



## Plant-Based Interventions for Cold Sores: The Role of Peppermint Oil and Liquorice Root in Topical Delivery Systems

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### ABSTRACT

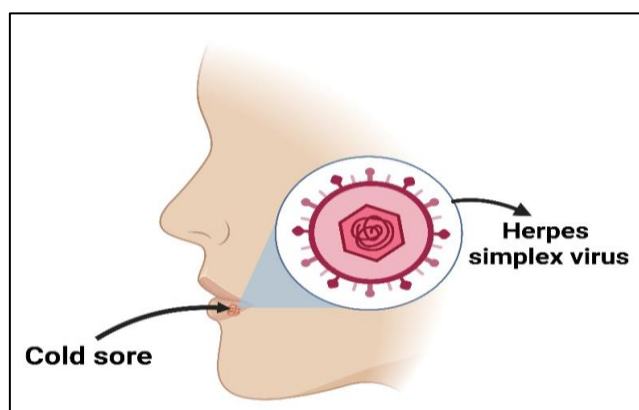
Cold sores, primarily caused by Herpes Simplex Virus type 1 (HSV-1), remain a prevalent viral infection with recurrent episodes and significant psychosocial impact. Current treatment options, including systemic and topical antivirals, provide only partial relief and are limited by issues such as drug resistance, cost, and side effects. In recent years, plant-based interventions have emerged as promising alternatives owing to their broad pharmacological activity and safety profile. This review highlights the therapeutic role of peppermint oil (*Mentha piperita*) and liquorice root (*Glycyrrhiza glabra*) in topical gel delivery systems for cold sore management. Both botanicals demonstrate potent antiviral, anti-inflammatory, antioxidant, and analgesic properties that target multiple stages of HSV infection, while enhancing patient comfort and healing. Their incorporation into bio-adhesive gel formulations offers localized action, improved compliance, and minimal systemic toxicity. Plant-based gels thus represent a sustainable, cost-effective, and patient-friendly approach to managing recurrent herpes labialis.

**Keywords:** Herpes simplex virus, cold sores, peppermint oil, liquorice root, topical gels, plant-based antivirals, HSV-1 therapy, natural remedies

### INTRODUCTION

Cold sores, commonly known as herpes simplex labialis (HSL), are a common viral illness caused largely by Herpes Simplex Virus type 1 (HSV-1) and, less often, HSV-2[1]. This infection manifests as recurrent vesicular eruptions predominantly around the lips and perioral region. HSV-1 is a double-stranded DNA virus from the Herpesviridae family, establishing lifelong latency in sensory ganglia after initial exposure[2]. Periodic reactivation of the virus, often triggered by environmental or physiological stressors, results in the symptomatic presentation of cold sores. HSV-1 is a highly contagious virus that is most commonly transmitted through direct contact with infected saliva, mucous membranes, or skin. The worldwide burden of HSL is significant, with seroprevalence estimates indicating that more than two-thirds of the world's population under the age of 50 has HSV-1[3]. HSL, although typically self-limiting in immunocompetent persons, may cause severe pain, social stigma, and problems in immunocompromised patients. The primary infection with HSV-1 usually occurs during childhood through direct contact with infected saliva or skin, often via kissing, sharing utensils, or other close personal interactions[4]. Upon initial exposure, the virus infects epithelial cells at the site of entry-typically the lips or surrounding skin-and then travels via sensory neurons to the trigeminal ganglion, where it establishes lifelong latency[5]. During latency, the viral genome persists in a non-replicating form, evading immune surveillance. The disorder develops through distinct clinical phases, starting with prodromal tingling or burning, then vesicle production, ulceration, and crusting, and finally healing[6]. HSV-1's capacity to elude host immune responses and establish latency in the trigeminal ganglion from a pathophysiological perspective serves as a reminder of the difficulty in achieving complete viral eradication[7]. Recurrences are frequent and can be influenced by a variety of factors, including immunosuppression, fatigue, hormonal fluctuations, ultraviolet (UV) exposure, and fever. It is crucial to note that recurrent infections may also be linked to secondary bacterial superinfections and impaired skin barrier function. Herpes Simplex Virus (HSV), a member of the Herpesviridae family, is a large, enveloped, double-stranded DNA virus responsible for herpes simplex infections, with HSV-1 primarily causing orofacial lesions such as cold sores (herpes simplex labialis)[8]. Structurally, the virus comprises a DNA core, icosahedral capsid, protein-rich tegument, and a glycoprotein-studded envelope, all contributing to its infectivity and immune evasion. HSV exhibits a biphasic life cycle consisting of a lytic phase-where active viral replication, cell lysis, and lesion formation occur-and a latent phase, in which the virus resides dormant in sensory ganglia like the trigeminal ganglion[9]. The virus has developed several immune evasion strategies, including downregulation of MHC class I molecules, inhibition of interferon responses, and expression of latency-associated transcripts, enabling persistent infection. HSV-1 infection is one of the most prevalent viral infections worldwide, with an estimated 3.7 billion people under the age of 50 (approximately 67% of the global population) infected, according to the World Health Organization

(WHO)[10]. The prevalence varies significantly across regions, age groups, and socioeconomic strata. In developing countries and lower-income populations, primary HSV-1 infection typically occurs during childhood through non-sexual transmission, such as contact with infected saliva or household surfaces. In contrast, in higher-income settings with improved hygiene, initial exposure often occurs later in adolescence or adulthood, sometimes through oral-genital contact, which has led to an increasing number of genital herpes cases caused by HSV-1. The seroprevalence is generally higher in Africa and Southeast Asia (above 90%) and lower in North America and Europe (40–60%). Epidemiological data show that HSV-1 infection is more common in females than males, potentially due to biological and behavioural factors. Moreover, recurrent herpes labialis affects approximately 20–40% of HSV-1-infected individuals, with 2 to 3 episodes annually being typical in otherwise healthy persons[11].



**Fig.1. Represent Cold Sore**

## CLINICAL MANIFESTATION

Herpes simplex labialis (HSL) follows a well-characterized pattern of clinical presentation, which includes distinct stages that unfold over a period of 7–14 days. The clinical manifestations are typically localized but can vary in severity based on the individual's immune status, history of HSV-1 infection, and presence of triggering factors.

### Stages of Cold Sore Development

The symptomatic progression of cold sores can be divided into five major stages:

- 1. Prodromal Stage (0–24 hours):** This is the earliest stage, marked by tingling, itching, burning, or tightness at the site where the lesion will eventually develop, most commonly on the lips or perioral skin. This phase reflects viral reactivation and migration along the sensory nerves to the skin.
- 2. Inflammatory and Erythematous Stage (Day 1–2):** Localized redness and swelling appear as the immune response is activated. The site becomes sensitive, and minor discomfort may increase as vesicle formation begins.
- 3. Vesicular Stage (Day 2–3):** Small, fluid-filled blisters (vesicles) form, often in clusters. These vesicles contain infectious viral particles and are a primary source of viral shedding. The area becomes painful and visibly inflamed.
- 4. Ulcerative Stage (Day 3–5):** Vesicles rupture, leading to shallow ulcers that may weep clear or yellow fluid. This stage is typically the most painful and is associated with the greatest risk of secondary bacterial infection.
- 5. Crusting and Healing Stage (Day 5–10):** Lesions dry out, forming yellowish-brown crusts. Eventually, scabs fall off, and healing is complete, usually without scarring unless there has been secondary infection or trauma[12].

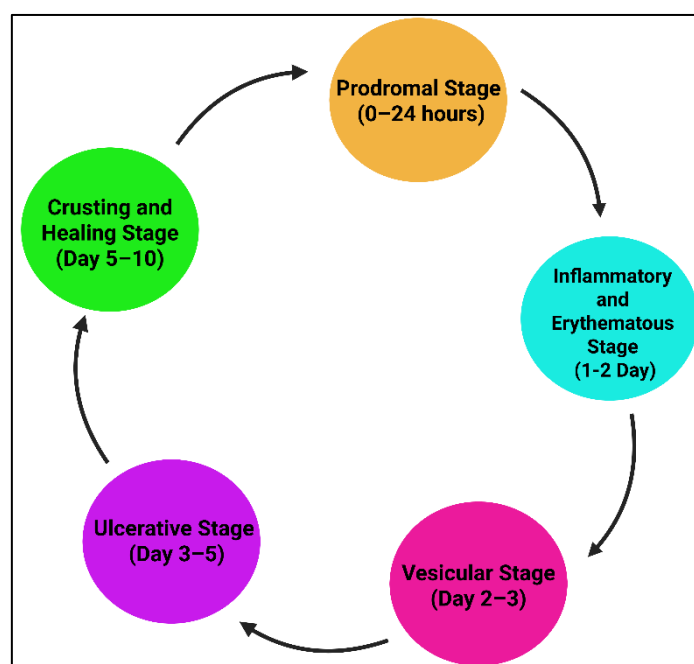


Fig.2. Represent Cold Sore

### Recurrent vs. Primary Infection

Primary HSV-1 infections may be asymptomatic or result in acute herpetic gingivostomatitis, particularly in children. This is a more severe condition characterized by widespread oral lesions, fever, malaise, and lymphadenopathy while recurrent infections are generally milder, more localized, and shorter in duration. They are often predictable in individuals with known triggers and may occur multiple times per year[13].

### Associated Symptoms

- Local pain or tenderness
- Mild fever or malaise (in some cases)
- Cervical or submandibular lymphadenopathy (occasionally)
- Psychosocial impact (e.g., embarrassment, anxiety)

### CURRENT TREATMENT OPTIONS AND LIMITATIONS

The management of herpes simplex labialis (cold sores) primarily focuses on relieving symptoms, accelerating lesion healing, reducing the duration of viral shedding, and preventing recurrence. The current standard of care includes topical and systemic antiviral agents, most notably acyclovir, penciclovir, valacyclovir, and famciclovir, which act by inhibiting viral DNA polymerase and preventing viral replication. Among these, topical formulations of acyclovir and penciclovir are widely used for mild or localized infections, offering moderate benefits when applied during the prodromal stage[14]. Systemic antivirals, such as valacyclovir and famciclovir, are more effective in reducing the duration and severity of symptoms, particularly in recurrent or severe cases, but they require prescription and may not be accessible or affordable in low-resource settings. Despite their efficacy, these antivirals are associated with several limitations: their effectiveness is time-sensitive, requiring early initiation; they do not eliminate latent virus, thus failing to prevent future outbreaks and they may cause adverse effects such as gastrointestinal disturbances, headaches, and in rare cases, nephrotoxicity or hypersensitivity reactions[15]. Additionally, prolonged or frequent use of antivirals can lead to the emergence of drug-resistant HSV strains, especially in immunocompromised patients. Over-the-counter treatments like docosanol, zinc oxide, or local anesthetics provide symptomatic relief but lack virucidal activity. These limitations highlight the need for alternative therapeutic approaches that are not only safe, effective and affordable but also target multiple aspects of the infection, such as inflammation, pain, viral replication, and healing[16]. In recent years, there has been a growing interest in herbal and plant-



based therapies as alternatives or adjuncts to conventional pharmaceuticals for the treatment of various viral infections, including herpes simplex labialis (cold sores). This shift is largely driven by the limitations of current antiviral drugs, such as the inability to target latent HSV infections, the emergence of drug-resistant viral strains, potential side effects, and the cost of long-term therapy. Furthermore, the global resurgence of interest in natural medicine, along with increased consumer preference for holistic and minimally processed treatments, has fueled the exploration of phytochemicals for dermatological and viral conditions[17]. Plant-derived compounds are often rich in bioactive constituents such as flavonoids, alkaloids, terpenes, polyphenols, and glycosides, many of which exhibit antiviral, anti-inflammatory, antioxidant, and immunomodulatory properties. Several in vitro and in vivo studies have demonstrated the ability of plant extracts to interfere with viral adsorption, entry, replication, and protein synthesis—mechanisms critical to HSV pathogenesis[18]. Additionally, some botanicals may enhance wound healing and provide symptomatic relief by reducing pain, swelling, and erythema. Notable among these are peppermint oil (*Mentha piperita*), which contains menthol and exhibits strong antiviral and cooling effects, and liquorice root (*Glycyrrhiza glabra*), rich in glycyrrhizin, known for its potent antiviral and anti-inflammatory action against HSV[19]. As research advances, the integration of these botanicals into topical gel formulations is being explored for their potential to deliver targeted, localized relief with minimal side effects. This phototherapeutic approach represents a promising, sustainable, and culturally accepted avenue for managing recurrent HSV infections, especially in populations with limited access to conventional healthcare or those seeking natural alternatives.

### Mechanisms of Antiviral Action

Plant-derived compounds combat HSV-1 infection through multifaceted mechanisms, targeting several stages of the viral life cycle:

- **Viral Entry Inhibition:** Compounds like menthol in peppermint oil and glycyrrhizin in liquorice root can block viral glycoproteins (e.g., gB and gD) from binding to host cell receptors, preventing virus-cell fusion and entry.
- **Suppression of Viral Replication:** Flavonoids and triterpenoids found in many plant extracts interfere with viral DNA polymerase activity, thereby reducing replication of viral DNA in infected cells.
- **Latency Interruption:** Some phytochemicals have shown potential to affect viral latency genes, which may help reduce reactivation, although this area is still under investigation.
- **Anti-inflammatory Effects:** HSV-induced inflammation exacerbates symptoms. Plant polyphenols like liquiritigenin and luteolin reduce the expression of pro-inflammatory cytokines (e.g., IL-6, TNF- $\alpha$ ), mitigating tissue damage.
- **Antioxidant Activity:** Oxidative stress plays a role in HSV pathogenesis. Many plant-based compounds scavenge free radicals and enhance endogenous antioxidant defense systems.
- **Immune Modulation:** Some herbs stimulate innate immunity by enhancing interferon production and macrophage activity, improving the host's antiviral response.

These multifactorial actions provide a broader therapeutic window compared to the mono-targeted action of synthetic antivirals[20].

### Benefits Over Synthetic Antivirals

Plant-based compounds offer several advantages over traditional antiviral medications:

- **Lower Risk of Resistance:** Unlike synthetic antivirals which often target a single viral enzyme (e.g., DNA polymerase), phytochemicals act on multiple targets, making the development of resistance less likely.
- **Fewer Side Effects:** Herbal compounds used topically are generally well-tolerated and have a low incidence of adverse effects, especially when compared to systemic antivirals that can cause gastrointestinal or renal toxicity.
- **Cost-Effectiveness and Accessibility:** Many medicinal plants are locally available and inexpensive, making them particularly attractive in low- and middle-income countries where access to pharmaceuticals is limited.
- **Synergistic Effects:** Herbal formulations often contain multiple active constituents that act synergistically, enhancing efficacy while reducing the dose of each component.
- **Enhanced Patient Acceptance:** Due to rising interest in natural, organic, and holistic therapies, patients may be more compliant with plant-based treatments, especially for recurring conditions like cold sores.



- **Additional Therapeutic Properties:** Besides antiviral action, these compounds often exhibit analgesic, wound-healing, and soothing effects, offering comprehensive symptomatic relief.

These benefits position plant-based formulations, such as peppermint oil and liquorice root gels, as effective and patient-friendly options in the long-term management of HSV-1 infections[21].

### Peppermint Oil (*Mentha piperita*): A Natural Antiviral Agent

Peppermint oil, derived from the leaves of *Mentha piperita*, is a well-known essential oil widely recognized for its cooling, analgesic, anti-inflammatory, and antimicrobial properties. Its antiviral potential has been increasingly explored in recent years, especially in the treatment of herpes simplex virus type 1 (HSV-1), the causative agent of cold sores[22]. The primary active constituents of peppermint oil include menthol, menthone, menthyl acetate, and limonene, which contribute to its broad-spectrum antiviral activity. In vitro studies have demonstrated that peppermint oil exerts a virucidal effect against HSV-1, especially when applied during the early stages of infection[23]. Menthol, the key component, is believed to disrupt the lipid envelope of the virus, interfering with viral attachment and entry into host cells. Additionally, peppermint oil has been reported to inhibit viral replication and reduce plaque formation in infected cell cultures. Apart from its direct antiviral action, peppermint oil provides symptomatic relief by acting on sensory nerve endings, thereby alleviating pain, itching, and burning commonly associated with cold sores[24]. Its anti-inflammatory activity helps reduce local swelling and redness, while the antioxidant properties protect surrounding tissues from oxidative stress induced by the viral infection. When incorporated into a topical gel formulation, peppermint oil not only enhances patient comfort through its cooling sensation but also promotes localized antiviral effects with minimal systemic absorption[25]. Furthermore, it has a favorable safety profile, making it suitable for repeated application in recurrent infections. The natural origin, multifaceted action, and ease of integration into topical systems make peppermint oil a promising candidate for complementary or alternative therapy in the management of herpes labialis. Peppermint oil exhibits significant antiviral activity against HSV-1 through multiple mechanisms. One of its primary modes of action involves the disruption of the viral lipid envelope, impairing the virus's ability to attach and penetrate host cells[26]. Studies have shown that pre-treatment of viral particles with peppermint oil leads to a substantial reduction in viral infectivity, especially when applied at the early stages of infection. Key constituents such as menthol and menthone have been reported to interfere with glycoprotein-mediated fusion between the viral envelope and the host cell membrane[27]. Additionally, peppermint oil may inhibit the expression of immediate early (IE) genes crucial for viral replication and spread. Beyond entry inhibition, it may exert virustatic effects by hindering the replication of viral DNA or disrupting protein synthesis. These actions collectively reduce plaque formation, limit lesion development, and shorten the duration of outbreaks, making peppermint oil an effective topical agent in cold sore management[28]. In addition to its antiviral effects, peppermint oil offers pronounced anti-inflammatory and analgesic benefits, which are vital in alleviating the discomfort and visible symptoms of cold sores[29]. Menthol, a major bioactive component, activates TRPM8 receptors, producing a cooling sensation that helps relieve itching, burning, and pain[30]. This sensory modulation contributes to a rapid improvement in patient comfort. Furthermore, peppermint oil has been shown to suppress the release of pro-inflammatory mediators such as interleukin-1 $\beta$  (IL-1 $\beta$ ), tumor necrosis factor-alpha (TNF- $\alpha$ ), and prostaglandin E2 (PGE2), which are typically elevated during HSV-induced inflammation. Its antioxidant activity, attributed to polyphenolic constituents also helps counter oxidative stress at the site of infection, reducing tissue damage and promoting faster healing. Together, these properties enhance the overall therapeutic potential of peppermint oil as a multifunctional agent in cold sore treatment[31].

### Safety and Toxicity Profile

Peppermint oil is generally recognized as safe for topical use, particularly in diluted forms as found in gels, ointments, or creams. The essential oil is well-tolerated by the skin when used in concentrations ranging from 1% to 5%, although higher concentrations may cause local irritation, burning, or allergic contact dermatitis in sensitive individuals[32]. Adverse reactions are rare and typically mild when formulations are prepared according to recommended guidelines. Menthol-containing products should be used with caution around the eyes and mucous membranes to avoid irritation[33]. In clinical and cosmetic use, peppermint oil has shown a low toxicity profile with minimal systemic absorption when applied topically, making it suitable for repeated short-term application, especially in the context of recurrent herpes labialis. Nevertheless, it is advised to conduct a patch test prior to use, particularly for individuals with a history of essential oil sensitivity or dermatological conditions. Overall, when properly formulated, peppermint oil offers a safe, natural, and effective alternative for managing the symptoms of HSV-1 infections[34].

### Liquorice Root (*Glycyrrhiza glabra*): A Traditional Remedy for Skin Infections

Liquorice root (*Glycyrrhiza glabra*), an ancient herbal remedy used in traditional systems of medicine such as Ayurveda, Traditional Chinese Medicine, and Unani, has garnered significant scientific attention for its therapeutic benefits in treating viral and inflammatory skin conditions, including herpes simplex labialis[35]. This medicinal plant is rich in pharmacologically active compounds that exhibit a broad spectrum of biological activities including antiviral, anti-inflammatory, antioxidant, antimicrobial



and immunomodulatory effects. Its use in dermatology has been widely explored, particularly in topical preparations aimed at alleviating cold sore symptoms and preventing recurrences[36]. The therapeutic potential of liquorice root is largely attributed to its major bioactive constituent, glycyrrhizin, a triterpenoid saponin glycoside known for its potent antiviral and anti-inflammatory properties. Upon hydrolysis in the body, glycyrrhizin yields glycyrrhetic acid, which also exhibits strong biological activity. In addition to glycyrrhizin, the root contains flavonoids (liquiritigenin, isoliquiritigenin), coumarins, glabridin, and other phenolic compounds that contribute to its therapeutic profile[37]. These phytochemicals not only exert antiviral actions but also provide soothing, healing, and protective effects on skin tissue affected by HSV infection.

Glycyrrhizin has demonstrated significant antiviral activity against HSV-1 and HSV-2 in various in vitro studies. It acts by inhibiting viral replication, reducing viral gene expression, and interfering with virus-host interactions at multiple stages of the HSV lifecycle. Specifically, it may impair viral adsorption and penetration, prevent nuclear translocation of viral proteins, and suppress immediate-early gene transcription, thereby reducing viral load[38]. Furthermore, glycyrrhizin has been shown to possess immunomodulatory properties—it can stimulate the production of interferons, enhance macrophage activity, and modulate cytokine expression to strengthen the host's antiviral response[39]. This dual activity—direct antiviral effect combined with immune enhancement—makes liquorice root a compelling therapeutic candidate for managing recurrent HSV infections. Cold sores are not only viral in origin but are also characterized by inflammatory responses that contribute to pain, swelling, and lesion formation. Glycyrrhizin and its metabolites exert corticosteroid-like anti-inflammatory activity without the associated side effects of synthetic steroids. They inhibit the cyclooxygenase (COX) and lipoxygenase (LOX) pathways, reducing the synthesis of inflammatory mediators such as prostaglandins and leukotrienes[40]. Additionally, they suppress pro-inflammatory cytokines like TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, mitigating tissue damage and accelerating lesion healing. These effects help reduce erythema, edema, and pain, thus improving patient comfort during outbreaks.

### Topical Delivery Systems for Cold Sore Treatment

Topical delivery systems are the cornerstone in the symptomatic and localized treatment of cold sores (herpes labialis), offering direct application of therapeutic agents to the site of viral activity. As the herpes simplex virus (HSV-1) remains dormant in peripheral sensory ganglia and reactivates in epithelial cells of the lips and surrounding areas, the targeted application of antiviral and anti-inflammatory agents provides rapid relief, improved therapeutic outcomes, and reduced systemic exposure. Topical gels, in particular, have gained prominence for their ease of use, rapid onset of action, and formulation versatility[41].

#### Advantages

Topical formulations for cold sores present several therapeutic advantages over systemic approaches:

- **Localized Action:** Delivers the active ingredients directly to the affected site, increasing drug concentration where needed and minimizing systemic side effects.
- **Rapid Symptom Relief:** Provides immediate analgesic, antiviral, and soothing effects at the site of infection, reducing pain, swelling, and itching.
- **Reduced Risk of Resistance and Toxicity:** Localized use minimizes the risk of systemic adverse effects and reduces viral resistance compared to long-term systemic antiviral therapy.
- **Patient Compliance:** Non-invasive, easy-to-apply formulations improve patient adherence and allow for frequent use during outbreaks.
- **Synergistic Combinations:** Allows incorporation of multiple natural or synthetic agents in a single formulation, such as combining peppermint oil and liquorice extract for dual antiviral and anti-inflammatory effects[42].

#### Types of Topical Gels and Their Properties

Topical gels are semi-solid systems that offer high patient acceptability due to their **non-greasy texture, cooling effect, and easy spreadability**. Depending on the formulation base and excipients, gels can be broadly categorized into:

- **Hydrogel-Based Gels:** Composed of water-soluble polymers (e.g., carbopol, HPMC) that provide hydration, bioadhesion, and enhance drug release at the affected site[43].



- **Oleogel or Lipophilic Gels:** Made using oils or hydrophobic carriers like polyethylene glycol or silicone oil, suitable for lipophilic herbal extracts and essential oils[44].
- **Emulgel Systems:** Combine the advantages of emulsions and gels, enabling delivery of both hydrophilic and lipophilic agents[45].
- **Thermosensitive Gels:** Exhibit sol-to-gel transition at skin temperature, enhancing drug residence time and sustained release[46].

### Role of Bio-adhesive Polymers and Penetration Enhancers

The efficacy of topical gels for HSV-1 also depends on retention at the application site and efficient skin penetration of active ingredients. This is facilitated by two key formulation strategies:

- **Bio-adhesive Polymers:** Polymers such as carbopol, chitosan, hydroxypropyl methylcellulose (HPMC) and sodium alginate are widely used to enhance gel adherence to the moist mucosal and lip surfaces. This prolongs contact time, improves drug residence, and enhances antiviral efficacy[47].
- **Penetration Enhancers:** Agents like ethanol, propylene glycol, isopropyl myristate, and essential oils (including menthol) disrupt the stratum corneum barrier and increase permeability of the active compound to deeper skin layers. Menthol itself acts as both an active antiviral and a penetration enhancer[48].

### Formulation Strategies for Herbal Gels

The development of effective herbal gels for the treatment of cold sores requires a careful balance between therapeutic efficacy, formulation stability, and patient acceptability. With increasing interest in natural remedies like peppermint oil and liquorice root extract, formulation scientists aim to create gels that ensure optimal drug release, penetration, and shelf-life while preserving the bioactivity of plant-derived constituents. Successful herbal gel formulation hinges on selecting appropriate excipients, optimizing physical and chemical stability, and achieving controlled release profiles[49].

### Selection of Gel Base and Excipients

The choice of gel base and excipients significantly influences the viscosity, spreadability, drug release behaviour, and bioadhesion of the final formulation:

**Gel Bases:** The gel base is a fundamental component in the formulation of topical gels, serving as the medium that carries active ingredients and delivers them efficiently to the skin or mucosal surface. In herbal formulations targeting cold sores (Herpes labialis), the gel base must be carefully selected to provide adequate viscosity, clarity, spreadability, compatibility with active constituents, and stability over time. Several natural and synthetic polymers are commonly used to create effective gel matrices, each offering unique physicochemical properties[50].

#### 1. Carbopol 940 (Carbomer)

- Carbopol 940 is a synthetic high molecular weight polymer of acrylic acid, crosslinked with polyalkenyl ethers. It is one of the most widely used gelling agents in pharmaceutical and cosmetic formulations due to the following properties[51]:
- **Excellent Clarity:** Forms transparent gels, making it suitable for cosmetic appeal and easy visualization of the applied area.
- **High Viscosity at Low Concentrations:** Effective even at concentrations of 0.5–2%, which makes it economical and light on the skin.
- **pH Sensitivity:** Requires neutralization (typically with triethanolamine (TEA) or NaOH) to form a gel. It performs best in the pH range of 5–6, which aligns well with skin compatibility.
- **Hydroalcoholic Compatibility:** Carbopol gels can incorporate a significant amount of alcohol, making it ideal for essential oil-based herbal gels, such as those containing peppermint oil which require ethanol for solubilization.



- **Stable and non-irritating:** Well tolerated by skin and mucosa, making it suitable for cold sore formulations where the lesion area is often inflamed or sensitive.

- However, Carbopol is sensitive to electrolytes, which can destabilize the gel structure if not formulated carefully.

## 2. HPMC (Hydroxypropyl Methylcellulose)

- HPMC is a semi-synthetic cellulose derivative widely used for gel formation due to its non-ionic nature, which provides excellent chemical stability and broad compatibility with active ingredients:

- **Water-Soluble:** Forms clear to slightly opaque gels depending on concentration and grade.

- **Viscosity Modifiable:** Available in various viscosity grades (e.g., HPMC K4M, K15M) to achieve desired texture and release profiles.

- **Non-Irritating and Biocompatible:** Safe for topical use, even on sensitive or damaged skin.

- **Controlled Release Carrier:** Forms a gel matrix that can sustain the release of active herbal compounds, enhancing their bioavailability and residence time.

- HPMC is particularly useful when formulating hydrophilic extracts, such as liquorice root, which contains water-soluble glycyrrhizin and flavonoids[52].

## 3. Sodium Alginate

- Derived from brown algae, sodium alginate is a natural, biodegradable, anionic polysaccharide that forms viscous gels in the presence of water or divalent cations (e.g., calcium ions):

- **Mucoadhesive Properties:** Enhances retention time on mucosal surfaces like the lips, which is beneficial for cold sore treatments.

- **Biodegradable and Non-Toxic:** Well tolerated and safe for use in herbal formulations.

- **Ionic Sensitivity:** Gelation can be induced or stabilized using calcium chloride, allowing control over gel strength and structure.

- **Compatible with Hydrophilic Extracts:** Suitable for incorporating liquorice extract, though less ideal for high concentrations of essential oils unless emulsifiers are included[53].

## 4. Chitosan

- Chitosan is a cationic polysaccharide obtained from deacetylation of chitin, known for its bio-adhesive, antimicrobial, and wound-healing properties:

- **Excellent Film-Forming Ability:** Forms a semi-occlusive barrier that protects the cold sore while allowing oxygen permeability.

- **Enhances Skin Permeation:** Opens tight junctions in epithelial tissue, improving penetration of herbal actives.

- **Mucoadhesive Nature:** Particularly useful in lip and mucosal applications.

- **Biocompatible and Antiviral:** Adds therapeutic value beyond being a gel base, contributing to healing and infection control.

- Chitosan requires an acidic environment (usually acetic acid) to dissolve and form gels, which may limit its compatibility with certain actives[54].



## 5. Xanthan Gum

- A natural polysaccharide derived from *Xanthomonas campestris* bacteria, xanthan gum is frequently used for its stabilizing and thickening properties:
- **Good Rheological Control:** Offers pseudoplastic behavior, which allows easy application under shear (e.g., when rubbed) but remains viscous at rest.
- **Stabilizes Emulsions:** Beneficial in emulgel systems, particularly when combining peppermint oil with aqueous liquorice extract.
- **Stable over Wide pH Range:** Maintains viscosity in both acidic and basic environments, useful for formulations requiring pH adjustment.
- **Synergistic with Other Polymers:** Often combined with Carbopol or HPMC to improve gel texture and drug delivery[55].

**Solvents and Co-solvents:** In the formulation of topical herbal gels, solvents and co-solvents play a crucial role in enhancing solubility, stability, and bioavailability of active plant-derived compounds. Herbal extracts often consist of a diverse range of hydrophilic (water-loving) and lipophilic (oil-loving) constituents, necessitating a combination of solvents that can dissolve and stabilize both types of compounds within a single gel system. Solvents also influence permeation through the skin, drug release kinetics, and physical properties of the final formulation[56].

### 1. Ethanol

- **Polarity and Solubility:** Ethanol is a polar, volatile solvent that can dissolve both moderately polar and nonpolar constituents, making it particularly effective for essential oils like peppermint oil that contain menthol and menthone.
- **Antimicrobial Property:** Acts as a natural preservative, reducing the microbial load in the formulation, which is especially important for plant-based extracts prone to contamination.
- **Skin Penetration Enhancer:** Ethanol disrupts the lipid bilayer of the stratum corneum, enhancing percutaneous absorption of lipophilic agents like menthol.
- **Volatility:** Its rapid evaporation after gel application provides a cooling and soothing effect, which can be beneficial for inflamed cold sores[57].

### 2. Propylene Glycol (PG)

- **Solubilizer and Humectant:** PG is a water-miscible co-solvent with the ability to dissolve both hydrophilic (e.g., glycyrrhizin) and lipophilic (e.g., essential oil components) molecules. It also acts as a humectant, helping to retain skin moisture.
- **Permeation Enhancer:** Like ethanol, propylene glycol enhances transdermal drug delivery by interacting with stratum corneum lipids, increasing drug penetration to deeper skin layers.
- **Stabilizer:** PG can prevent crystallization of some actives and contributes to the physical stability of gels.
- **Safety Profile:** Generally regarded as safe and well-tolerated in topical applications, although it may occasionally cause mild irritation in very sensitive individuals[58].

### 3. Polyethylene Glycol-400 (PEG-400)

- **Solubilizing Agent:** PEG-400 is a low molecular weight hydrophilic polymer, often used to solubilize water-insoluble drugs and blend with other solvents to enhance the miscibility of diverse components in gels.
- **Viscosity Modifier:** Though primarily a solvent, PEG-400 can slightly increase the viscosity of the formulation and contribute to gel texture.



- **Compatibility:** Well, tolerated with many polymers (like Carbopol, HPMC) and does not interact negatively with herbal actives, making it an ideal co-solvent in complex phytochemical formulations.

- **Skin Friendly:** PEG-400 has low toxicity and is suitable for both dermal and mucosal applications, making it a safe choice for use in lip and facial cold sore treatments[59].

#### 4. Glycerine (Glycerol)

- **Natural Humectant:** Glycerine is a trihydroxy alcohol known for its moisture-retaining properties, which helps maintain hydration and soothe dry or cracked skin during a cold sore episode.

- **Solubilizing Effect:** Primarily dissolves hydrophilic components like glycyrrhizin and flavonoids found in liquorice root.

- **Soothing Agent:** Its emollient properties provide a cooling, protective film on the skin that reduces irritation, supports healing, and enhances user comfort.

- **Stabilizing Role:** Glycerine stabilizes aqueous gels and prevents syneresis (gel shrinkage or water separation), improving long-term formulation stability[60].

**pH Adjusters:** The pH of a topical gel formulation plays a critical role in ensuring stability, efficacy, and skin compatibility. For herbal gels containing both hydrophilic plant extracts (e.g., glycyrrhizin from liquorice) and lipophilic essential oils (e.g., menthol from peppermint oil), achieving an optimal pH is essential to maintain chemical integrity, prevent irritation, and ensure maximum therapeutic effect.

#### Why pH Matters in Topical Gels

- **Skin Compatibility:** Human skin has a slightly acidic pH (typically 4.5–6.0). A gel with a pH in this range supports the skin's natural acid mantle, minimizing irritation and enhancing tolerability.

- **Polymer Functionality:** Many gelling agents such as Carbopol 940 require pH adjustment to form proper gels. For example, Carbopol dispersions gel effectively only after neutralization to a pH of ~5.0–6.5.

- **Active Compound Stability:** pH affects the solubility and stability of herbal actives. For instance, glycyrrhizin (an acidic compound) remains more stable in slightly acidic to neutral pH, while peppermint oil components remain more stable in a mildly acidic environment[61].

#### Common pH Adjusters in Herbal Gel Formulations

##### 1. Triethanolamine (TEA)

- **Most Commonly Used with Carbopol:** TEA is a weak base used to neutralize acidic polymers like Carbopol 940, triggering gel formation by ionizing the carboxylic groups and enabling network crosslinking.

- **Acts as Emulsifier:** TEA can also stabilize oil-in-water emulsions when essential oils like peppermint are incorporated.

- **Safe and Non-Irritating:** At concentrations typically used (0.2–1%), TEA is considered safe for topical application.

##### 2. Sodium Hydroxide (NaOH)

- **Strong Alkali:** Used in very dilute form to raise the pH of acidic gels, particularly when high buffering capacity is needed.

- **Fast-acting and Precise:** Offers quick adjustment of pH during formulation, especially useful during titration of polymers or actives.

- **Requires Caution:** NaOH must be used carefully to avoid overshooting the desired pH, which could destabilize the gel or cause skin irritation.



### 3. Citric Acid

- **Weak Organic Acid:** Used to lower the pH of formulations that are too alkaline. It is **naturally derived** and widely used in herbal and cosmetic formulations.
- **Antioxidant Properties:** Helps stabilize actives and prevent oxidation, especially important in gels containing essential oils, which are prone to oxidative degradation.
- **pH Buffering:** Also acts as a buffer when used with its conjugate base (sodium citrate), maintaining pH stability over time.

### 4. Lactic Acid

- **Alpha-Hydroxy Acid (AHA):** Naturally found in the skin, it can be used to gently acidify a formulation.
- **Skin-Friendly:** Enhances moisturizing effect and supports the skin barrier, making it particularly useful in mucosal or lip applications like cold sore treatments.
- **Mild Action:** Less irritating compared to stronger acids, making it safer for sensitive skin.

### 5. Acetic Acid / Vinegar

- **Natural Acidifier:** Occasionally used in natural/herbal systems, especially when chitosan is the gelling agent (chitosan requires acidic pH to dissolve).
- **Antimicrobial Action:** Acetic acid can also contribute to mild antimicrobial effects, adding to the formulation's preservative capacity[62].

#### Preservatives:

#### 1. Parabens (Methylparaben, Propylparaben)

- Broad-spectrum antimicrobial agents effective against fungi and bacteria.
- Stable over a wide pH range (4–8), ideal for gels containing Carbopol or HPMC.
- Used in low concentrations (0.1–0.3%), making them cost-effective[63].
- **Limitations:** Growing consumer concerns and regulatory restrictions in certain countries due to possible endocrine-disrupting effects, though largely considered safe in topical products at regulated levels.

#### 2. Phenoxyethanol

- Widely used in natural or green formulations due to a better safety profile.
- Effective against Gram-negative bacteria, especially when combined with ethylhexylglycerin or parabens for synergistic activity.
- Suitable for pH 4.5–8, making it compatible with both peppermint and liquorice-based formulations.
- Non-irritating and well-tolerated for facial/lip application in cold sore treatments.

#### 3. Benzyl Alcohol

- A natural aromatic alcohol that acts as both a preservative and solvent.
- Broad-spectrum action, especially against Gram-positive bacteria.
- Often used in conjunction with EDTA (a chelating agent) for enhanced efficacy.



- Approved for natural and organic formulations, making it a preferred choice for herbal products.
- Usage: typically, at 0.5–1% concentration [64].

#### 4. Sorbic Acid / Potassium Sorbate

- Effective fungistatic agents used primarily to prevent mold and yeast growth.
- Suitable for slightly acidic formulations (pH 4–6.5), ideal for herbal cold sore gels.
- Low toxicity and good compatibility with most polymers and actives.
- Often used in combination with other preservatives to broaden antimicrobial coverage[65].

#### 5. Sodium Benzoate

- A mild antifungal and antibacterial agent most effective at low pH (<5.5).
- Often used in combination with citric acid or sorbic acid.
- Safe and well-tolerated in mucosal and dermal applications, making it suitable for cold sore gels applied to the lips.[66]

#### 6. Natural Preservatives (e.g., Essential Oils, Organic Acids)

- Some essential oils (like peppermint, tea tree, eucalyptus) possess inherent antimicrobial properties, contributing to preservative effects.
- However, they are not sufficient alone to provide comprehensive microbial protection.
- Can be used as preservative boosters in combination with standard preservatives.

### DISCUSSION

Cold sores, primarily caused by Herpes Simplex Virus type 1 (HSV-1), represent a widespread viral infection with significant recurrence and discomfort. Conventional antiviral agents like acyclovir and penciclovir are commonly employed to manage outbreaks; however, their use is often associated with limitations such as resistance development, adverse effects, cost, and restricted suitability for long-term use. This has spurred interest in alternative, plant-based therapies that are both efficacious and well-tolerated[67].

In this context, the integration of peppermint oil (*Mentha piperita*) and liquorice root (*Glycyrrhiza glabra*) into topical gel delivery systems emerges as a promising strategy. Both botanicals exhibit multifaceted pharmacological properties, including antiviral, anti-inflammatory, analgesic, and antioxidant effects, which directly address the pathophysiological mechanisms involved in HSV infections[68]. Peppermint oil is particularly rich in menthol and menthone, compounds that have demonstrated inhibitory activity against HSV-1 by disrupting viral envelopes and preventing replication. Additionally, its analgesic and cooling properties provide symptomatic relief from the burning and pain associated with cold sore lesions[22]. Liquorice root, on the other hand, contains glycyrrhizin, a saponin-like compound with antiviral and immunomodulatory capabilities. Glycyrrhizin has been shown to interfere with viral gene expression, modulate cytokine release, and reduce local inflammation, thereby supporting both acute symptom relief and long-term control[69]. One of the critical strengths of plant-based therapies is their ability to target multiple molecular pathways simultaneously, potentially enhancing efficacy and reducing the likelihood of resistance. Unlike synthetic antivirals that often act at a single stage of the viral life cycle, phytochemicals such as those found in peppermint and liquorice modulate host–virus interactions, including viral adhesion, replication, and host immune response[69]. Topical delivery systems offer additional advantages for the management of cold sores. They enable localized drug delivery, minimize systemic side effects, and improve patient compliance[70]. The formulation of bio-adhesive gels using polymers like Carbopol, HPMC, and chitosan enhances residence time at the site of infection, ensuring sustained drug release. The inclusion of co-solvents (e.g., ethanol, propylene glycol) and penetration enhancers supports the effective delivery of both hydrophilic (glycyrrhizin) and lipophilic (menthol) compounds[71].



Furthermore, the safety profiles of peppermint oil and liquorice root are favorable when used in appropriate concentrations. However, it is essential to consider that high doses or prolonged use—especially of glycyrrhizin—may lead to toxicity or hypersensitivity, warranting careful formulation design and dosage control. The selection of compatible preservatives (e.g., phenoxyethanol, potassium sorbate) and pH adjusters (e.g., TEA, citric acid) is equally crucial to maintain stability, microbiological safety, and user acceptability.

In summary, the incorporation of peppermint oil and liquorice root into topical gel formulations represents a rational, evidence-based approach for managing cold sores. These natural compounds offer broad-spectrum therapeutic benefits with relatively low toxicity, especially when formulated using advanced gel technologies. Future research should focus on clinical evaluations, pharmacokinetic profiling, and synergistic combinations to validate the full potential of such plant-based interventions as mainstream therapeutics for HSV-1 infections.

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