because formulation variables significantly influence drug release, mucoadhesion, patient acceptability, and clinical performance [28].

Evaluation parameters commonly assessed include appearance, homogeneity, pH, viscosity, spreadability, extrudability, drug content, mucoadhesive strength, stability, and microbial quality.

11.1 Organoleptic Evaluation

Organoleptic characteristics provide preliminary information regarding formulation acceptability and quality.

The following parameters are generally assessed:

- Color
- Odor
- Texture
- Appearance
- Consistency
- Homogeneity

An ideal oral gel should possess a smooth texture, uniform appearance, pleasant odor, and absence of grittiness. These characteristics improve patient compliance and facilitate application over ulcerated mucosal surfaces [29].

11.2 pH Determination

The pH of oral gels is particularly important because extreme pH values may cause irritation and discomfort.

The normal oral cavity pH generally ranges from 6.2 to 7.6. Therefore, herbal gels intended for oral application should possess a pH close to physiological conditions [30].

Maintaining an appropriate pH also contributes to:

- Stability of phytoconstituents
- Patient comfort
- Preservation of oral microflora
- Enhanced wound healing

11.3 Viscosity Measurement

Viscosity determines the rheological behavior of the gel and directly influences retention time at the site of application.

An ideal oral gel should possess sufficient viscosity to remain localized while allowing easy spreading over the lesion [31].

Higher viscosity generally results in:

- Increased residence time
- Improved bioavailability
- Enhanced patient convenience
- However, excessively viscous formulations may hinder uniform application and reduce patient acceptance.

11.4 Spreadability

Spreadability indicates the ease with which a gel can be distributed over the oral mucosa.

Good spreadability ensures:

- Uniform coverage
- Reduced mechanical irritation
- Improved therapeutic performance
- Spreadability is usually evaluated by measuring the time required for two glass plates to separate under standardized conditions [32].

11.5 Extrudability

Extrudability refers to the ease with which the gel can be expelled from its container or tube.

An ideal formulation should:

- Extrude easily
- Maintain structural integrity
- Avoid leakage during storage
- Appropriate extrudability contributes significantly to patient convenience and dosage uniformity [33].

11.6 Drug Content Uniformity

Uniform distribution of herbal extracts throughout the formulation is critical for therapeutic consistency.

Drug content analysis ensures:

- Accurate dosing
- Batch-to-batch consistency
- Quality assurance

Spectrophotometric and chromatographic techniques are commonly employed for this purpose [79].

11.7 Mucoadhesive Strength

Mucoadhesion is one of the most important properties of oral gels.

Strong mucoadhesion provides:

- Prolonged contact time
- Improved drug absorption
- Reduced dosing frequency
- Enhanced clinical efficacy

Mucoadhesive polymers such as Carbopol and HPMC contribute significantly to formulation performance [34].

11.8 Stability Studies

Stability testing evaluates the ability of a formulation to maintain its quality during storage.

Parameters monitored include:

- Appearance
- pH
- Viscosity
- Drug content
- Microbial contamination

Accelerated stability studies are generally conducted according to regulatory guidelines to predict shelf life [35].

Table 12: Physicochemical Evaluation Parameters of Polyherbal Oral Gels

Parameter	Significance
Appearance	Patient acceptability
Homogeneity	Uniformity of formulation
pH	Oral compatibility
Viscosity	Retention and application
Spreadability	Ease of administration
Extrudability	User convenience
Drug content	Dosage accuracy
Mucoadhesion	Prolonged retention
Stability	Shelf-life prediction
Microbial limit test	Product safety

The parameters listed in Table 12 are routinely employed to assess the quality and performance of polyherbal oral gel formulations [36].

12. Preclinical Evidence Supporting Polyherbal Oral Gel Formulations

Preclinical studies provide essential evidence regarding the safety and efficacy of herbal formulations before clinical application.

Numerous investigations have demonstrated the therapeutic potential of guava, aloe vera, and acacia extracts individually and in combination.

12.1 In Vitro Antimicrobial Studies

Oral ulcers are frequently associated with microbial colonization, which may delay healing and aggravate inflammation. Studies have shown that guava leaf extracts exhibit inhibitory activity against:

- *Streptococcus mutans*
- *Staphylococcus aureus*
- *Escherichia coli*
- *Candida albicans* [37].

Similarly, aloe vera demonstrates broad-spectrum antimicrobial activity owing to its anthraquinones and phenolic compounds [38].

Acacia extracts have also shown effectiveness against oral pathogens through tannin-mediated protein precipitation and membrane disruption mechanisms [39].

The combined antimicrobial activities of these plants may significantly reduce microbial burden within ulcerated tissues.

12.2 Antioxidant Studies

Oxidative stress is recognized as a major contributor to ulcer progression.

Experimental investigations have reported strong antioxidant activity for all three plants using assays such as:

- DPPH radical scavenging
- ABTS assay
- Ferric reducing antioxidant power assay
- Lipid peroxidation inhibition assay
- Polyphenols, flavonoids, and polysaccharides are primarily responsible for these effects [40].

12.3 Anti-Inflammatory Studies

Several experimental models have demonstrated the anti-inflammatory potential of guava, aloe vera, and acacia.

Reported mechanisms include:

- Suppression of TNF- α
- Reduction of IL-1 β
- Inhibition of prostaglandin synthesis
- Downregulation of COX-2 expression

These activities are directly relevant to oral ulcer healing [41].

12.4 Wound-Healing Studies

Animal studies consistently demonstrate accelerated wound closure following treatment with extracts of guava, aloe vera, and acacia [42].

Reported outcomes include:

- Increased collagen deposition
- Enhanced fibroblast proliferation
- Improved epithelialization
- Increased angiogenesis
- Reduced inflammatory infiltration

These findings strongly support the use of these botanicals in oral ulcer therapy.

Table 13: Summary of Preclinical Studies on Guava, Aloe Vera, and Acacia

Plant	Study Type	Major Findings
Guava	Antimicrobial study	Inhibition of oral pathogens
Guava	Wound-healing study	Increased collagen synthesis
Aloe vera	Ulcer-healing study	Accelerated epithelialization
Aloe vera	Anti-inflammatory study	Reduced cytokine production
Acacia	Antimicrobial study	Reduced microbial growth
Acacia	Antioxidant study	Strong free radical scavenging
Polyherbal combination	Experimental wound model	Enhanced healing compared with individual extracts

The studies summarized in Table 13 collectively support the therapeutic potential of polyherbal oral gel formulations [43].

13. Clinical Evidence

Although most evidence originates from experimental studies, clinical investigations involving guava, aloe vera, and acacia have yielded encouraging results.

13.1 Clinical Studies on Aloe Vera

Several randomized clinical trials have investigated aloe vera gel in patients with recurrent aphthous stomatitis.

Reported benefits include:

- Reduced pain intensity

- Faster healing
- Decreased ulcer size
- Improved patient satisfaction

Many studies have shown outcomes comparable to standard topical corticosteroids [44].

13.2 Clinical Studies on Guava

Guava leaf preparations have been traditionally employed as mouth rinses and topical applications.

- Clinical observations indicate:
- Reduction in oral microbial load
- Improved wound healing
- Decreased inflammation

These effects are attributed to the plant's antimicrobial and antioxidant properties [45].

13.3 Clinical Studies on Acacia

Clinical investigations involving acacia-containing formulations have demonstrated improvements in:

- Gingival inflammation
- Oral wound healing
- Microbial control

Its high tannin content contributes significantly to tissue protection and repair [46].

13.4 Potential Clinical Benefits of Polyherbal Gels

The combination of guava, aloe vera, and acacia may offer several advantages over single-herb preparations:

- Broader pharmacological activity
- Faster healing
- Reduced recurrence
- Enhanced patient compliance
- Lower risk of adverse effects

However, large-scale multicenter clinical trials remain necessary to establish definitive efficacy and safety profiles [47].

Table 14: Summary of Clinical Findings Relevant to Oral Ulcer Management

Plant	Clinical Outcome
Guava	Reduced inflammation and microbial burden
Aloe vera	Faster healing and pain reduction
Acacia	Improved tissue repair
Polyherbal formulations	Potential synergistic healing effects

As shown in **Table 14**, existing clinical evidence supports the therapeutic utility of these medicinal plants in oral healthcare [48].

14. Safety and Toxicological Considerations

Safety is a critical consideration in herbal formulation development.

14.1 Acute Toxicity

Studies have generally demonstrated low toxicity for guava, aloe vera, and acacia extracts when used at therapeutic concentrations [49].

14.2 Local Irritation

Topical herbal formulations should be evaluated for:

1. Mucosal irritation
2. Allergic reactions
3. Sensitization
4. Most investigations have reported excellent tolerability for these botanicals [50].

14.3 Microbial Safety

Herbal products are susceptible to microbial contamination during:

- Collection
- Processing
- Storage

Therefore, adherence to good manufacturing practices is essential [51].

14.4 Standardization Challenges

Variability in phytochemical composition may arise due to:

- Geographic location
- Climate
- Harvesting season
- Extraction method

Standardization is therefore essential to ensure consistent therapeutic outcomes [52].

15. Regulatory Considerations and Quality Control

The growing popularity of herbal medicines has prompted regulatory agencies worldwide to establish quality standards for herbal products.

Important regulatory requirements include:

- Botanical authentication
- Phytochemical standardization
- Safety assessment
- Stability testing
- Microbial limit testing
- Packaging validation

Organizations such as the World Health Organization (WHO) have issued guidelines for quality control and standardization of herbal medicines [53].

16. Future Perspectives

The future development of polyherbal aqueous gels for oral ulcer management is likely to focus on improving efficacy, stability, and patient acceptability.

Several emerging technologies may enhance therapeutic outcomes.

16.1 Mucoadhesive Drug Delivery Systems

Advanced mucoadhesive systems can prolong retention time and improve localized delivery of phytoconstituents [54].

16.2 Nanotechnology-Based Herbal Formulations

Nanoparticles, nanogels, and nanoemulsions may improve:

- Stability
- Bioavailability
- Penetration into tissues
- Controlled release properties

Such approaches could significantly enhance the effectiveness of herbal oral gels [55].

16.3 Standardized Phytopharmaceuticals

Future research should focus on identifying bioactive markers for:

- Guava
- Aloe vera
- Acacia

This will facilitate reproducible manufacturing and regulatory approval [56].

16.4 Clinical Translation

Well-designed randomized controlled trials are needed to establish:

- Optimal formulation composition
- Dosage regimen
- Long-term safety
- Comparative effectiveness

Such evidence will be crucial for widespread clinical adoption [57].

Table 15: Advantages and Limitations of Polyherbal Oral Gels

Advantages	Limitations
Multiple mechanisms of action	Variability in plant composition
Reduced adverse effects	Standardization challenges
Improved patient compliance	Limited large-scale clinical studies
Cost-effective therapy	Stability concerns
Enhanced wound healing	Regulatory complexity
Broad antimicrobial spectrum	Need for quality control

The information presented in Table 15 highlights both the opportunities and challenges associated with polyherbal oral gel development [58].

17. CONCLUSION

Oral ulcers remain a prevalent and clinically significant condition that adversely affects patient comfort, nutrition, communication, and overall quality of life. Despite the availability of conventional therapeutic agents, limitations such as adverse effects, recurrence, antimicrobial resistance, and inadequate healing continue to encourage the search for safer and more effective alternatives.

The present review demonstrates that *Psidium guajava*, *Aloe vera*, and *Acacia* species possess substantial therapeutic potential for oral ulcer management. Their phytochemical constituents exhibit antimicrobial, anti-inflammatory, antioxidant, analgesic, immunomodulatory, and wound-healing activities that directly target the major pathological processes involved in ulcer formation and progression.

The integration of these medicinal plants into a polyherbal aqueous gel formulation offers a rational and scientifically supported therapeutic strategy. Guava contributes potent antimicrobial and antioxidant effects, aloe vera enhances tissue regeneration and epithelial repair, while acacia provides astringent, anti-inflammatory, and protective actions. Together, these plants exhibit complementary and potentially synergistic effects that may improve healing outcomes compared with individual herbal therapies.

Aqueous gel formulations further enhance therapeutic efficacy by providing prolonged mucosal contact, localized drug delivery, improved patient compliance, and reduced systemic exposure. Available preclinical and clinical evidence supports the effectiveness and safety of these botanicals; however, additional standardized studies and large-scale clinical trials are required to validate their long-term therapeutic value.

Overall, polyherbal aqueous gels containing guava, aloe vera, and acacia leaves represent a promising, affordable, safe, and patient-friendly approach for oral ulcer management and warrant further pharmaceutical and clinical development.

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CONFLICT OF INTEREST

Not applicable

INFORM CONSENT AND ETHICAL DECLARATIONS

Not Applicable

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