

Phytotherapeutic Approaches to Herpes Simplex Virus: Mechanisms, Efficacy and Clinical Potential

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ABSTRACT

A Herpes simplex virus (HSV) infection remains a widespread global health challenge with no definitive cure, prompting extensive interest in alternative and complementary medicine. Herbal cures have gained attention for their antiviral, anti-inflammatory, and immunomodulatory properties that may support symptom management and reduce recurrence frequency. This review summarizes current knowledge on plant-based treatments traditionally used for herpes, including *Melissa officinalis* (lemon balm), *Aloe vera*, *Hypericum perforatum*, *Glycyrrhiza glabra* (licorice), and *Echinacea purpurea*. Evidence from in vitro studies, animal models, and limited clinical trials suggests that certain herbal extracts may inhibit HSV replication, alleviate lesion severity, and enhance healing time. However, variations in formulation, dosage, and study design highlight the need for more rigorous clinical research. This review emphasizes the therapeutic potential of herbal remedies as complementary options within holistic herpes management while underscoring the importance of safety evaluation and evidence-based application.

Keywords: HSV1, HSV2, Natural antivirals, Herbal medicine, Phytotherapy.

INTRODUCTION

Herpes simplex virus is the second most common virus after chickenpox and is highly contagious. They have an icosahedra protein capsid and large double-stranded linear DNA. There are two types of HSV with comparable antigenicity: HSV type 1 and HSV type 2. Lip and mouth sores are caused by HSV-1(1). A common human infection, herpes simplex virus (HSV) is primarily associated with genital and orofacial lesions. Its infection occurs latently and latently in neurons, affecting the skin and mucosa. About 80% of individuals exhibit no symptoms, which may result in unknowing infection to spouses or infants. For newborns and people with weakened immunity, effective control measures are essential (2). Herpes simplex virus type 2 (HSV-2) infection affected approximately 491 million people worldwide in 2016, including more than 13% of the population between the ages of 15 and 49 years. Meningitis, keratitis, and oral and genital herpes are among the chronic disease caused by HSV-2. Due to its broad

clinical spectrum and low transmission threshold, it also increases the risk of HIV transmission(3). Recurrence rates may be influenced by premorbid personality, and multiple recurrences may have adverse effects on personality. Long-term acyclovir suppression reduces psychological morbidity, and long-term treatment requires social support, cognitive coping mechanisms, and problem-solving abilities(4)



Fig. No. 1 Clinical Variants of Herpesvirus Lesions

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1.1 Implications of herpes simplex virus infections for psychology and psychosexuality

70% of the world's population, or 3.8 billion individuals under the age of 50, have lifelong herpes simplex virus type 1 (HSV). Reactivation of latent reservoirs in the dorsal root ganglia or trigeminal ganglia, which allows viral persistence, is the cause of symptomatic outbreaks (5). Additionally, HSV-1 can spread throughout the nervous system, causing problems such as encephalitis and Alzheimer's disease in older people (6). Herpes simplex virus type 1 causes herpes labialis, a skin disease that appears as blisters or sores. After spreading into sensory nerve cells, it remains dormant until it is reactivated. Stress, trauma from surgery, menstruation, heat, sunlight and certain medications can cause recurrence (7). Herpes simplex virus type 1 causes herpes labialis, a skin disease that appears as blisters or sores. After spreading into sensory nerve cells, it remains dormant until it is reactivated. Recurrence can be caused by stress, trauma from surgery, menstruation, heat, sunlight and certain medication (8). Herpes simplex virus (HSV) infection usually results in benign, self-limited vesicular skin or mucosal lesions. Similar to other Herpesviridae family members, HSV develops permanent latency after primary infection, with the potential for reactivation by various triggers or immunosuppression. Hepatitis is one of the serious consequences that HSV can sometimes cause (9). 137 cases of HSV-associated hepatitis, commonly referred to as herpetic hepatitis or HH, were documented as of 2018; the majority of these cases involved pregnant women and immunocompromised individuals. However, some examples of immunocompetent, non-pregnant patients have been documented. Without antiviral therapy (10). Nowadays, the most popular medication for treating HSV-1 and HSV-2 is acyclovir (ACV), an acyclic guanosine analog present in the sponge *Cryptotathea crypta* (11).

The development and course of neurodegenerative disorders are strongly influenced by neuroinflammation. A practical way to address the complex pathogenic pathways of neuroinflammation may be a multicomponent and multitarget approach. Using integrated network pharmacology, molecular

docking, and experimental bioassays, this study sought to create synergistic herbal ingredient formulas to reduce neuroinflammation. In this investigation, eight phytochemicals with the ability to reduce neuroinflammation were selected. To demonstrate the mode of action of each phytochemical and the molecular relationships between them, a network of compound-gene target-signaling pathways was created (12). Glycoprotein and protein subunit-based vaccines elicit protective immune responses. They have not had success in clinical trials against HSV, but they have demonstrated better safety, stability, and efficacy than HPV vaccines (13). To prevent viral entry, shedding, and immune evasion, these vaccines use viral glycoproteins and employ antigenic mediators like gB/gD/gE and viral glycoproteins. To improve subunit vaccine efficacy against HSV, ongoing research efforts are being made to integrate peptide epitopes and herpes antigens into a single vaccination strategy, taking into account the Multi-omics technologies have identified between 80 and 300 open reading frames (ORFs) (14).

1. Pathogenesis of herpes

Herpesvirus pathogenesis involves a complex interplay between viral latency, immune evasion, and host cell reprogramming. Recent advances reveal that viral entry is governed by glycoprotein-mediated fusion “switches” determining tissue tropism (15). Once in the nucleus, herpesviral genomes rapidly chromatinize, establishing an epigenetically poised state that balances latency and replication. Latency is now recognized as a metabolically active equilibrium, regulated by noncoding RNAs that fine-tune host signaling and metabolism. Herpesviruses evade immunity by manipulating phase separation dynamics and silencing antiviral pathways through microRNAs and lncRNAs (16). Reactivation arises from stochastic epigenetic remodeling rather than mere stress responses, leading to intermittent, often subclinical replication cycles. Persistent infection induces long-term epigenetic and immune alterations, contributing to oncogenesis and chronic inflammation. Overall, herpesvirus persistence represents a dynamic, multi-omic equilibrium shaped by continuous host–virus adaptation (17).



Cold sores and genital herpes are caused by Herpes Simplex Virus (HSV)—HSV-1 usually causes oral lesions, while HSV-2 more commonly causes genital lesions, though both types can infect either site (18). Infection begins when the virus enters the body through tiny breaks in the skin or mucous membranes. HSV first replicates in epithelial cells, causing cell death and inflammation that produce painful blisters or ulcers. After the initial infection, the virus travels along sensory nerves to the dorsal root (or trigeminal) ganglia, where it becomes latent. During latency, the viral DNA remains inside neurons without producing new virus (19). Reactivation occurs when triggers such as stress, fever, UV light, illness, or immunosuppression disturb the balance. The virus then travels back down the nerve to the skin or mucosa, causing recurrent lesions. Each recurrence tends to be milder because the immune system responds more quickly, but the virus remains lifelong (20). The pathogenesis of herpes simplex virus (HSV-1 and HSV-2) involves a dynamic interplay between lytic replication in epithelial tissues and lifelong latency within sensory neurons. Primary infection begins with direct mucocutaneous transmission, followed by viral attachment to epithelial cells through heparan sulfate and the entry receptors nectin-1 and HVEM (21). After fusion with the host membrane, the virus initiates lytic replication, characterized by sequential expression of immediate-early (α), early (β), and late (γ) genes that regulate transcription, DNA synthesis, and structural

assembly. This replication leads to cytopathic effects including cell lysis, multinucleated giant cells, and intranuclear inclusions, which clinically manifest as vesicular lesions on oral or genital mucosa (22). Following replication in epithelial cells, HSV enters sensory nerve endings and travels retrogradely via dynein motors to neuronal cell bodies in the trigeminal or sacral ganglia, where it establishes latency. During latency, the viral genome persists as an episome with suppression of most lytic genes and selective expression of latency-associated transcripts (LATs), which help maintain latency by inhibiting apoptosis and promoting heterochromatin formation. HSV uses multiple immune evasion strategies, such as inhibition of interferon pathways, downregulation of MHC class I via ICP47, and persistence in immune-privileged (23). Reactivation occurs in response to triggers like stress, UV light, fever, or immunosuppression, leading to derepression of lytic genes, renewed viral replication, and anterograde transport of virions back to the skin or mucosa, resulting in recurrent lesions or asymptomatic shedding (24). In certain cases, HSV causes severe disease, including herpes simplex encephalitis from spread to the temporal lobes, neonatal herpes from perinatal transmission, and recurrent ocular infection leading to keratitis and corneal scarring. Overall, HSV pathogenesis is defined by its ability to alternate between productive lytic infection and immune-evasive neuronal latency, allowing lifelong persistence and episodic transmission (25).

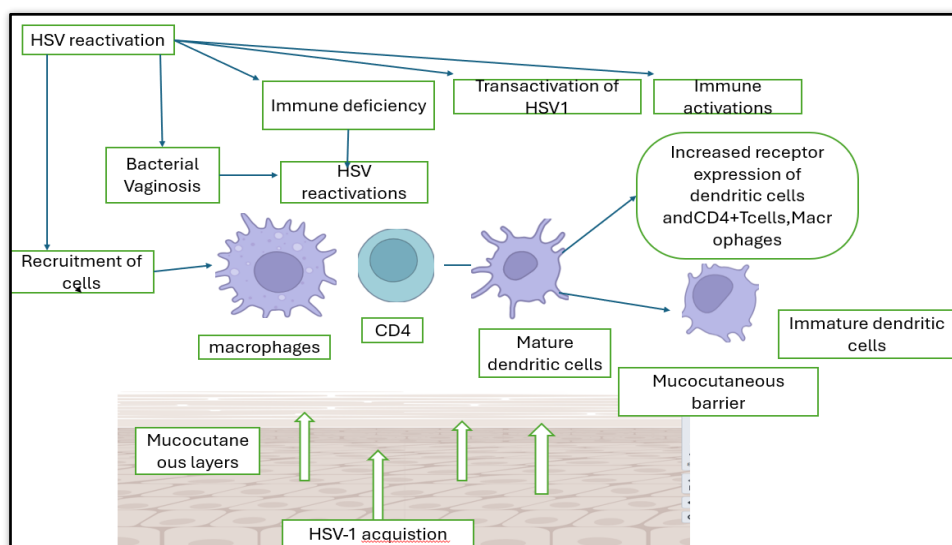


Fig. No. 2 Mechanisms of HSV-1 Reactivation and Immune Interaction.

This diagram shows how HSV-1 reactivation alters immune function and mucocutaneous tissues, leading to recruitment and activation of immune cells and increased receptor expression. These changes weaken the mucocutaneous barrier and enhance susceptibility to HSV-1 acquisition.

2. Mechanistic Basis of Herbal Antiviral Activity Against HSV

2.1 Inhibition of Viral Attachment

Herbal antivirals exhibit diverse mechanisms against HSV by targeting multiple stages of the viral life cycle. Polyphenolic tannins such as chebulagic acid and punicalagin block viral attachment and entry by binding HSV glycoproteins gB and gC, preventing their interaction with host glycosaminoglycans (26). Flavonoids like wogonin inhibit HSV replication by suppressing immediate-early viral genes (ICP0, ICP4, ICP27) through downregulation of NF- κ B, MAPK, and AP-1 signaling pathways (27). Host-directed actions are also evident, as compounds like carnosic acid reduce cellular ATP production by inhibiting glycolysis, the TCA cycle, and oxidative phosphorylation, thereby limiting viral growth. Additionally, carvacrol modulates virus-induced necroptosis by suppressing RIP3 signaling and restoring ubiquitination balance (28).

3.2 Disruption of Viral Replication & Gene Expression

Wogonin, a flavonoid derived from *Scutellaria* species, exhibits potent anti-HSV activity by suppressing the expression of key immediate-early viral genes, including ICP0, ICP4, and ICP27, which are essential for initiating the viral transcriptional program (29). Its antiviral effect is mediated through modulation of host cell signaling pathways: wogonin inhibits NF- κ B activation by preventing I κ B- α degradation and p65 nuclear translocation, and it also suppresses MAPK signaling (JNK, p38) and downstream AP-1 transcription factors (c-Jun, ATF-2). Because immediate-early gene expression is required to activate all subsequent phases of the HSV replicative cycle, these combined effects result in a marked reduction in viral replication (30).

3.3 Metabolic Host-Energy Modulation

Carnosic acid, a diterpenoid compound from *Salvia rosmarinus* (rosemary), exhibits a distinctive host-targeted antiviral mechanism against HSV-2 by suppressing cellular ATP synthesis (31). It disrupts multiple metabolic pathways, including glycolysis, the tricarboxylic acid (TCA) cycle, and oxidative phosphorylation, leading to a broad reduction in cellular energy production. Because HSV replication is highly energy-dependent, this metabolic suppression results in a significant decrease in viral replication. Proteomic analyses combined with high-resolution respirometry confirmed the downregulation of key host metabolic enzymes and pathways, highlighting carnosic acid as a potent example of a metabolic-targeting antiviral strategy (32).

3.4 Modulation of Cell Death / Necrosis Pathways

Carvacrol, a monoterpenoid phenol found in oregano and related herbs, exhibits notable anti-HSV-2 activity in vitro by modulating the RIP3-mediated necroptosis pathway (33). It reduces the expression of key necroptosis-associated proteins, including RIP3 and MLKL, while simultaneously restoring ubiquitination levels that are disrupted during HSV-2 infection (34). Through this regulation of programmed cell necrosis and protein homeostasis, carvacrol appears to alter or limit virus-induced cell death, thereby restricting viral propagation and contributing to its overall antiviral effect (35).

3.5 Synergy with Conventional Antivirals

Several herbal extracts have been shown to enhance the antiviral efficacy of acyclovir (ACV) (36). In vivo studies combining ACV with extracts from *Geum japonicum*, *Rhus javanica*, *Syzygium aromaticum*, or *Terminalia chebula* demonstrated greater reductions in viral load and improved survival in mice compared to ACV treatment alone (37). These findings suggest that certain herbal compounds can act as adjuvants, potentially potentiating standard antiviral therapy or helping to overcome drug resistance (38).

3.6 Pleiotropic and Multi-Stage Action



Polyphenols, including phenolic acids and tannins, exhibit multi-target antiviral activity against HSV by interfering with multiple stages of the viral life cycle, such as attachment, entry, replication, and egress, while also modulating host pathways involved in signaling and immune responses (39). This broad-spectrum, multi-pronged mechanism reduces the likelihood of the virus developing resistance compared to conventional single-target antiviral drugs, highlighting the therapeutic potential of polyphenols as emphasized in mechanistic reviews (40).

4. Overview of Herbal Compounds with Anti-Herpetic Activity

4.1 Flavonoid-Containing Plants

Flavonoids are plant-derived polyphenolic secondary metabolites with diverse chemical structures and biological functions, contributing to plant coloration, UV protection, and defense against microbial and viral infections. Structurally based on a 15-carbon skeleton (C6-C3-C6), flavonoids comprise several subclasses, including flavones, isoflavones, flavanones, flavonols, catechins, anthocyanins, and chalcones, with modifications such as glycosylation, prenylation, and hydroxylation further diversifying their properties (41). Due to their low toxicity and multifunctional biological activities, flavonoids like baicalin from *Scutellaria baicalensis* have gained attention as potential antiviral agents. Baicalin exhibits antioxidant, anti-apoptotic, vascular- and neuroprotective effects and is clinically used in parts of Asia to treat inflammation and cancer (42). Importantly, it shows broad-spectrum antiviral activity against viruses including influenza, dengue, chikungunya, and Zika, and modulates ferroptosis. Recent studies provide the first evidence that baicalein, a related flavonoid, exerts protective effects against HSV-1 infection in both ex vivo and in vivo models, highlighting its potential as a therapeutic antiviral agent (43).

4.2 Licorice Root



Fig. No. 3 Licorice Root

Glycyrrhizin, also known as *glycyrrhizic acid*, is the active ingredient in licorice root, which has shown antiviral properties against a variety of viruses, including HIV, hepatitis, herpes, and influenza. In addition, it has demonstrated efficacy against several animal viruses, including swine epidemic diarrhea virus, infectious bronchitis virus, duck hepatitis virus, and infectious bursal disease virus (44). After drying the licorice roots and grinding them into powder, four grams were suspended in 100 ml of sterile distilled water at 37 °C for 24 h. This was followed by incubation for eight hours at room temperature with magnetic mixing (45). After passing through a 0.45 µL filter, the prepared mixture was kept at 4°C for storage. Mechanisms such as prevention of HSV attachment, which can be accomplished by directly inactivating the virus or by blocking HSV-1 adherence to Vero cells in vitro, are thought to be responsible for the antiherpetic action of licorice root extract (46).

4.3 *Camellia Sinesis*:



Fig. No. 4 *Camellia Sinesis*

Camellia sinensis (green tea) is rich in polyphenols and flavonoids, particularly catechins, which have

demonstrated antiviral properties (47). These compounds can inhibit HSV replication by blocking viral entry, attachment, and replication in host cells, and by modulating host immune responses (48). Green tea extracts may also reduce virus-induced oxidative stress and inflammation, further limiting viral propagation. While generally safe, its caffeine content should be considered in excessive consumption. Overall, *C. sinensis* polyphenols offer a promising natural adjunct for managing HSV infections (49).

4.4 Polyphenols and Terpenoids: 5.4 lemon balm



Fig. No. 5 Lemon balm

Melissa officinalis (lemon balm) contains essential oils rich in citral, citronellal, geraniol, rosmarinic acid, eugenol, and flavonoids, which contribute to its antiviral activity against HSV-1 and HSV-2 (50). These compounds act by interfering with viral attachment and entry, disrupting viral envelopes, and inhibiting replication in host cells (51). In vitro studies have demonstrated that lemon balm essential oils significantly reduce the infectivity of HSV, making its polyphenols and terpenoids promising natural agents for herpes management (52).

4.5 Hypericum Perforatum



Fig. No. 6 Hypericum perforatum

Hypericum perforatum (St. John's Wort) exhibits antiviral activity against HSV, largely due to its bioactive compounds hypericin, hyperforin, flavonoids, and naphthodianthrone (53). These constituents can inactivate viral particles, inhibit viral replication, and interfere with viral entry into host cells (54). Additionally, its antioxidant and anti-inflammatory properties help reduce virus-induced cellular damage, making St. John's Wort a promising natural agent for managing herpes infections (55).

4.6 Eucalyptus plants:



Fig. No. 7 Eucalyptus plants

Eucalyptus species, particularly *Eucalyptus globulus*, contain essential oils rich in eucalyptol (1,8-cineole), α -pinene, limonene, and other terpenoids, which exhibit antiviral activity against HSV (56). These compounds can disrupt viral envelopes, inhibit viral replication, and reduce infectivity in host cells (57). The antioxidant and anti-inflammatory properties of eucalyptus oils further help mitigate virus-induced cellular damage, making them promising natural agents for herpes management (58).

Alkaloids and Saponins:

4.7 Withania somnifera



Fig. No. 8 Withania somnifera

Withania somnifera (Ashwagandha) contains bioactive compounds such as withanolides, alkaloids, glycosides, and steroidal lactones, which contribute to its antiviral potential against HSV (59). These constituents can inhibit viral replication, modulate host immune responses, and reduce virus-induced oxidative stress and inflammation (60). The diverse phytochemicals present in roots, leaves, and other plant parts make *W. somnifera* a promising natural agent for managing herpes virus infections (61).

4.8 Panax Ginseng:



Fig. No. 9 Panax Ginseng

The effectiveness of ginseng root extract for many conditions was not conclusively demonstrated by systematic evaluation of randomized controlled trials. The research also highlights how important it is to evaluate the safety profile of *P. ginseng* in view of its widespread use to identify any potential health threats to users. Its goal is to record and assess all the safety information that is currently known about *P. ginseng* root extract (62). This study assessed the antiviral activity of several ginsenosides from steamed (red) and natural (white) ginseng against HSV-1 and HSV-2. Rb1, Rb2, Rb3, Rc, Rd, Re, Rf, Rg1, 20(R)-Rg2, 20(S)-Rg2, 20(R)-Rg3, 20(S)-Rg3, 20(R)-Rh1, 20(S)-Rh1, 20(R)-Rh1, 20(R)-Rh2, and 20(S)-Rh2 are among the important ginsenosides evaluated. The last eight are the products of steaming, which transforms white ginseng into red ginseng (63). For thousands of years, Asian traditional medicine has used the roots of *P. ginseng* and *P. noto ginseng*, mostly for the treatment of heart disease, first aid and medical care. *P. noto Ginseng*, commonly known as Sanqi or Sanchi, can be traced back approximately 500 years to ethnic minorities in southwest China (64).

Table No. 2 Herbal Extracts and Plant Compounds

Herb / Extract	Active Constituents	Actions / Benefits	Usage Forms	References
Lemon Balm (<i>Melissa officinalis</i>)	Rosmarinic acid, caffeic acid, flavonoids	antiviral and anti-inflammatory qualities that hasten recovery and lower the likelihood of recurrence.	Creams, tinctures, teas.	(65)
Licorice Root (<i>Glycyrrhiza glabra</i>)	Glycyrrhizin, liquiritigenin	Antiviral and anti-inflammatory qualities aid in healing and lower the chance of recurrence.	Creams or teas; avoid long-term internal use (can raise blood pressure).	(66)
Echinacea (<i>Echinacea purpurea</i>)	Cichoric acid, alkamides, polysaccharides	may lessen the frequency of breakouts by boosting the immune system.	Capsules, tinctures, teas.	(67)
St. John's Wort (<i>Hypericum perforatum</i>)	Hypericin, hyperforin	Antiviral and wound-healing; can inhibit HSV in vitro.	Topical oils or salves; caution with sunlight exposure and drug interactions.	(68)
Aloe Vera	Polysaccharides, anthraquinones	Speeds up lesion healing, soothes pain and itching.	Use pure gel directly on sores.	(69)
Propolis (bee product)	Flavonoids, phenolic acids	Natural antiviral and healing agent; studies show faster healing than acyclovir cream in some cases.	Creams or tinctures.	(70)

<i>Olive Leaf</i> (<i>Olea europaea</i>)	Oleuropein, hydroxytyrosol	Antiviral, antioxidant; may reduce HSV replication.	Capsules, teas, tinctures.	(71)
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5. Essential Oils and Plant Extracts

Table No.1 Essential Oils with Antiviral Properties Against HSV:

Essential Oil	Active Compounds	Actions & Evidence	Usage (Topical)	References
<i>Tea Tree</i> (<i>Melaleuca alternifolia</i>)	Terpinen-4-ol, α -terpineol	It has been shown to have strong antiviral and antibacterial activities, particularly lowering HSV infectivity	Apply to the lesion two to three times a day after diluting to 1-2% in a carrier oil, like coconut oil.	(72)
<i>Lemon balm</i>	Citral, citronellal, geranial	clinically proven to reduce herpes lesion recurrence rates and speed up healing.	Use 1–2% dilution or Melissa-infused cream.	(73)
<i>Peppermint</i> (<i>Mentha piperita</i>)	Menthol, menthone	prevents HSV-1 and HSV-2 from replicating in the early stages of infection.	Itching can be relieved and cooled by applying diluted oil.	(74)
<i>Eucalyptus</i> (<i>Eucalyptus globulus</i>)	Eucalyptol (1,8-cineole)	antiviral activity that helps cleanse the skin and dry up blemishes.	1% dilution on affected area.	(75)
<i>Lavender</i> (<i>Lavandula angustifolia</i>)	Linalool, linalyl acetate	lessens pain and inflammation while encouraging healing.	Add blends for a relaxing effect and skin repair.	(76)
<i>Thyme</i> (<i>Thymus vulgaris</i>)	Thymol, carvacrol	Strong antiviral and antibacterial properties have been demonstrated, particularly in preventing HSV proliferation.	For extremely potent formulations, use a modest concentration (0.5–1%).	(77)

Herb / Extract	Active Constituents	Actions / Benefits	Usage Forms	References
<i>Lemon Balm</i> (<i>Melissa officinalis</i>)	Rosmarinic acid, caffeic acid, flavonoids	antiviral and anti-inflammatory qualities that hasten recovery and lower the likelihood of recurrence.	Creams, tinctures, teas.	(65)
<i>Licorice Root</i> (<i>Glycyrrhiza glabra</i>)	Glycyrrhizin, liquiritigenin	Antiviral and anti-inflammatory qualities aid in healing and lower the chance of recurrence.	Creams or teas; avoid long-term internal use (can raise blood pressure).	(66)
<i>Echinacea</i> (<i>Echinacea purpurea</i>)	Cichoric acid, alkamides, polysaccharides	may lessen the frequency of breakouts by boosting the immune system.	Capsules, tinctures, teas.	(67)
<i>St. John's Wort</i> (<i>Hypericum perforatum</i>)	Hypericin, hyperforin	Antiviral and wound-healing; can inhibit HSV in vitro.	Topical oils or salves; caution with sunlight exposure and drug interactions.	(68)
<i>Aloe Vera</i>	Polysaccharides, anthraquinones	Speeds up lesion healing, soothes pain and itching.	Use pure gel directly on sores.	(69)



<i>Propolis (bee product)</i>	Flavonoids, phenolic acids	Natural antiviral and healing agent; studies show faster healing than acyclovir cream in some cases.	Creams or tinctures.	(70)
<i>Olive Leaf (Olea europaea)</i>	Oleuropein, hydroxytyrosol	Antiviral, antioxidant; may reduce HSV replication.	Capsules, teas, tinctures.	(71)

Essential oils, especially those made from tea tree oil (*Melaleuca alternifolia*), have strong antiviral effects against many viruses, such as herpes simplex and polio type 1. Using a 50% plaque reduction assay, the antiviral activity of the primary components of the essential oil—terpinen-4-ol, α -terpene, γ -terpene, p-cymene, terpinoline, and α -terpineol—was evaluated. As a topical treatment for cutaneous infections, tea tree oil is used due to its broad-spectrum antibacterial effectiveness (78). Tea tree oil is formally referred to as "TTO" by the Australian Therapeutic Goods Administration. Local common names complicate matters; For example, "tea tree" can also mean "paperbark tree", which belong to several hundred species of the genera *Melaleuca* and *Leptospermum*. For example, *M. cajuputi* is called "swamp tea tree" and "paperbark tea tree", but *M. quinquenervia* is called "broad-leaved tea tree" and "broad-leaved paperbark". Additionally, several species of *Leptospermum* are grown for their aesthetic qualities and are commonly believed to be bona fide TTO sources (79). Tea tree oil components disrupt lipid membranes, inactivate free virions, and inhibit early gene expression, thereby significantly reducing viral infectivity. Topical formulations have shown rapid symptomatic relief and lesion regression in HSV-infected skin models (80).

5.1 Oregano oil

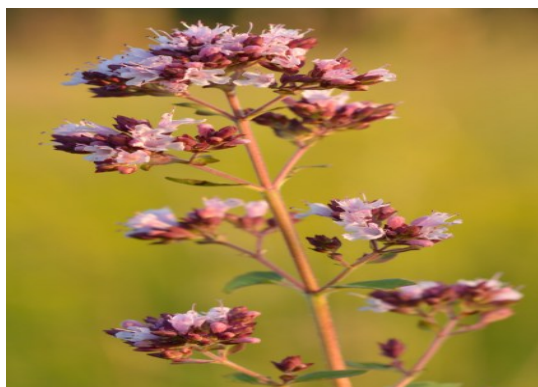


Fig. No. 10 Oregano Oil

Oregano oil (*Origanum vulgare*), which contains thymol and carvacrol, exhibits antiviral properties by destroying viral envelopes and preventing replication in host cells (81). By focusing on the viral capsid and making changes to the RNA, it can inactivate murine norovirus in just one hour. According to research, oregano oil efficiently destroys lipid-encapsulated viruses. Carvacrol and thymol inhibit viral fusion without interfering with virion binding (82).

5.2 *Syzygium aromaticum* (clove oil)

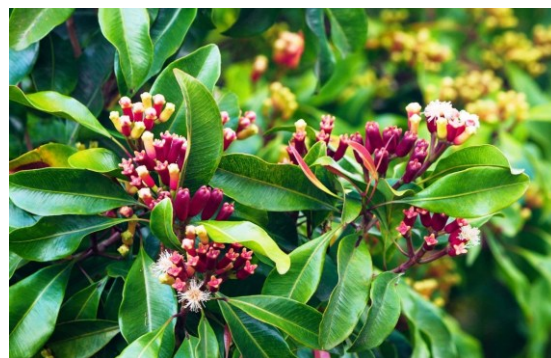


Fig. No. *Syzygium aromaticum*

Cloves are the dried flower buds of *Syzygium aromaticum*. They come as whole buds, powdered spices, and essential oils, with the oil being the strongest. Due to the oil content, the potency of whole cloves is medium, while that of crushed cloves (83). Clove essential oil (EOCA), which is rich in minerals such as manganese and magnesium, has important medicinal properties, especially a powerful antioxidant capacity due to the phenolic components. The main component is eugenol, and EOCA has demonstrated antiviral effectiveness, particularly against hepatitis A virus, with little selectivity against herpes simplex virus (84).

6. Nanotechnology-based Delivery Systems (Liposomes, Nanoparticles, Nanoemulsions)

The solubility and permeability of VAC extracts can be improved by nanoemulsion, which should increase

the oral bioavailability of the extract. The hydrophobic surfaces of phytoconstituents can be modified using nanoparticle systems (85). The formulation must release the active substance, the chemical complexity of the extract being essential for its efficacy. As a result, drugs must simultaneously increase drug solubility, postpone drug breakdown, reduce toxicity, and mask taste while regulating biological response and active absorption (86). Similar to nanoemulsions, solid-lipid nanoparticles are inexpensive, have good release profiles, are stable, can be scaled up for industrial manufacturing, and are food safe. Unlike emulsions or liposomes, they provide greater stability and retention of phytochemicals because they encapsulate bioactive molecules at their core. Specifically, these nanoparticles protect the molecules from gastrointestinal enzymes and inhibitors and other harmful environmental effects (87). As a result, the pharmaceutical field is increasingly using them to release biologically active substances – such as drugs, vaccines and enzymes – in a controlled manner to prevent a variety of disease.

6.1 Topical gels, creams, and transdermal patches

Lazolux Gel successfully reduces itching, burning and pain associated with genital herpes and herpes labialis. According to the results, 50% of patients should see resolution of their symptoms within two days for HSV-1 and three days for HSV-2 after treatment (88). Networks of water-dispersed, highly absorbent hydrophilic polymer chains form hydrogels. Due to the high water content in them, they are flexible to some extent. Since ancient times, these hydrogels have been observed in nature; Bacterial biofilm and plant structure.

6.2 Synergistic Formulations with Conventional Antivirals (e.g., Acyclovir + Herbal Extract Combinations:

To improve localized treatment, topical antiviral therapy delivers antiviral drugs directly to the infection site on skin or mucosal surfaces. Compared to systemic administration, this approach has several advantages, including greater patient compliance, fewer systemic adverse effects, and localized drug delivery. It works especially well for viral infections of the skin and mucosa brought about by molluscum

contagiosum virus, human papillomavirus, and herpes simplex virus (HSV) types 1 and 2. Acyclovir is a nucleoside antiviral drug that acts against herpes viruses and is authorized for use in intravenous, oral, and to some extent topical treatments to treat herpes simplex infections (89). Variable cross-resistance to other antivirals may result from changes in the viral thymidine kinase gene, which may lead to resistance to acyclovir. Acyclovir-resistant strains are uncommon in clinical settings and are mostly seen in patients with chronic mucocutaneous lesions who are immunocompromised (90).

7. Bioavailability Enhancement Techniques

Although herbal medicines and extracts demonstrate encouraging in vitro results, their in vivo effectiveness is often hindered due to poor lipid solubility or unsuitable molecular size, leading to inadequate absorption and bioavailability (91). Oral bioavailability problems prevent drugs from reaching the minimum effective concentration required for medicinal action. Because only a small percentage of the supplied dose enters the systemic circulation to reach the target organ, their oral doses are often large (92). The primary drugs approved to treat herpesvirus infections work as nucleoside analogs that compete with natural nucleosides or nucleotides by inhibiting DNA polymerase. Acyclovir, penciclovir, valacyclovir, famciclovir, valomaciclovir, ganciclovir, valganciclovir, cidofovir and brincidofovir are important antiviral drugs (93).

8. Cytotoxicity and Selectivity Indices

Cytotoxicity testing is the first biocompatibility assessment performed before animal studies, as recommended by ISO 10993-2, to reduce unnecessary animal use. These in vitro tests provide results within a few days and help determine whether materials are safe enough to proceed to animal research (94). Although animal studies remain important for evaluating drug safety and efficacy, their use has significantly declined—dropping from near-universal testing in the 1970s to around 30% today. Animal models continue to play a key role in bridging basic research and human clinical trials. For HSV-1 and HSV-2, there is still no cure; however, antiviral drugs—particularly acyclic guanosine analogs that inhibit viral DNA replication—remain the standard



treatment for reducing the frequency and severity of outbreaks (95).

Table No. 3 Safety, Tolerability and Efficacy Outcomes:

Herbal Product Extract	Formulation & Study Type	Efficacy Outcomes	Safety Tolerability Outcomes	References
<i>Melissa officinalis</i> (Lemon balm)	Topical cream	decreased lesion size, healing duration, and pain as compared to a placebo; if given early, it may also prevent recurrence.	It is well tolerated and infrequently causes moderate local discomfort.	(96)
<i>Sage + Rhubarb extract</i>	Topical cream	Rhubarb-sage have comparable healing times of 6.5 and 6.7 days, respectively.	Good tolerance and little local discomfort.	(97)
<i>Propolis extract</i>	Topical ointment (multiple RCTs)	In addition to a decrease in symptoms, recovery happens more quickly than a placebo.	A few subjects reported mild irritation, but the intervention was deemed safe overall.	(98)
<i>Olea europaea</i> (Olive leaf extract)	Topical gel, oral supplement (pilot study)	Although there is little information available, minor HSV infections have been shown to provide antiviral and anti-inflammatory benefits.	No major adverse events reported.	(99)
<i>Uncaria tomentosa</i> (Cat's claw)	50 mg/g topical gel (open-label, n=150; HSV-1 & HSV-2)	By day 10, 68% of lesions had healed completely, and comfort had increased.	A tolerability assessment of "Very Good" at 54% was indicated by the reporting of ten mild to moderate transitory side events.	(100)
<i>Elaeocarpus sylvestris</i> var. <i>ellipticus</i> (ES16001)	Oral extract	Its potential as an antiviral against herpes viruses, especially varicella-zoster, has been studied.	There was a little and transient increase in ALT, and no significant side effects were noted. Up to 1,440 mg in a single dose is thought to be safe.	(101)

Table No. 4 Preclinical research focuses on identifying antiviral, anti-inflammatory, and immunomodulatory compounds from plants.

Herb/Plant	Active Compounds	Mechanism of Action	Reference
<i>Melissa officinalis</i> (Lemon balm)	Rosmarinic acid, caffeic acid	Inhibits HSV-1 adsorption and replication	(102)
<i>Glycyrrhiza glabra</i> (Licorice root)	Glycyrrhizin, liquiritigenin	Blocks viral gene expression and reduces inflammation	(103)
<i>Hypericum perforatum</i> (St. John's Wort)	Hypericin	Virucidal activity, inhibits HSV-1 entry	(104)
<i>Camellia sinensis</i> (Green tea)	EGCG (Epigallocatechin gallate)	Inhibits HSV-1 and HSV-2 replication and cell entry	(105)
<i>Aloe vera</i>	Polysaccharides, anthraquinones	Enhances healing, reduces viral titers	(69,106)



<i>Echinacea purpurea</i>	Alkamides, caffeic acid derivatives	Immunomodulatory effects; reduces HSV recurrence	(107)
<i>Zingiber officinale</i> (Ginger)	Gingerols, shogaols	Anti-inflammatory and antiviral synergy	(108)
<i>Hypericum perforatum</i>	Polysaccharides, rosmarinic acid	Inhibits HSV attachment and penetration	(109)

challenges and gaps:

Despite promising antiviral activity, several challenges limit the translational potential of herbal compounds against HSV. Most evidence comes from in vitro studies or animal models, with limited clinical trials evaluating safety and efficacy in humans. Many polyphenols and tannins also exhibit poor bioavailability, making it difficult to achieve therapeutically relevant concentrations in target tissues. While their multi-target mechanisms offer advantages, they complicate precise mechanistic elucidation, requiring detailed molecular studies to identify specific viral and host targets. Additionally, long-term safety, pharmacokinetics, and potential off-target effects on host metabolism and signaling remain poorly understood. Finally, variability in plant extract composition underscores the need for standardization of active compounds, such as quantifying wogonin or specific tannins, to ensure reproducibility and reliable therapeutic outcomes.

13. Summary & Conclusion

Herpes simplex virus (HSV) remains a global health challenge due to its lifelong latency and periodic reactivation. Standard antivirals help reduce symptoms and viral shedding but face limitations such as resistance, incomplete suppression, cost, and patient preference for natural options. These factors have driven interest in herbal and plant-based therapies. Extracts from plants such as lemon balm, Aloe vera, *Prunella vulgaris*, licorice root, *Echinacea*, tea tree oil, and propolis show antiviral, anti-inflammatory, and immune-modulating effects, with some interfering with viral attachment or replication and supporting lesion healing. Lemon balm, propolis, and *Prunella vulgaris* currently have the strongest evidence, though most studies remain small and lack standardized dosing and formulations. Overall, herbal remedies may serve as safe and accessible complementary options for HSV management but

should not replace established antiviral drugs. More rigorous clinical trials are needed to confirm their efficacy, mechanisms, and long-term safety.

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