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Review of Whole Plant Extracts With Activity Against Herpes Simplex Viruses In Vitro and In Vivo

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Abstract

Herpes simplex viruses, HSV-1 and HSV-2, are highly contagious and cause lifelong, latent infections with recurrent outbreaks of oral and/or genital lesions. No cure exists for HSV-1 or HSV-2 infections, but antiviral medications are commonly used to prevent and treat outbreaks. Resistance to antivirals has begun to emerge, placing an importance on finding new and effective therapies for prophylaxis and treatment of HSV outbreaks. Botanicals may be effective HSV therapies as the constituents they contain act through a variety of mechanisms, potentially making the development of antiviral resistance more challenging. A wide variety of plants from different regions in the world have been studied for antiviral activity against HSV-1 and/or HSV-2 and showed efficacy of varying degrees. The purpose of this review is to summarize research conducted on whole plant extracts against HSV-1 and/or HSV-2 in vitro and in vivo. The majority of the research reviewed was conducted in vitro using animal cell lines, and some studies used an animal model design. Also summarized are a limited number of human trials conducted using botanical therapies on HSV lesions.

Keywords

plant extract, botanical, herbal medicine, herpes simplex, HSV

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Introduction

Herpes simplex viruses (HSV) are highly contagious, double-stranded DNA viruses that cause recurrent lesions.[1] They affect all age groups around the world, have no seasonal variation, and infect both humans and animals.[2,3] Appearance of lesions at the primary site of infection can occur following initial infection of abraded skin or mucosal epithelial cells.[2] Subsequently, the virus can establish a lifelong, latent infection in trigeminal or lumbosacral ganglia, which can be reactivated in certain conditions.[1] These conditions include physiological and psychological stress, fatigue, ultraviolet irradiation, physical trauma, abnormal hormone levels, immunosuppression, menstruation, fever, and upper respiratory tract infections.[4,5] Both primary and recurrent HSV infections may be symptomless, however, reactivation typically produces ulcerations at the primary site.[6] During reactivation, but before physical symptoms arise, HSV can be virally shed, thereby having the ability to be transmitted asymptomatically.[1] This makes HSV difficult to contain and efficient in spreading person-to-person.

HSV are categorized into 2 types: type 1 (HSV-1) and type 2 (HSV-2), which share >80% amino acid similarity.[1] Both types can cause oral and genital lesions, although HSV-1 mainly causes infection in or around the mouth (herpes labalis), and HSV-2 mainly causes infection in the genital or anal region (herpes genitalis).[2] HSV-1 is typically transmitted via oral-to-oral contact, but oral-genital contact is possible in transmitting the virus.[2] Although HSV-1 has been traditionally known to cause herpes labialis, it is currently the leading cause of newly acquired herpes genitalis and neonatal herpes in high income countries.[1] HSV-2 is considered a sexually transmitted infection and mainly transmitted during sexual activity.[2] HSV-2 is

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the leading cause of genital ulcer disease worldwide and also causes neonatal herpes, which is transmitted vertically from mother to newborn during birth.[1] According to 2012 data, the World Health Organization estimates the prevalence of HSV-1 and HSV-2 in the Americas to be 40-50% and 14%, respectively.[7]

Primary symptoms of herpes labialis infection include erythema, blisters, and ulcers that are 2 to 10 mm in diameter in and around the mouth, on the tongue, and particularly on the lips.[5] Burning pain precedes and accompanies the lesions.[5] Fever may also be present, and it is common for adults to present with a sore throat and cervical lymph node swelling.[5] Primary symptoms of herpes genitalis infection include macules and papules in the genital or anal region that progress to vesicles, pustules, and ulcers.[8] Pain at the site of lesions and tender regional adenopathy is also common.[8] Initial infection may be accompanied with urethritis, cervicitis, headache, fever, malaise, and/or myalgias.[8] Diagnosis of herpes labialis and herpes genitalis is typically done through taking patients' histories, presentation of symptoms, and performing physical exams.[6] Viral culture or detection of HSV DNA in the urine can confirm diagnosis, and blood tests testing antibodies against HSV can confirm previous infection.[6]

Biological properties of HSV are neuroinvasiveness, neurotoxicity, and latency.[2] Less common than HSV infections, serious complications include meningitis, encephalitis, neonatal infection, and keratitis.[1] HSV-1 has also been found to increase the risk of Alzheimer's Disease,[9] and HSV-2 increases the risk of acquiring an HIV infection.[1] Although HSV sequelae can be serious, HSV infection is rarely fatal.[2] However, HSV infections negatively affect individuals' quality of life. Individuals with herpes labialis have reported limitation of time and difficulties in daily activities, reduction in physical efforts and social activities, increase in physical pain, tiredness, and exhaustion, and a strong limitation on work and household duties.[10] Moreover, quality of life is reduced for individuals with herpes genitalis as they report poorer general, mental, and emotional health, vitality, social functioning, and increased bodily pain.[11] Management of HSV infections is therefore important in improving the health and general well-being of individuals that suffer from these recurrent infections.

There is no cure for HSV-1 or HSV-2, but antiviral medications are commonly used to prevent, shorten, or reduce severity of recurrent outbreaks.[6] Acyclic guanosine analogues that target viral DNA replication are the first-line therapy in the management of HSV.[12] Of this class, acyclovir has been considered the gold standard for both prophylaxis and treatment since the 1980s.[12] However, the evidence for the use of acyclovir and other nucleoside analogues for both herpes labialis and herpes genitalis in this manner has produced inconsistent results.[13-16] Considering the chronic nature of HSV infections, long-term use of antiviral medications has led to cases of drug resistance, particularly in immunocompromised individuals.[12] This places an importance in exploring new and effective strategies and therapies to prevent and treat HSV outbreaks.

Non-pharmaceutical strategies such as zinc, vitamin C, lysine, and a diet low in arginine have shown some beneficial effects for managing HSV infections, but results are modest and inconsistent.[5,17-21] In 2 studies, the application of a zinc-containing cream for treatment of herpes labialis outbreaks was found to modestly reduce severity of associated symptoms and healing time.[5] Moreover, topical treatment with a strong ascorbic acid-containing solution was found to shorten the persistence of scabs caused by HSV by 2.5 days.[17] An older study found herpes labialis outbreaks to be cleared in 4.2 days on average after oral administration of a water-soluble bioflavonoid-ascorbic acid complex.[18] More recently, a pilot study used an oral combination of pine cone lignin and ascorbic acid to treat active HSV-1 lesions and found subjects did not develop characteristic lesions when treatment was initiated within the first 48 hours of symptoms.[19] If treatment was initiated later, subjects reported a reduction in symptoms and healing time compared to previous outbreaks.[19] These studies shed light on the idea that combination therapies for managing HSV infections could be more effective than single therapies.

Moreover, the use of oral lysine, an amino acid, in preventing and treating HSV infections has been found to be ineffective at doses of 1 gram per day without consumption of a low arginine diet.[20] The rationale for using lysine comes from tissue culture findings that demonstrate viral replication is suppressed when the ratio of lysine-to-arginine is high.[22] This is also the rationale for why a diet low in arginine can help manage outbreaks, but evidence does not support the use of one without the other.[20] However, treatment with greater than 3 grams of lysine per day has shown to improve the subjective experience associated with HSV infections.[20] Furthermore, one study using a herbal-based ointment consisting of lysine combined with ingredients such as zinc oxide, echinacea, and goldenseal found complete resolution of herpes labialis outbreaks by day three in 40% of participants.[21] The benefits of this herbal ointment could be due to the diverse constituents in combined botanicals that act through various mechanisms of actions, compared to a single ingredient as treatment.

The various mechanisms of action that botanical therapies can elicit on HSV give them potential to have beneficial effects on prophylaxis and treatment of the infection. Particularly, some have demonstrated strong antiviral activity that acts at various stages of viral growth.[23] Natural remedies also have fewer side effects, less resistance to medications, and lower toxicity than pharmacological treatments.[23] For these reasons, many botanicals have been studied for their effects on HSV.

Methods

The aim of this review is to summarize research on botanicals that have been studied for their antiviral effects against HSV-1 and/or HSV-2. An article search was conducted on Pubmed using the following MeSH terms: plant extracts; plants, medicinal; phytotherapy; herbal medicine; herpes simplex; and/or simplexvirus. Results were reviewed, and studies that used whole plant extracts up to a publication date of April 2020 were included. Studies were excluded if the

article's full-text was not available. Studies that investigated antiviral effects of constituents from plant extracts were also excluded as the topic of this review is whole plant extracts. A list of all botanicals studied in the articles reviewed is presented in Table 1. The review is organized by single herbs studied in vitro (organized geographically by continent of plant origin) and in vivo, herbal combinations studied in vitro and in vivo, and lastly human trials with either single or combination herbs.

Single Herbs In vitro

Africa

The antiviral activity of 4 methanolic extracts of Combretum micranthum was tested against HSV-1 (strain F) and HSV-2 (strain G) by Ferrea et al.[72] Dried leaves were used to prepare the extracts using 4 different solvents: regular methanol, aqueous methanol, aqueous methanol with addition of HCl and NaOH, and NaOH autoxidized methanol. Only the NaOH autoxidized methanolic extract showed anti-HSV activity. The authors believe this is due to inactive precursors in the plant being transformed to active compounds by alkaline catalysis. The extract was more effective when cells were treated at the same time of viral infection (EC_{50} was 8 μg/ml and 19 μg/ml for HSV-1 and HSV-2, respectively) compared to treatment after 1 hour of viral adsorption (EC_{50} was 150 μg/ml and 227 μg/ml for HSV-1 and HSV-2, respectively). These results show that C. micranthum is potentially more effective against HSV-1 than HSV-2.

Beuscher et al.[68] tested 56 extracts of African medicinal plants for antiherpetic activity and found 6 to be effective against HSV-1 (Mclntyre strain). However, toxicity to green monkey kidney (GMK) cells was noted with increasing concentrations of each extract before 100% plaque reduction could be obtained. The extracts that exhibited anti-HSV activity in vitro were the dichloromethane extract of Chironia krebsii (EC range = 6.25-12.5 μg/ml); the 25% ethanolic extract of Jasminum fluminense (EC range = 50-200μg/ml); the methanolic extract of Mitragyna inermis (EC range = 50-100 μg/ml); the 25% ethanolic extract of Polygala virgata (EC range = 400-600 μg/ml); the methanolic extract of Securidaca longepedunculata (EC range = 12.5-25 μg/ml); and the 25% ethanolic extract of Securidaca longepedunculata (EC range = 2.5-6 μg/ml).

Another African plant, Helichrysum aureonitens, was tested by Meyer et al.[103] for its reported antimicrobial properties and showed antiviral activity against HSV-1 in human lung fibroblast cells. A crude aqueous extract was prepared from plant shoots, excluding its flowers, and simultaneously added with HSV-1 viral suspension to cells. After 1 week of incubation, no cytotoxic effect was noted in cells and significant antiviral activity was exhibited at an extract concentration of 1.35 mg/ml.

Furthermore, Kudi and Myint[35] investigated 17 Nigerian medicinal plants for antiherpetic activity in human colonic cancer cells (HT-29 cells). The plants are locally used for indications such as fever, diarrhea, worms, sexually-transmitted infections, enteric conditions, and skin conditions. Ethanolic extracts were prepared of each plant using either the leaves, bark, or whole plant. Extracts were added to cells after HSV-1 adsorption, and authors deemed an extract to have antiviral activity if it inhibited the cytopathologic effect of the virus by 100%. Of the 17 plant extracts, 4 showed anti-HSV activity: Bauhinia thonningii, Anacardium occidentale, Dichrostachys glomerata, and Sterculia setigera. These extracts did not exhibit cytotoxicity to HT-29 cells at a dose of 400 μg/100 μl, and their antiviral effects were noted at a dose of 100 μg/100 μl for each extract.

Another group of researchers, Fortin et al.,[70] studied a collection of medicinal plants from La Réunion Island that are traditionally used for ailments such as insomnia, diarrhea, hypertension, abdominal pain, skin manifestations, and fever. Methanolic extracts of each herb were tested against HSV-1 (strain H29). Of the 36 plants tested, 5 exhibited antiviral activity: Obetia ficifolia (EC_{50} = 7 μg/ml), Lomatophyllum macrum (EC_{50} = 64 μg/ml), Citrus hystrix (EC_{50} = 91 μg/ml), Erythroxylum laurifolium (EC_{50} = 125 μg/ml), and Senecio ambavilla (EC_{50} = 170 μg/ml). The authors also tested the antiviral activity of acyclovir and found its EC_{50} to be 3.3 μg/ml. O. ficifolia and E. laurifolium were noted to have the strongest anti-HSV activity, but the authors did not further explain their reasoning for this remark.

Tolo et al.[62] investigated the anti-HSV activity of Carissa edulis, a medicinal plant that grows locally in Kenya and used traditionally for a variety of ailments such as skin conditions and sexually transmitted infections. An aqueous extract was prepared from C. edulis roots, freeze-dried, and tested against wild-type HSV-1 (strain 7401 H) and HSV-2 (strain Ito-1262), thymidine kinase-deficient HSV-1 (strain B2006), and acyclovir-resistant 7401 H HSV-1. The extract inhibited plaque formation of all 4 strains, but wild-type HSV-2 (EC_{50} = 6.9 μg/ml and SI = 69.6) and thymidine kinase-deficient HSV-1 strain (EC_{50} = 8.1 μg/ml and SI = 59.3) were more susceptible to the extract. Moreover, at 200 μg/ml, the extract reduced viral yields of acyclovir-resistant HSV-1 strain by 100%, wild-type HSV-2 strain by 99.5%, wild-type HSV-1 strain by 97.8%, and thymidine kinase-deficient HSV-1 strain by 96.3%. These results are significant considering acyclovir at 5 μg/ml was tested against thymidine kinase-deficient HSV-1 strain and acyclovir-resistant HSV-1 strain and showed a viral yield reduction of only 3.0% and 1.5%, respectively.

Fifty extracts from 15 Tunisian medicinal plants were studied for their antiviral activity against HSV-1 (strain 17) by Sassi et al.[84] Four extracts from 3 plants exhibited antiherpetic activity, defined by the authors as inhibiting more than 50% of HSV-1. These extracts were the methanolic extract of Erica multiflora (EC_{50} = 132.6 μg/ml and SI >3.77), the acetonic (EC_{50} = 489.5 μg/ml and SI >1.02) and methanolic (EC_{50} = 486.2 μg/ml and SI >1.03) extracts of Frankenia pulverulenta, and the acetonic extract of Zygophyllum album (EC_{50} = 390.7 μg/ml and SI >1.28). Both the methanolic extract of E. multiflora and the acetonic extract of Z. album showed complete cell protection against HSV-1 at 2000 μg/ml.

Schnitzler et al.[136] tested an aqueous extract of the African medicinal plant Pelargonium sidoides for its ability to act

Table 1. Whole Plant Extracts That Demonstrate Anti-HSV Activity.

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
Single herb studies									
Achyranthes aspera	Devil's horsewhip	Amaranthaceae	Root	Methanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1 and HSV-2, but was more potent against HSV-1.	Mukherjee et al., 2013[24]
Achyrocline flaccida		Asteraceae	Aerial parts	Water	In vitro	Vero cells		Extract demonstrated ability to prevent HSV-1 adsorption and penetration.	Garcia et al., 1999[25]
Achyrocline satureioides		Asteraceae	Not specified	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Faral-tello et al., 2012[26]
Adiantum latifolium	Broadleaf maidenhair	Pteridaceae	Aerial parts	Methanol	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Lopez et al., 2001[27]
Aglaia odorata	Chinese perfume plant	Meliaceae	Leaf	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral effects against HSV-1 and was more effective on the wild-type strain.	Lipipun et al., 2003[28]
			Leaf	Ethanol	In vivo		BALB/c mice	Extract decreased size and development of skin lesions from HSV-1, reduced mortality of the mice, and increased survival time.	Lipipun et al., 2003[28]
Agrimonia pilosa	Hairy agrimony	Rosaceae	Whole plant	Water	In vitro	Vero cells		Extract demonstrated antiviral effects against 3 HSV-1 strains, but was more effective on the acyclovir-resistant strain.	Li et al., 2004[29]
Aloe vera	Aloe	Asphodelaceae	Leaf	Glycerine	In vitro	Vero cells		Extract demonstrated antiviral activity during and post-HSV-2 infection.	Zandi et al., 2007[30]
Aloysia gratissima	Whitebrush	Verbenaceae	Not specified	Hydroethanol Water	In vitro	Vero cells		Hydroethanolic extract demonstrated antiviral activity against 2 HSV-1 strains.	Montanha et al., 2004[31]
			Leaf Fruit	Essential oil	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Garcia et al., 2004[32]
Alpinia officinarum	Lesser galangal	Zingiberaceae	Rhizome	Water	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Kurokawa et al., 1993[33]
			Rhizome	Water	In vivo		BALB/c mice	Extract significantly delayed the development and progression of HSV-1 lesions.	Kurokawa et al., 1993[33]
Alternanthera sessilis	Sessile joyweed	Amaranthaceae	Leaf	Ethanol	In vitro	Vero cells HeLa cells		Extract demonstrated antiviral activity against HSV-1.	Abdul et al., 1996[34]
Ampelozizyphus amazonicus		Rhamnaceae	Leaf	Methanol	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Lopez et al., 2001[27]
Anacardium occidentale	Cashew	Anacardiaceae	Bark	Ethanol	In vitro	HT-29 cells		Extract demonstrated complete HSV-1 inhibition.	Kudi and Myint, 1999[35]
Anemone obtusiloba	Ratanjot Rikabe	Ranunculaceae	Root	Methanol	In vitro	Vero cells		Extract demonstrated partial HSV-1 inhibition.	Taylor et al., 1996[36]
Anemopaegma setilobum		Bignoniaceae	Leaf Stem	Ethanol	In vitro	Vero cells		Both ethanolic leaf and stem extracts demonstrated minimal antiviral activity against HSV-1.	Brandao et al., 2010[37]
Annona muricata	Soursop	Annonaceae	Stembark	Water Ethanol	In vitro	Vero cells		Ethanolic extract demonstrated complete cytopathic effects against HSV-1.	Padma et al., 1998[38]
Antrodia camphorata		Polyporaceae	Mycelia	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1 and HSV-2.	He et al., 2016[39]
Arachis hypogaea	Peanut	Fabaceae	Seed	Water	In vitro	BCC-1/KMC cells		Extract demonstrated moderate antiviral activity against HSV-2.	Chiang et al., 2003[40]
Araucaria angustifolia	Brazilian pine	Araucariaceae	Leaf	Dichloromethane Ethyl acetate n-Butanol	In vitro	Vero cells		Ethyl acetate and n-butanol extracts demonstrated similar antiviral activity against one HSV-1 strain.	Andrighetti-Frohner et al., 2005[41]
Arctium lappa	Greater burdock	Asteraceae	Fruit	Hydroethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Dias et al., 2017[42]

(continued)

Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
Ardisia squamulosa	Tagpo	Myrsinaceae	Stem Leaf	Water	In vitro	BCC-1/KMC cells		Extract demonstrated moderate antiviral activity against HSV-1.	Chiang et al., 2003[43]
Arisaema tortuosum	Whipcord cobra lily	Araceae	Leaf	Ethanol n-Hexane Chloroform Ethyl acetate n-Butanol	In vitro	Vero cells		Chloroform extract showed strong antiviral activity against HSV-2 and moderate activity against HSV-1.	Ritta et al., 2020[44]
Aristotelia chilensis	Maqui Chilean Wineberry	Elaeocarpaceae	Leaf	Hydroethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-2.	Pacheco et al., 1993[45]
Arrabidaea craterophora		Bignoniaceae	Leaf Stem	Ethanol	In vitro	Vero cells		Ethanolic stem extract demonstrated minimal antiviral activity against HSV-1.	Brandao et al., 2010[37]
Arrabidaea formosa		Bignoniaceae	Leaf Stem Fruit	Ethanol	In vitro	Vero cells		Leaf and stem ethanolic extracts demonstrated moderate antiviral activity against HSV-1, while the fruit ethanolic extract had minimal antiviral activity.	Brandao et al., 2010[37]
Arrabidaea pulchra		Bignoniaceae	Leaf	Ethanol	In vitro	Vero cells		Extract demonstrated minimal antiviral activity against HSV-1.	Brandao et al., 2010[37]
Arrabidaea sceptrum		Bignoniaceae	Leaf Stem	Ethanol	In vitro	Vero cells		Stem ethanolic extract demonstrated minimal antiviral activity against HSV-1.	Brandao et al., 2010[37]
Artemisia douglasiana	California mugwort	Asteraceae	Leaf	Essential oil	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Garcia et al., 2004[32]
Atractylis macrophylla		Asteraceae	Not specified	Acetone Methanol	In vitro	Vero cells		Acetonic extract demonstrated modest antiviral activity against HSV-1 and HSV-2.	Jaeger Greer et al., 2010[46]
Auriporia aureus		Polyporaceae	Mycelia	Sodium chloride	In vitro	RK-13 cells		Extract demonstrated antiviral activity against HSV-2.	Krupodorova et al., 2014[47]
Avicenna marina	Gray/white mangrove	Acanthaceae	Leaf	Methanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-2.	Behbahani et al., 2013[48]
Azadirachta indica	Neem tree	Meliaceae	Leaf	Water	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Lipipun et al., 2003[28]
			Bark	Water	In vitro	CHO-K1 cells HeLa cells Vero cells RPE cells		Extract blocked HSV-1 entry into cells, inhibited viral attachment, and blocked viral glycoprotein mediated cell-cell fusion.	Tiwari et al., 2010[49]
Baccharis anomala		Asteraceae	Aerial parts	Water	In vitro	Vero cells		Extract demonstrated antiviral activity against 2 HSV-1 strains.	Venturi et al., 2017[50]
Baccharis erioclada		Asteraceae	Not specified	Hydroethanol Water	In vitro	Vero cells		Hydroethanolic and water extracts demonstrated antiviral activity against 3 HSV-1 strains.	Montanha et al., 2004[31]
Baccharis genistelloides	Carqueja	Asteraceae	Not specified	Ethanol water	In vitro	HeLa cells Vero cells		Water extract demonstrated antiviral activity against HSV-1, but the upper limit of its effective range was cytotoxic.	Abad et al., 1999[51]
Baccharis megapotamica		Asteraceae	Not specified	Hydroethanol Water	In vitro	Vero cells		Hydroethanolic extract demonstrated antiviral activity against one HSV-1 strain.	Montanha et al., 2004[31]
Baccharis rubricaulis	Rubby	Asteraceae	Not specified	Ethanol Water	In vitro	HeLa cells Vero cells		Water extract demonstrated antiviral activity against HSV-1, but the upper limit of its effective range was cytotoxic.	Abad et al., 1999[51]
Baccharis trinervis		Asteraceae	Not specified	Water Ethanol	In vitro	HeLa cells		Water extract completely inhibited HSV-1 replication.	Abad et al., 1999[52]
Baccharis uncinella		Asteraceae	Not specified	Hydroethanol Water	In vitro	Vero cells		Hydroethanolic extract demonstrated antiviral activity against 2 HSV-1 strains.	Montanha et al., 2004[31]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
Barleria lupulina	Hophead	Acanthaceae	Leaf Twig	Methanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-2 standard strain and clinical isolates, but activity was much weaker than acyclovir.	Yoosook et al., 1999[53]
Bauhinia candicans		Fabaceae	Not specified	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Faral-tello et al., 2012[26]
Bauhinia thonningii	Kalgo	Fabaceae	Leaf	Ethanol	In vitro	HT-29 cells		Extract demonstrated complete viral inhibition against HSV-1.	Kudi and Myint, 1999[35]
Bauhinia variegata	Orchid tree Mountain ebony	Fabaceae	Stem Leaf	Water	In vitro	BCC-1/KMC cells		Extract demonstrated moderate antiviral activity against HSV-1 and HSV-2.	Chiang et al., 2003[40]
Blumea chinensis	Katarai	Compositae	Leaf	Ethanol	In vitro	Vero cells HeLa cells		Extract demonstrated antiviral activity against HSV-1.	Abdul et al., 1996[34]
Blumea lacera	Lettuce-leaf blumea	Compositae	Whole plant	Water	In vitro	BCC-1/KMC cells		Extract demonstrated potent antiviral activity against HSV-1 and HSV-2.	Chiang et al., 2004[54]
Boletus edulis	Porcini mushroom	Boletaceae	Fruit	Water Methanol	In vitro	Vero cells		Water extract demonstrated greater antiviral activity against HSV-1 than the methanolic extract.	Santoyo et al., 2012[55]
Boswellia ameero		Burseraceae	Bark	Water Methanol	In vitro	Vero cells		Methanolic extract demonstrated antiviral activity against HSV-1.	Mothana et al., 2006[56]
Boswellia elongata		Burseraceae	Bark	Water Methanol	In vitro	Vero cells		Methanolic extract demonstrated strong antiviral activity against HSV-1.	Mothana et al., 2006[56]
Boussingaultia gracilis		Basellaceae	Whole plant	Water	In vitro	BCC-1/KMC cells		Extract demonstrated potent antiviral activity against HSV-1 and moderate activity against HSV-2.	Chiang et al., 2003[43]
Brainia insignis		Blechnaceae	Rhizome	Water	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Kurokawa et al., 1993[33]
Buxus hildebrandtii	Box wood	Buxaceae	Leaf	Water Methanol	In vitro	Vero cells		Methanolic extract demonstrated strong antiviral activity against HSV-1.	Mothana et al., 2006[56]
Byrsonima verbascifolia		Malphigiaceae	Leaf Root bark	Methanol	In vitro	Vero cells		Both leaf and root bark extracts demonstrated complete HSV-1 inhibition.	Lopez et al., 2001[27]
Caesalpinia pulcherrima	Peacock flower	Fabaceae	Flower Stem and leaf Fruit and seed	Water	In vitro	BCC-1/KMC cells		Flower extract showed moderate antiviral activity against HSV-1 and HSV-2. The other extracts showed weaker antiviral activity to both viruses.	Chiang et al., 2003[57]
Caesalpinia sappan	Sappanwood	Fabaceae	Bark	Water	In vivo		BALB/c mice	Extract significantly delayed the development and progression of HSV-1 lesions.	Kurokawa et al., 1993[33]
Cajanus cajan	Pigeon pea	Fabaceae	Aerial parts	Water Ethanol	In vitro	RC-37 cells		Ethanolic extract demonstrated stronger antiviral effects against HSV-1 and HSV-2 compared to the water extract.	Zu et al., 2010[58]
Calotropis gigantea	Giant milkweed	Asclepiadaceae	Leaf	Ethanol	In vitro	Vero cells HeLa cells		Extract demonstrated antiviral activity against HSV-1.	Abdul et al., 1996[34]
Camelia sinensis	Green tea	Theaceae	Leaf	Water	In vitro	Hep-2 cells		Extract demonstrated significant antiviral effects against HSV-1 at one and 2 hours post-treatment.	Farahani et al., 2014[59]
Campomanesia eugenioides	Gabiroba	Myrtaceae	Leaf	Water Hydroalcohol	In vitro	Vero cells		All extracts demonstrated antiviral activity against HSV-1, but the 70% hydroalcoholic extract was most potent.	Moura-costa et al., 2012[60]
Capparis sinaica	Egyptian caper	Capparaceae	Aerial parts	Hydroethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Soltan and Zaki, 2009[61]
Carissa edulis	Egyptian carissa	Apocynaceae	Root	Water	In vitro	Vero cells		Extract showed antiviral activity against different HSV-1 and HSV-2 strains.	Tolo et al., 2006[62]
			Root	Water	In vivo		BALB/c mice		Tolo et al., 2006[62]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
								Extract reduced time to onset of infection with 2 HSV-1 strains, and additionally increased survival time and reduced mortality rates with wild-type HSV-1.	
Cassia socotrana		Caesalpiniaceae	Leaf Fruit	Water Methanol	In vitro	Vero cells		Methanolic extract demonstrated antiviral activity against HSV-1.	Mothana et al., 2006[56]
Cassia stipulaceae		Caesalpiniaceae	Aerial parts	Hydroethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Pacheco et al., 1993[45]
Ceanothus Coeruleus	California lilac	Rhamnaceae	Root	Ethyl acetate	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1 and HSV-2.	Silva-Mares et al., 2019[63]
Cecropia glaziovii		Urticaceae	Leaf	Hydroethanol	In vitro	Vero cells		Extract demonstrated strong antiviral activity against acyclovir-resistant HSV-1.	Petronilho et al., 2012[64]
Cedrus libani	Cedar of Lebanon	Pinaceae	Cone Leaf Bark	Ethanol Essential oil	In vitro	Vero cells		All extracts demonstrated antiviral activity against HSV-1.	Loizzo et al., 2008[65]
Centella asiatica	Gotu kola	Apiaceae	Aerial parts	Water	In vitro	Vero cells		Extract showed antiviral activity against HSV-1 and HSV-2. Combination with Mangifera indica showed an additive effect on HSV-2.	Yoosook et al., 2000[66]
Centipeda minima	Hachhyun Hachhi mran	Asteraceae	Aerial parts	Methanol	In vitro	Vero cells		Extract demonstrated partial HSV-1 inhibition.	Taylor et al., 1996[36]
Ceramium rubrum	Red hornweed	Ceramiaceae	Whole plant	Water	In vitro	Vero cells E6SM cells		Extract demonstrated antiviral activity against HSV-2 and 2 HSV-1 strains.	Serkedjieva et al., 2004[67]
Cerbera odollam	Suicide tree	Apocynaceae	Leaf	Water	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Lipipun et al., 2003[28]
Chenopodium ambrosioides	Wormseed	Amaranthaceae	Not specified	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Faral-tello et al., 2012[26]
Chironia krebsii	Kreb's chironia	Gentianaceae	Root	Dichloromethane	In vitro	GMK cells		Extract demonstrated antiviral activity against HSV-1.	Beuscher et al., 1994[68]
Chondracanthus acicularis		Gigartinaceae	Whole plant	Dichloromethane and methanol	In vitro	Vero cells		Extract demonstrated strong antiviral activity against acyclovir-resistant HSV-2, but not against acyclovir-resistant HSV-1.	Soares et al., 2012[69]
Chrysactinia mexicana	Damianita daisy	Asteraceae	Root	Ethyl ether	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1 and HSV-2.	Silva-Mares et al., 2019[63]
Cissus hamaderohensis		Vitaceae	Leaf	Methanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Mothana et al., 2006[56]
Cissus subaphylla		Vitaceae	Leaf	Water Methanol	In vitro	Vero cells		Methanolic extract demonstrated strong antiviral activity against HSV-1.	Mothana et al., 2006[56]
Citrus hystrix	Combava	Rutaceae	Leaf	Methanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Fortin et al., 2002[70]
Clematis cirrhosa	Freckles Clematis	Ranunculaceae	Not specified	Acetone Methanol	In vitro	Vero cells		Acetonic extract demonstrated antiviral activity against HSV-1 and HSV-2.	Jaeger Greer et al., 2012[46]
Clematis drummondii	Old man's beard Texas virgin's bower Barba de chivato	Ranunculaceae	Aerial parts	Methanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1 and HSV-2.	Silva-Mares et al., 2019[63]
Clinacanthus nutans		Acanthaceae	Whole plant	Methanol	In vitro	Vero cells		Extract only demonstrated antiviral activity against HSV-2 standard strain and clinical isolates at its highest non-cytotoxic dose.	Yoosook et al., 1999[53]
			Leaf	n-Hexane Dichloromethane Methanol	In vitro	Vero cells		All extracts demonstrated antiviral activity against HSV-1 and HSV-2. The n-hexane extract was most potent against HSV-1, while the methanolic extract was most potent against HSV-2.	Kunsorn et al., 2013[71]
		Acanthaceae	Leaf		In vitro	Vero cells			Kunsorn et al., 2013[71]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
Clinacanthus siamensis				n-Hexane Dichloromethane Methanol				All extracts demonstrated antiviral activity against HSV-1 and HSV-2. The methanolic extract was most potent against HSV-1, while the n-hexane extract was most potent against HSV-2.	
Codium decorticatum		Codiaceae	Whole plant	Dichloromethane and methanol	In vitro	Vero cells		Extract demonstrated strong antiviral activity against acyclovir-resistant HSV-1, but not against acyclovir-resistant HSV-2.	Soares et al., 2012[69]
Combretum micranthum	Kinkeliba	Combretaceae	Leaf	Methanol	In vitro	Vero cells		The NaOH autoxidized methanolic extract demonstrated antiviral activity against HSV-1 and HSV-2, but was more effective against HSV-1.	Ferrea et al., 1993[72]
Commiphora parvifolia		Burseraceae	Bark	Water Methanol	In vitro	Vero cells		Methanolic extract demonstrated antiviral activity against HSV-1.	Mothana et al., 2006[56]
Copaifera reticulata	Copaiba	Fabaceae	Leaf	Hydroethanol	In vitro	Vero cells		Extract demonstrated antiviral and virucidal activity against HSV-2, particularly by preventing viral adsorption.	Churqui et al., 2017[73]
			Leaf	Hydroethanol	In vivo		C57bl/6 mice	Extract prevented HSV-2 infection when administered with the virus.	Churqui et al., 2017[73]
Corallodiscus lanuginosus	Kumkum	Gesneriaceae	Whole plant	Methanol	In vitro	Vero cells		Extract demonstrated partial HSV-1 inhibition.	Taylor et al., 1996[36]
Cordia americana	Guajuvira	Boraginaceae	Bark Leaf	Water Hydroalcohol	In vitro	Vero cells		All extracts except the water bark extract demonstrated antiviral activity against HSV-1. The 70% hydroalcoholic bark extract and the 50% hydroalcoholic leaf extract were most potent.	Moura-costa et al., 2012[60]
Cordia salicifolia	Cha de bugre Raintree	Boraginaceae	Leaf and twig	Chloroform and ethanol	In vitro	HeLa cells		Extract demonstrated antiviral activity against HSV-1 throughout the viral infection cycle.	Hayashi et al., 1990[74]
Cornus canadensis	Creeping dogwood	Cornaceae	Stem and leaf	Water Water: ethanol Ethanol	In vitro	Vero cells		All extracts demonstrated antiviral activity against HSV-1, particularly at adsorption and pre-infection.	Lavoie et al., 2017[75]
Costus speciosus	Crepe ginger	Zingiberaceae	Leaf	Ethanol	In vitro	Vero cells HeLa cells		Extract demonstrated antiviral activity against HSV-1.	Abdul et al., 1996[34]
Crossostephium chinense	Chinese wormwood	Compositae	Stem Leaf	Water	In vitro	BCC-1/KMC cells		Extract demonstrated moderate antiviral activity against HSV-2.	Chiang et al., 2003[43]
Croton lechleri	Dragon's blood	Euphorbiaceae	Stem bark	Hydroethanol	In vitro	Vero cells		Extract demonstrated antiviral and virucidal activity against HSV-2, particularly by preventing viral adsorption.	Churqui et al., 2017[73]
			Stem bark	Hydroethanol	In vivo		C57bl/6 mice	Extract prevented HSV-2 infection when administered with the virus.	Churqui et al., 2017[73]
Cryptostegia grandiflora	Palai	Asclepidaceae	Whole plant	Methanol	In vitro	Vero cells		Extract demonstrated partial antiviral activity against HSV-1.	Vijayan et al., 2004[76]
Cuphea carthagenensis	Colombian waxweed	Lythraceae	Aerial parts	Dichloromethane Ethyl acetate n-Butanol	In vitro	Vero cells		All extracts demonstrated antiviral activity against one HSV-1 strain, but the ethyl acetate extract was most potent.	Andrighetti-Frohner et al., 2005[41]
Cyperus rotundus	Purple nutsedge	Cyperaceae	Tuber	Hydroethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Soltan and Zaki, 2009[61]
Cystoseira myrica		Sargassaceae	Whole plant	Water	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Zandi et al., 2007[77]
Dichrostachys glomerata	Dundu	Mimosaceae	Leaf	Ethanol	In vitro	HT-29 cells		Extract demonstrated complete HSV-1 inhibition.	Kudi and Myint, 1999[35]
Dorstenia socotrana		Moraceae	Stem Leaf	Water Methanol	In vitro	Vero cells		Water extract demonstrated antiviral activity against HSV-1.	Mothana et al., 2006[56]
Dracaena cinnabari	Socotra dragon tree Dragon blood tree	Agavaceae	Leaf Flower	Water Methanol	In vitro	Vero cells		Methanolic extract demonstrated antiviral activity against HSV-1.	Mothana et al., 2006[56]
Drimys winteri		Winteraceae	Leaf	Hydroethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-2.	Pacheco et al., 1993[45]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
	Winter's Bark Canelo								
Drynaria fortunei		Polypodiaceae	Rhizome	Water	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Kurokawa et al., 1993[33]
Dunaliella salina		Dunaliellaceae	Whole plant	Hexane Ethanol Water	In vitro	Vero cells		All extracts demonstrated antiviral activity against HSV-1, but the aqueous extract was more potent. Extracts were more effective with treatment prior to infection.	Santoyo et al., 2012[78]
Duroia hirsuta		Rubiaceae	Leaf	Methanol	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Lopez et al., 2001[27]
Echinacea atrorubens	Topeka purple coneflower	Asteraceae	Root	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Binns et al., 2002[79]
Echinacea laevigata	Smooth coneflower	Asteraceae	Root	Ethanol n-Hexane Ethyl acetate	In vitro	Vero cells		The n-hexane and ethyl acetate fractions demonstrated slightly stronger antiviral activity against HSV-1.	Binns et al., 2002[79]
Echinacea pallida	Pale purple coneflower	Asteraceae	Root	Ethanol n-Hexane Ethyl acetate	In vitro	Vero cells		Ethanolic extract and n-hexane fraction demonstrated antiviral activity against HSV-1, but the ethanolic extract was most potent.	Binns et al., 2002[79]
			Aerial parts	Hydroethanol Pressed juice with ethanol	In vitro	Vero cells		All extracts demonstrated antiviral activity against HSV-1 and HSV-2, but the pressed juice was most potent.	Schneider et al., 2009[80]
Echinacea purpurea	Purple coneflower	Asteraceae	Root	Ethanol n-Hexane Ethyl acetate	In vitro	Vero cells		Ethanolic extract and n-hexane fraction demonstrated antiviral activity against HSV-1, but the n-hexane fraction was most potent.	Binns et al., 2002[79]
Echium amoenum	Red feather	Boraginaceae	Leaf	Water	In vitro	Hep-2 cells		Extract demonstrated antiviral activity against HSV-1 during the first hour post-treatment.	Farahani et al., 2014[59]
Ecklonia stolonifera		Lessoniaceae	Whole plant	Methanol	In vitro	Vero cells		Extract demonstrated moderate plaque inhibition against one HSV-1 strain and was mildly cytotoxic to cells.	Park et al., 2005[81]
Elaeocarpus grandiflorus	Fairy petticoat Lily of the valley tree	Elaeocarpaceae	Fruit	Water	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Kurokawa et al., 1993[33]
Eleusine indica	Indian goosegrass	Gramineae	Leaf	Ethanol	In vitro	Vero cells HeLa cells		Extract demonstrated antiviral activity against HSV-1.	Abdul et al., 1996[34]
Elytranthe globosa	Benalu	Loranthaceae	Aerial parts	Methanol	In vitro	Vero cells		Extract demonstrated modest antiviral activity against HSV-1.	Lohezic-Le Devehat et al., 2002[82]
Elytranthe maingayi	Benalu	Loranthaceae	Aerial parts	Methanol	In vitro	Vero cells		Extract demonstrated modest antiviral activity against HSV-1.	Lohezic-Le Devehat et al., 2002[82]
Elytranthe tubaeflora	Benalu	Loranthaceae	Aerial parts	Methanol	In vitro	Vero cells		Extract demonstrated moderate antiviral activity against HSV-1.	Lohezic-Le Devehat et al., 2002[82]
Elytropus chilensis	Quilmay Poroto del campo	Apocynaceae	Aerial parts	Water Hydroethanol	In vitro	Vero cells		Hydroethanolic extract demonstrated antiviral activity against HSV-2. Aqueous extract was cytotoxic to cells.	Pacheco et al., 1993[45]
Ephedra alata	Alanda	Ephedraceae	Aerial parts	Hydroethanol	In vitro	Vero cells		Extract demonstrated strong antiviral activity against HSV-1.	Soltan and Zaki, 2009[61]
Epimedium koreanum		Berberidaceae	Bark	Water	In vitro	RAW264.7 cells HEK293 T cells		Extract demonstrated antiviral activity against HSV in both cell types. Type of HSV used was not specified.	Cho et al., 2015[83]
Equisetum giganteum	Giant horsetail	Equisetaceae	Root Stem	Hydroethanol	In vitro	Vero cells		Extract demonstrated antiviral and virucidal activity against HSV-2, particularly by preventing viral adsorption.	Churqui et al., 2017[73]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
			Root Stem	Hydroethanol	In vivo		C57bl/6 mice	Extract prevented HSV-2 infection when administered with the virus.	Churqui et al., 2017[73]
Erica multiflora	Mediterranean heath	Ericaceae	Aerial parts	Hexane Acetone Methanol	In vitro	Vero cells		Methanolic extract demonstrated antiviral activity against HSV-1.	Sassi et al., 2008[84]
Eriobotrya japonica	Japanese plum	Rosaceae	Not specified	Methanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1 and HSV-2.	Ruffa et al., 2004[85]
Erythrina speciosa	Coral tree	Fabaceae	Leaf	Methanol and ethyl acetate	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1	Fahmy et al., 2019[86]
Erythroxylum laurifolium	Bois de rongue	Erythroxylaceae	Leaf Stem	Methanol	In vitro	Vero cells		Extract demonstrated strong antiviral activity against HSV-1.	Fortin et al., 2002[70]
Eschweilera rufifolia		Lecythidaceae	Bark	Methanol	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Lopez et al., 2001[27]
Eucalyptus globulus	Eucalyptus	Myrtaceae	Leaf	Essential oils	In vitro	RC-37 cells		Oil demonstrated antiviral activity against HSV-1 and HSV-2.	Schnitzler et al., 2001[87]
Eugenia caryophyllus *Aka Syzygium aromaticum	Clove	Myrtaceae	Flower bud	Ethanol	In vitro	GMK cells		Extract demonstrated mild antiviral activity against HSV-1 and HSV-2.	Tragoolpua et al., 2007[88]
Eugenia michelii	Surinam cherry	Myrtaceae	Leaf	Ethanol	In vitro	Vero cells HeLa cells		Extract demonstrated antiviral activity against HSV-1.	Abdul et al., 1996[34]
Eupatorium arnottianum		Asteraceae	Aerial parts	Essential oil	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Garcia et al., 2010[25]
Eupatorium articulatum		Asteraceae	Not specified	Water Ethanol	In vitro	HeLa cells		Water extract demonstrated antiviral activity against HSV-1.	Abad et al., 1999[52]
Eupatorium catarium		Asteraceae	Aerial parts	Essential oil	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Garcia et al., 2010[25]
Eupatorium patens		Asteraceae	Leaf Flower Fruit	Essential oil	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Garcia et al., 2004[32]
Euphorbia cestrifolia		Euphorbiaceae	Leaf Stem	Petroleum ether Dichloromethane Ethanol	In vitro	Vero cells HEp-2 cells		Ethanolic stem extract and dichloromethane leaf extract demonstrated moderate antiviral activity against HSV-2.	Betancur-Galvis et al., 2002[89]
Euphorbia cotinifolia		Euphorbiaceae	Leaf Stem Leaf/Stem	Petroleum ether Dichloromethane Ethanol Hydromethanol	In vitro	Vero cells HEp-2 cells		Hydromethanolic leaf/stem extract demonstrated strong antiviral activity and the ethanolic stem and dichloromethane leaf extracts demonstrated moderate activity against HSV-2.	Betancur-Galvis et al., 2002[89]
Euphorbia hirta	Garden spurge	Euphorbiaceae	Leaf	Ethanol	In vitro	Vero cells HeLa cells		Extract demonstrated antiviral activity against HSV-1.	Abdul et al., 1996[34]
Euphorbia spinidens		Euphorbiaceae	Aerial parts	Methanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1, working best within 2 hours post-infection.	Karimi et al., 2016[90]
Euphorbia tirucalli		Euphorbiaceae	Stem Leaf/Stem	Petroleum ether Dichloromethane Ethanol Hydromethanol	In vitro	Vero cells HEp-2 cells		Hydromethanolic leaf/stem extract demonstrated strong antiviral activity and the ethanolic stem extract demonstrated moderate antiviral activity against HSV-2.	Betancur-Galvis et al., 2002[89]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
Euphorbia thymifolia		Euphorbiaceae	Whole plant	Ethyl acetate	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-2 multiplication.	Yang et al., 2005[91]
Eurycoma longifolia	Malaysian ginseng Pasak bumi Tongkat Ali	Simaroubaceae	Stem	Water Methanol	In vitro	Vero cells		Methanolic extract demonstrated complete antiviral activity against HSV-1.	Nawawi et al., 1999[92]
Ficus benjamina	Weeping ficus	Moraceae	Stem	Methanol	In vivo		BALB/c mice	Extract delayed the appearance of local vesicles and limited further development to mild zosteriform lesions, but did not reduce survival time or mortality.	Nawawi et al., 1999[92]
Euryops arabicus		Compositae	Leaf Flower	Water Methanol	In vitro	Vero cells		Methanolic extract demonstrated strong antiviral activity against HSV-1.	Mothana et al., 2006[56]
Exacum affine	Persian violet	Gentianaceae	Leaf Flower	Water Methanol	In vitro	Vero cells		Methanolic extract demonstrated antiviral activity against HSV-1.	Mothana et al., 2006[56]
Fagonia luntii		Zygophyllaceae	Leaf Stem	Water Methanol	In vitro	Vero cells		Methanolic extract demonstrated antiviral activity against HSV-1.	Mothana et al., 2006[56]
Ficus benjamina	Weeping fig	Moraceae	Leaf Fruit Stem	Ethanol	In vitro	Vero cells		Leaf extract demonstrated strong antiviral activity against HSV-1 and HSV-2 and was synergistic with acyclovir.	Yarmolinsky et al., 2009[93]
Ficus carica	Common fig	Moraceae	Latex	Hexane Ethyl acetate Methanol Chloroform Hexane-ethyl acetate	In vitro	Vero cells		Hexane and hexane-ethyl acetate extracts elicited antiviral activity against HSV-1, preventing viral penetration, adsorption, and intracellular replication.	Lazreg Aref et al., 2011[94]
Ficus religiosa	Sacred fig Bodhi tree Bo tree	Moraceae	Leaf Bark	Water Methanol Ethyl acetate Chloroform	In vitro	Vero cells		Water and chloroform bark extracts demonstrated the greatest antiviral effects against HSV-2.	Ghosh et al., 2016[95]
Filicium decipiens	Fern tree	Sapindaceae	Stem bark	Water Methanol	In vitro	Vero cells		Methanolic extract demonstrated complete antiviral activity against HSV-1.	Nawawi et al., 1999[92]
Fomes fomentarius	Hoof fungus	Polyporaceae	Mycelia	Sodium chloride	In vitro	RK-13 cells		Extract demonstrated antiviral activity against HSV-2.	Krupodorova er al., 2014[47]
Frankenia pulverulenta	Sea heath	Frankeniaceae	Stem bark	Methanol	In vivo		BALB/c mice	Extract delayed the appearance of local vesicles, but did not limit further development to mild zosteriform lesions, reduce survival time, or reduce mortality.	Nawawi et al., 1999[92]
Frankenia pulverulenta	European sea-heath	Frankeniaceae	Whole plant	Petroleum ether Acetone Methanol	In vitro	Vero cells		Acetone and methanolic extracts demonstrated antiviral activity against HSV-1.	Sassi et al., 2008[84]
Freycinetia malaccensis	Climbing pandanus	Pandanaceae	Leaf	Ethanol	In vitro	Vero cells HeLa cells		Extract demonstrated antiviral activity against HSV-1.	Abdul et al., 1996[34]
Gallesia gorazema	Pau-d'alho	Phytolaccaceae	Leaf Root	Ethanol Dichloromethane	In vitro	Vero cells		Dichloromethane root extract demonstrated antiviral activity against HSV-1, but not HSV-2.	Silva Junior et al., 2013[96]
Garcinia griffithii	Kandis Gajah	Guttiferae	Aerial parts	Ethanol Ethyl acetate	In vitro	Vero cells		Both extracts demonstrated modest antiviral activity against HSV-1.	Lohezic-Le Devehat et al., 2002[82]
Garcinia mangostana	Mangosteen	Guttiferae	Leaf	Water Methanol	In vitro	Vero cells		Methanolic extract demonstrated complete antiviral activity against HSV-1.	Nawawi et al., 1999[92]
	Bloody geranium	Geraniaceae	Leaf	Methanol	In vivo		BALB/c mice		Nawawi et al., 1999[92]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
Geranium sanguineum								Extract delayed the appearance of local vesicles, but did not limit further development to mild zosteriform lesions, reduce survival time, or reduce mortality.	
Geranium sanguineum	Bloody cranesbill	Geraniaceae	Aerial root parts Overground parts	Ethanol Methanol Hydroethanol	In vitro	Vero cells E6SM cells		All extracts showed antiviral activity against HSV-1, but the hydroethanolic extract was the strongest. The hydroethanolic extract also inhibited HSV-2.	Serkedjieva and Ivancheva, 1999[97]
Geum japonicum	Asian herb bennet	Rosaceae	Whole plant	Water	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Kurokawa et al., 1993[33]
			Whole plant	Water	In vivo		BALB/c mice	Extract significantly delayed the development and progression of HSV-1 lesions.	Kurokawa et al., 1993[33]
			Whole plant	Water	In vitro	Vero cells		Extract demonstrated synergistic antiviral effects on HSV-1 when combined with acyclovir.	Kurokawa et al., 1995[98]
			Whole plant	Water	In vivo		BALB/c mice	Extract demonstrated synergistic antiviral effects on HSV-1 when combined with acyclovir.	Kurokawa et al., 1995[98]
			Whole plant	Water	In vivo		BALB/c mice	Extract reduced incidence of recurrence, severity of vesicles, and duration of lesions from HSV-1 infection.	Kurokawa et al., 1997[99]
Glechon marifolia		Lamiaceae	Not specified	Hydroethanol Water	In vitro	Vero cells		Hydroethanolic extract demonstrated antiviral activity against 2 HSV-1 strains.	Montanha et al., 2004[31]
Glechon spathulata		Lamiaceae	Not specified	Hydroethanol Water	In vitro	Vero cells		Hydroethanolic extract demonstrated antiviral activity against 3 HSV-1 strains.	Montanha et al., 2004[31]
Glycyrrhiza glabra	Licorice	Fabaceae	Root	Water	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1, particularly pre-infection.	Ghannad et al., 2014[100]
			Root	Water	In vitro	Vero cells		Extract demonstrated modest antiviral activity against HSV-1.	Fukuchi et al., 2016[101]
Gnaphalium chilense		Asteraceae	Not specified	Acetone Methanol	In vitro	Vero cells		Acetonic extract demonstrated antiviral activity against HSV-1.	Jaeger Greer et al., 2012[46]
Graptopetalum paraguayense	Sedum weinbergii Mother-of-pearl-plant Ghost plant	Crassulaceae	Leaf	Hydromethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against both wild-type and acyclovir-resistant strains of HSV-1 and HSV-2.	Zaharieva et al., 2019[102]
Haematococcus pluvialis		Haematococcaceae	Whole plant	Hexane Ethanol Water	In vitro	Vero cells		All extracts demonstrated antiviral activity against HSV-1, but the ethanolic extract was more potent. Extracts were more effective with treatment prior to infection.	Santoyo et al., 2012[78]
Hamelia patens	Firebush	Rubiaceae	Leaf	Methanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1 and HSV-2.	Silva-Mares et al., 2019[63]
Harpullia arborea	Tulipwood tree	Sapindaceae	Leaf	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Lipipun et al., 2003[28]
Hedyotis auricularia		Rubiaceae	Leaf	Ethanol	In vitro	Vero cells HeLa cells		Extract demonstrated antiviral activity against HSV-1.	Abdul et al., 1996[34]
Heisteria acuminata		Oleaceae	Not specified	Water Ethanol	In vitro	HeLa cells		Ethanolic extract demonstrated antiviral activity against HSV-1.	Abad et al., 1999[52]
Helichrysum aureonitens	Golden everlasting	Asteraceae	Shoot	Water	In vitro	Human lung fibroblast cells		Extract demonstrated antiviral activity against HSV-1.	Meyer et al., 1996[103]
Hemidesmus indicus	Indian sarsaparilla	Apocynaceae	Root	Hydromethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1 and HSV-2, eliciting stronger effects pre-infection.	Bonvicini et al., 2018[104]
Hura crepitans	Sandbox tree	Euphorbiaceae	Leaf	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Lipipun et al., 2003[28]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
Houttuynia cordata	Chameleon plant	Saururaceae	Aerial parts	Water	In vitro	HeLa cells		Extract demonstrated antiviral activity against HSV-1 and prevented viral adsorption when HSV-1 was pretreated with the extract.	Hayashi et al., 1995[105]
			Leaf Stem	Water	In vitro	Vero cells		Extract inhibited HSV-2 associated cell death, plaque formation, and NF-κB activation.	Chen et al., 2011[106]
			Not specified	Water	In vitro	Vero cells HEp-2 cells A549 cells		Extract demonstrated antiviral activity against HSV-1 and HSV-2 through multiple mechanisms.	Hung et al., 2015[107]
Hymenoclea salsola Aka Ambrosia salsola	Cheesebush Winged ragweed	Asteraceae	Not specified	Acetone Methanol	In vitro	Vero cells		Acetonic extract demonstrated antiviral activity against HSV-1 and HSV-2.	Jaeger Greer et al., 2012[46]
Hypericum cordifolium	Marmhendo	Hypericaceae	Aerial parts	Methanol	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Taylor et al., 1996[36]
Hypericum hookerianum	Hypericum	Hypericaceae	Aerial parts	Methanol	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Vijayan et al., 2004[76]
Hypericum mysorense	Hypericum	Hypericaceae	Aerial parts	Methanol	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Vijayan et al., 2004[76]
Hypericum uralum	Urali phul	Hypericaceae	Whole plant	Methanol	In vitro	Vero cells		Extract demonstrated partial HSV-1 inhibition.	Taylor et al., 1996[36]
Hypnea spinella		Cystocloniacae	Whole plant	Dichloromethane and methanol	In vitro	Vero cells		Extract demonstrated strong antiviral activity against acyclovir-resistant HSV-1, but not against acyclovir-resistant HSV-2.	Soares et al., 2012[69]
Ilex brevicuspis	Holly	Aquifoliaceae	Not specified	Hydroethanol Water	In vitro	Vero cells		Water extract demonstrated antiviral activity against 2 HSV-1 strains.	Montanha et al., 2004[31]
Ilex paraguariensis	Yerba mate	Aquifoliaceae	Leaf	Water	In vitro	Vero cells		Extract demonstrated antiviral activity against 2 HSV-1 strains.	Muller et al., 2007[108]
			Leaf	Hydroethanol Butanol Water Ethyl acetate	In vitro	Vero cells GMK AH1		Hydroethanolic extracts and all fractions demonstrated antiviral activity against HSV-1 and HSV-2, but effects were more potent against HSV-2. Most potent activity was demonstrated by the ethyl acetate fraction by preventing viral attachment and penetration.	Luckemeyer et al., 2012[109]
Ilex theezans	Holly	Aquifoliaceae	Not specified	Hydroethanol Water	In vitro	Vero cells		Water extract demonstrated antiviral activity against 2 HSV-1 strains.	Montanha et al., 2004[31]
Illinita		Saxifragaceae	Leaf	Hydroethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Pacheco et al., 1993[45]
Indigofera heterantha	Himalayan indigo	Fabaceae	Root	Hydromethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-2.	Kaushik et al., 2015[110]
			Root	Hydromethanol	In vivo		BALB/c mice	Extract demonstrated therapeutic and prophylactic effects against HSV-2 infection, reducing lesion formation and scores, clinical symptoms, extravaginal disease, and survival.	Kaushik et al., 2015[110]
Inonotus obliquus	Chaga mushroom	Hymenochaeteceae	Mycelia	Water	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Pan et al., 2014[111]
Iryanthera megistophylla		Menispermaceae	Bark	Methanol	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Lopez et al., 2001[27]
Ixeris chinensis		Compositae	Whole plant	Water	In vitro	BCC-1/KMC cells		Extract demonstrated moderate antiviral activity against HSV-1 and HSV-2.	Chiang et al., 2004[54]
Jasminum fluminense	Brazilian jasmine	Oleaceae	Stem and twig	Ethanol	In vitro	GMK cells		Extract demonstrated antiviral activity against HSV-1.	Beuscher et al., 1994[68]
Jatropha unicostata	Sibru	Euphorbiaceae	Bark	Water Methanol	In vitro	Vero cells		Methanolic extract demonstrated antiviral activity against HSV-1.	Mothana et al., 2006[56]
Juglans australis	Nogal	Juglandaceae			In vitro	Vero cells			Ruffa et al., 2004[85]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
			Not specified	Methanol Infusion				Infusion demonstrated antiviral activity against both HSV-1 and HSV-2, while the methanolic extract demonstrated activity against only HSV-1.	
Juglans mandshurica	Manchurian walnut	Juglandaceae	Bark	Water	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Kurokawa et al., 1993[33]
Juglans mollis		Juglandaceae	Cortex	Methanol	In vitro	Vero cells		Extract demonstrated strong antiviral activity against HSV-1 and HSV-2.	Silva-Mares et al., 2019[63]
Kalanchoe farinacea		Crassulaceae	Leaf Flower	Methanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Mothana et al., 2006[56]
Kalanchoe pinnata Aka Bryophyllum pinnatum	Miracle leaf Cathedral bells	Crassulaceae	Not specified	Acetone Methanol	In vitro	Vero cells		Both extracts demonstrated significant antiviral activity against HSV-1 and HSV-2.	Jaeger Greer et al., 2012[46]
Lafoensia pacari		Lythraceae	Leaf	Methanol	In vitro	Vero cells		Extract demonstrated antiviral activity against one HSV-1 strain.	Muller et al., 2007[108]
Lantana camara	Common lantana Shrub verbena	Verbenaceae	Aerial parts	Essential oil	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Garcia et al., 2010[25]
Lantana grisebachii		Verbenaceae	Aerial parts	Essential oil	In vitro	Vero cells		Extract demonstrated strong antiviral activity against HSV-1, HSV-2, and acyclovir-resistant HSV-1.	Garcia et al., 2010[25]
Laurencia dendroidea		Rhodomelaceae	Whole plant	Dichloromethane and methanol	In vitro	Vero cells		Extract demonstrated strong antiviral activity against acyclovir-resistant HSV-1, but not against acyclovir-resistant HSV-2, and exhibited some cytotoxicity.	Soares et al., 2012[69]
Leea indica	Bandicoot berry	Leeaceae	Leaf	Ethanol	In vitro	Vero cells HeLa cells		Extract demonstrated antiviral activity against HSV-1.	Abdul et al., 1996[34]
Lentinus edodes	Shiitake mushroom	Omphalotaceae	Mycelia	Cultured medium and filtered	In vitro	Vero cells		Extract prevented release of HSV-1 virions from cells.	Sarkar et al., 1993[112]
			Fruit	Methanol Water	In vitro	Vero cells		Water extract demonstrated stronger antiviral activity against HSV-1 than the methanolic extract.	Santoyo et al., 2012[55]
Lepechinia floribunda		Lamiaceae	Aerial parts	Essential oil	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Garcia et al., 2010[25]
Leptospermum scoparium	Manuka oil	Myrtaceae	Not specified	Essential oil	In vitro	RC-37 cells		Extract demonstrated antiviral activity against HSV-1 and HSV-2, particularly with viral pre-treatment.	Reichling et al., 2005[113]
Licania tomentosa		Chrysobalanaceae	Seed	Glycerol	In vitro	HEp-2 cells		Extract demonstrated antiviral activity against acyclovir-resistant HSV-1, particularly with cellular pretreatment or after viral attachment.	Miranda et al., 2002[114]
Lilium candidum	Madonna lily	Liliaceae	Leaf Petal Bulb	Ethanol	In vitro	Vero cells		Leaf extract demonstrated strong antiviral activity against HSV-1 and HSV-2 and was synergistic with acyclovir.	Yarmolinsky et al., 2009[93]
Limonium brasiliense	Kuntze	Plumbaginaceae	Not specified	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Faral-tello et al., 2012[26]
Lippia alba	Bushy lippia	Verbenaceae	Leaf	Dichloromethane Ethyl acetate n-Butanol	In vitro	Vero cells		n-Butanol extract demonstrated antiviral activity against acyclovir-resistant HSV-1.	Andrighetti-Frohner et al., 2005[41]
Lithospermum officinale	European stoneseed	Boraginaceae	Not specified	Acetone Methanol	In vitro	Vero cells		Acetonic extract demonstrated antiviral activity against HSV-1 and HSV-2.	Jaeger Greer et al., 2012[46]
Lithraea molleoides		Anacardiaceae	Leaf Aerial parts	Water	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Kott et al., 1998[115]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
Lobelia chinensis	Chinese lobelia	Campanulaceae	Not specified	Methanol	In vitro	HeLa cells		Extract demonstrated antiviral activity against HSV-1.	Kuo et al., 2008[116]
			Not specified	Methanol	In vivo		BALB/c mice	Extract was able to prevent HSV-1 lesion formation.	Kuo et al., 2008[116]
Lobophora variegata		Dictyotaceae	Whole plant	Dichloromethane and methanol	In vitro	Vero cells		Extract demonstrated strong antiviral activity against acyclovir-resistant HSV-1, but not against acyclovir-resistant HSV-2.	Soares et al., 2012[69]
Lomatophyllum macrum	Mazambron marron	Aloaceae	Leaf	Methanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Fortin et al., 2002[70]
Luehea paniculatum		Tiliaceae	Bark	Water Hydroalcohol	In vitro	Vero cells		Both extracts demonstrated antiviral activity against HSV-1, but the 50% hydroalcoholic extract was more potent.	Moura-Costa et al., 2012[60]
Luma apiculata	Temu Chilean myrtle	Myrtaceae	Leaf	Water	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-2.	Pacheco et al., 1993[45]
Macaranga pustulata	Malato Kala	Euphorbiaceae	Bark	Methanol	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Taylor et al., 1996[36]
Macrocystidia cucumis		Marasmiaceae	Mycelia	Culture broth	In vitro	BHK-21 cells		Dilutions up to 64-fold were antiviral against HSV-1 when the fungi were cultivated for 21 days.	Saboulard et al., 1998[117]
Madura cochinchinensis		Moraceae	Root	Water	In vitro	Vero cells		Extract showed antiviral activity against HSV-1 and HSV-2.	Yoosook et al., 2000[66]
Maesa macrophylla	Bhogati	Myrsinaceae	Bark	Methanol	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Taylor et al., 1996[36]
Mangifera indica	Mango	Anacardiaceae	Leaf	Water	In vitro	Vero cells		Extract showed antiviral activity against HSV-1 and HSV-2. Combination with Centella asiatica showed an additive effect on HSV-2.	Yoosook et al., 2000[66]
Margyricarpus pinnatus	Pearl Berry	Rosaceae	Not specified	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Faral-tello et al., 2012[26]
Maytenus ilicifolia	Espinheira santa	Celastraceae	Not specified	Hydroethanol Water	In vitro	Vero cells		Water and hydroethanolic extracts demonstrated antiviral activity against 2 HSV-1 strains.	Montanha et al., 2004[31]
Melia toosendan		Meliaceae	Fruit	Water Ethanol Ethanolic acid Methanol	In vitro	Vero cells		Ethanolic acid and methanolic extracts demonstrated antiviral activity against HSV-1.	Hsiang et al., 2001[118]
Melaleuca alternifolia	Tea tree	Myrtaceae	Leaf	Essential oils	In vitro	RC-37 cells		Oil demonstrated antiviral activity against HSV-1 and HSV-2.	Schnitzler et al., 2001[87]
Melaleuca armillaris	Bracelet honey myrtle	Myrtaceae	Leaf	Essential oils	In vitro	Vero cells		Oil demonstrated antiviral activity against HSV-1.	Farag et al., 2004[119]
Melaleuca ericifolia	Swamp paperbark	Myrtaceae	Leaf	Essential oils	In vitro	Vero cells		Oil demonstrated antiviral activity against HSV-1.	Farag et al., 2004[119]
Melaleuca leucadendron	Weeping paperbark	Myrtaceae	Fruit	Methanol	In vivo		BALB/c mice	Extract delayed the appearance of local vesicles and further development to mild zosteriform lesions, reduced survival time, and reduced mortality.	Nawawi et al., 1999[92]
			Leaf	Essential oils	In vitro	Vero cells		Oil demonstrated antiviral activity against HSV-1.	Farag et al., 2004[119]
Melastoma malabathricum	Daun halendong Mua e bong Sendudok	Melastomataceae	Aerial parts	Methanol	In vitro	Vero cells		Extract demonstrated moderate antiviral activity against HSV-1.	Lohezic-Le Devehat et al., 2002[82]
Melia dubia	Malaivanbu	Meliaceae	Fruit	Alcohol and ethyl acetate	In vitro	Vero cells		Extract demonstrated partial antiviral activity against HSV-1.	Vijayan et al., 2004[76]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
Melissa officinalis	Lemon balm	Lamiaceae	Leaf	Ethyl alcohol Ethanol Ethyl acetate Water	In vitro	RK cells		All extracts inactivated HSV-1 when treated extracellularly, but failed to demonstrate antiviral activity when treated to cells pre- or post-infection.	Dimitrova et al., 1993[120]
			Leaf	Water	In vitro	RC-37 cells		Extract demonstrated antiviral activity against 2 HSV-1 strains and HSV-2 with treatment prior to infection, but not post-infection.	Nolkemper et al., 2006[121]
			Leaf	Essential oil	In vitro	RC-37 cells		Extract demonstrated strong antiviral activity against HSV-1 and HSV-2 with treatment prior to infection.	Schnitzler et al., 2008[122]
			Leaf	Hydroethanol	In vitro	Vero cells		Extract demonstrated strong antiviral activity against HSV-2 post-infection, but did not prevent viral penetration.	Mazzanti et al., 2008[123]
			Leaf	Water	In vitro	RC-37 cells		Extract demonstrated strong antiviral activity against HSV-1, inhibiting viral attachment and inactivating virions.	Astani et al., 2012[124]
Mentha arvensis	Field mint	Labiatae	Leaf	Ethanol	In vitro	Vero cells HeLa cells		Extract demonstrated antiviral activity against HSV-1.	Abdul et al., 1996[34]
Mentha piperita	Peppermint	Lamiaceae	Leaf	Water	In vitro	RC-37 cells		Extract demonstrated antiviral activity against 2 HSV-1 strains and HSV-2 with treatment prior to infection, but not post-infection.	Nolkemper et al., 2006[121]
			Leaf	Water	In vitro	Vero cells		Extract demonstrated antiviral effects against HSV-1 when exposed to cells pre-infection, during viral adsorption, and after viral adsorption.	Omidian et al., 2014[125]
			Leaf	Ethanol	In vitro	RC-37 cells		Extract demonstrated antiviral activity against 3 HSV-1 strains.	Reichling et al., 2008[126]
			Not specified	Essential oil	In vitro	RC-37 cells		Extract demonstrated antiviral activity against HSV-2 and 2 HSV-1 strains.	Schuhmacher et al., 2003[127]
Mentha suaveolens	Apple mint Pineapple mint Woolly mint	Lamiaceae	Leaf	Essential oil	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1, particularly by inhibiting intracellular viral metabolism, and showed synergistic effects with acyclovir.	Civitelli et al., 2014[128]
Mitragyna inermis		Rubiaceae	Leaf	Methanol	In vitro	GMK cells		Extract demonstrated antiviral activity against HSV-1.	Beuscher et al., 1994[68]
Moringa oleifera	Drumstick tree	Moringaceae	Leaf	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral effects against HSV-1 and was more effective on the phosphonoacetate-resistant strain.	Lipipun et al., 2003[28]
			Leaf	Ethanol	In vivo		BALB/c mice	Extract decreased size and development of skin lesions from HSV-1, reduced mortality, and increased survival time.	Lipipun et al., 2003[28]
Moringa peregrina	Ben tree	Moringaceae	Seed	Hydroethanol	In vitro	Vero cells		Extract demonstrated strong antiviral activity against HSV-1.	Soltan and Zaki, 2009[61]
Myrteola nummularia	Cranberry-myrtle	Myrtaceae	Aerial parts	Methanol	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Lopez et al., 2001[27]
Nauclea latifolia	African Peach	Rubiaceae	Root	Dichloromethane and methanol	In vitro	Vero cells		Extract demonstrated antiviral activity against 2 strains of HSV-2.	Donalisio et al., 2013[129]
Nelumbo nucifera	Indian lotus Sacred lotus	Nelumbonaceae	Seed	Ethanol	In vitro	HeLa cells		Extract demonstrated complete HSV-1 inhibition.	Kuo et al., 2005[130]
Nephelium lappaceum	Rambutan	Sapindaceae	Pericarp	Water Methanol	In vitro	Vero cells		Both extracts demonstrated complete antiviral activity against HSV-1.	Nawawi et al., 1999[92]
Obetia ficifolia	Bois d'ortie	Urticaceae	Pericarp	Methanol	In vivo		BALB/c mice	Extract delayed the appearance of local vesicles and limited further development to mild zosteriform lesions, reduced survival time, and reduced mortality.	Nawawi et al., 1999[92]
Ocimum basilicum	Basil	Lamiaceae	Leaf	Water Ethanol	In vitro	BCC-1/KMC cells			Chiang et al., 2005[131]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
								Water extract had potent antiviral activity against HSV-1 and HSV-2. Ethanolic extract had potent activity against HSV-1. Water extract elicited greater effects than the ethanolic extract.	
Ocimum gratissimum	Clove basil	Lamiaceae	Whole plant	Hydroalcohol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Moura-costa et al., 2012[60]
Ophirrhiza nicobarica		Rubiaceae	Leaf	Methanol	In vitro	Vero cells		Extract demonstrated moderate antiviral activity against HSV-1 and HSV-2.	Chattopadhyay et al., 2006[132]
Opuntia streptacantha	Prickly pear	Cactaceae	Leaf	Water	In vitro	BHK-21 cells Human cervical cells		Extract demonstrated antiviral activity against HSV-2, particularly with pre-treatment of cells.	Ahmad et al., 1996[133]
Orthosiphon aristatus	Cat's whiskers	Labiatae	Leaf	Ethanol	In vitro	Vero cells HeLa cells		Extract demonstrated antiviral activity against HSV-1.	Abdul et al., 1996[34]
Paeonia suffruticosa	Moutan peony	Paeoniaceae	Root bark	Water	In vivo		BALB/c mice	Extract significantly delayed the development and progression of HSV-1 lesions.	Kurokawa et al., 1993[33]
			Root	Water Ethanol Ethanolic acid Methanol	In vitro	Vero cells		Hot water, cold water, and methanolic extracts demonstrated significant antiviral activity against HSV-1	Hsiang et al., 2001[118]
Passiflora edulis	Passion flower	Passifloraceae	Root	Hydroethanol Water	In vitro	Vero cells		Water extract demonstrated antiviral activity against one HSV-1 strain.	Muller et al., 2007[108]
Pedilanthus tithymaloides	Devil's-backbone	Euphorbiaceae	Leaf	Methanol	In vitro	Vero cells		Extract demonstrated antiviral activity against 4 HSV-2 strains.	Ojha et al., 2015[134]
Peganum harmala	Wild rue	Nitrariaceae	Leaf Stem Seed Flower	Hexane, dichloromethane, ethyl acetate, methanol, and ethanol	In vitro	Vero cells		Seed extract demonstrated antiviral and virucidal activity against HSV-2.	Benzekri et al., 2017[135]
Pelargonium sidoides	South African geranium	Geraniaceae	Root	Water	In vitro	RC-37 cells		Extract prevented viral penetration of HSV-1 and HSV-2.	Schnitzler et al., 2008[136]
Penicillus capitatus		Udoteaceae	Whole plant	Dichloromethane and methanol	In vitro	Vero cells		Extract demonstrated strong antiviral activity against both acyclovir-resistant HSV-1 and acyclovir-resistant HSV-2.	Soares et al., 2012[69]
Persea americana	Avocado	Lauraceae	Leaf	Methanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1 and HSV-2.	Silva-Mares et al., 2019[63]
Petunia nyctaginiflora		Solanaceae	Aerial parts	Water Ethanol	In vitro	Vero cells		Aqueous extract demonstrated complete cytopathic effects against HSV-1.	Padma et al., 1998[38]
Phellodendron amurense	Amur cork tree Huang Bai	Rutaceae	Bark	Water	In vivo		BALB/c mice	Extract significantly delayed the development and progression of HSV-1 lesions and prolonged mean survival time.	Kurokawa et al., 1993[33]
			Bark	Ethanol	In vitro	RC-37 cells		Extract demonstrated antiviral activity against HSV-1, showing the strongest effect when the virus was pre-treated with the extract.	Wang et al., 2009[137]
Phoradendron crassifolium		Santalaceae	Not specified	Ethanol Water	In vitro	HeLa cells Vero cells		Water extract demonstrated antiviral activity against HSV-1, but the upper limit of its effective range was cytotoxic.	Abad et al., 1999[51]
Phyllanthus amarus	Carry me seed	Euphorbiaceae	Whole plant	Water	In vitro	Vero cells		Extract inhibited replication of HSV-1 and HSV-2, but demonstrated slightly more potent effects on HSV-1 compared to HSV-2.	Tan et al., 2013[138]
Phyllanthus niruri	Gale of the wind	Euphorbiaceae	Whole plant	Water	In vitro	Vero cells		Extract inhibited replication of HSV-1 and HSV-2, but demonstrated slightly more potent effects on HSV-1 compared to HSV-2.	Tan et al., 2013[138]
				Ethanol	In vitro	Vero cells		Extract demonstrated strong antiviral activity against HSV-1.	Faral-tello et al., 2012[26]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
			Not specified						
Phyllanthus orbicularis	Wedge leaf flower	Euphorbiaceae	Stem and leaves	Water	In vitro	Human foreskin fibroblasts		Extract demonstrated antiviral activity against HSV-2.	del Barrio et al., 2000[139]
			Stem and leaves	Diethyl ether Chloroform Butanol Ethanol Acetic acid-water	In vitro	Human foreskin fibroblasts Vero cells		Butanolic and acetic acid extracts demonstrated significant antiviral activity against 2 strains of HSV-1 in both cell types, particularly in the early stages of viral infection.	Fernandez Romero et al., 2003[140]
Phyllanthus urinaria	Chamber bitter	Euphorbiaceae	Whole plant	Acetone Benzene Chloroform Ethanol Ethyl acetate n-Hexane Methanol	In vitro	Vero cells		Acetone, ethanolic, and methanolic extracts demonstrated moderate antiviral activity against HSV-1 and significant activity against HSV-2, specifically when added to cells just after viral infection.	Yang et al., 2005[141]
			Whole plant	Water	In vitro	Vero cells		Extract inhibited replication of HSV-1 and HSV-2 to similar degrees.	Tan et al., 2013[138]
Phyllanthus watsonii		Euphorbiaceae	Whole plant	Water	In vitro	Vero cells		Extract inhibited replication of HSV-1 and HSV-2, but demonstrated slightly more potent effects on HSV-1 compared to HSV-2.	Tan et al., 2013[138]
Piper aduncum	Cordoncillo Yanggona Yaqona	Piperaceae	Leaf Flower	Methanol	In vitro	Vero cells		Extract demonstrated modest antiviral activity against HSV-1.	Lohezic-Le Devehat et al., 2002[82]
Pistacia vera	Pistachio	Pistaciaceae	Seed Kernel Leaf Stem Branch Shell skins	n-Hexane	In vitro	Vero cells		Kernel, shell skin, and seed extracts demonstrated the strongest antiviral activity against HSV (type not specified).	Ozcelik et al., 2005[142]
Pithecellobium clypearia		Fabaceae	Leaf	Water	In vitro	Vero cells		Extract demonstrated antiviral effects against 3 HSV-1 strains, but was more effective on the standard strain.	Li et al., 2004[29]
Plantago asiatica	Chinese plantain	Plantaginaceae	Whole plant	Water	In vitro	BCC-1/KMC cells		Extract demonstrated weak antiviral activity against HSV-2 and no activity against HSV-1.	Chiang et al., 2003[143]
Plantago major	Greater Plantain	Plantaginaceae	Whole plant	Water	In vitro	BCC-1/KMC cells		Extract demonstrated weak antiviral activity against HSV-2 and no activity against HSV-1.	Chiang et al., 2002[144]
			Whole plant	Water	In vitro	BCC-1/KMC cells		Extract demonstrated weak antiviral activity against HSV-2 and no activity against HSV-1.	Chiang et al., 2003[143]
Pleurotus ostreatus	Oyster mushroom	Pleurotaceae	Fruit	Methanol Water	In vitro	Vero cells		Water extract demonstrated greater antiviral activity against HSV-1 than the methanolic extract.	Santoyo et al., 2012[55]
			Mycelia	Sodium chloride	In vitro	RK-13 cells		Extract demonstrated antiviral activity against HSV-2.	Krupodorova er al., 2014[47]
Polygala tenufolia	Common polygala seed	Polygalaceae	Root	Water	In vivo		BALB/c mice	Extract significantly delayed the development and progression of HSV-1 lesions.	Kurokawa et al., 1993[33]
Polygala virgata	Purple broom	Polygalaceae	Aerial parts	Ethanol	In vitro	GMK cells		Extract demonstrated antiviral activity against HSV-1.	Beuscher et al., 1994[68]
Polygonum cuspidatum	Japanese knotweed	Polygonaceae	Root Rhizome	Water	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Kurokawa et al., 1993[33]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
Polygonum minus	Knotweed	Polygonaceae	Leaf	Ethanol	In vitro	Vero cells HeLa cells		Extract demonstrated antiviral activity against HSV-1.	Abdul et al., 1996[34]
Polygonum punctatum	Dotted smartweed	Polygonaceae	Leaf Aerial parts	Water	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Kott et al., 1998[115]
			Not specified	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Faral-tello et al., 2012[26]
			Aerial parts	Methanol	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Lopez et al., 2001[27]
Polysiphonia denudata		Rhodomelaceae	Whole plant	Water	In vitro	Vero cells E6SM cells		Extract demonstrated antiviral activity against HSV-2 and different strains of HSV-1, particularly when added at adsorption or post-infection.	Serkedjieva et al., 2000[145]
Pongamia pinnata	Pongam tree	Papillionaceae	Seed	Water	In vitro	Vero cells		Extract demonstrated complete HSV-1 and HSV-2 inhibition, but effects were more potent on HSV-1.	Elanchezhiyan et al., 1993[146]
Princepia utilis		Rosaceae	Leaf	Methanol	In vitro	Vero cells		Extract demonstrated partial HSV-1 inhibition.	Taylor et al., 1996[36]
Protium serratum	Indian red pear	Burseraceae	Leaf	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Lipipun et al., 2003[28]
Prunella vulgaris	Prunella	Lamiaceae	Spike	Water	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Kurokawa et al., 1993[33]
			Leaf	Water	In vitro	RC-37 cells		Extract demonstrated antiviral activity against 2 HSV-1 strains and HSV-2 with treatment prior to infection, but not post-infection.	Nolkemper et al., 2006[121]
			Leaf	Ethanol	In vitro	RC-37 cells		Extract demonstrated antiviral activity against 3 HSV-1 strains.	Reichling et al., 2008[126]
Psidium incanum		Myrtaceae	Not specified	Ethanol	In vitro	Vero cells		Extract demonstrated strong antiviral activity against HSV-1.	Faral-tello et al., 2012[26]
Psidium luridum		Myrtaceae	Not specified	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Faral-tello et al., 2012[26]
Psilostrophe cooperi	Whitestem paper flower	Asteraceae	Not specified	Acetone Methanol	In vitro	Vero cells		Acetonic extract demonstrated antiviral activity against HSV-1 and HSV-2.	Jaeger Greer et al., 2012[46]
Psychotria serpens	Creeping psychotria	Rubiaceae	Not specified	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Kuo et al., 2001[147]
Pulicaria stephanocarpa		Compositae	Leaf Flower	Water Methanol	In vitro	Vero cells		Both extracts demonstrated antiviral activity against HSV-1, but the methanolic extract was significantly more potent.	Mothana et al., 2006[56]
Punica granatum	Pomegranate	Punicaceae	Root bark	Water	In vivo		BALB/c mice	Extract significantly delayed the development and progression of HSV-1 lesions.	Kurokawa et al., 1993[33]
			Pericarp	Water Methanol	In vitro	Vero cells		Both extracts demonstrated complete antiviral activity against HSV-1.	Nawawi et al., 1999[92]
			Pericarp	Methanol	In vivo		BALB/c mice	Extract delayed the appearance of local vesicles, but did not limit further development to mild zosteriform lesions, reduce survival time, or reduce mortality.	Nawawi et al., 1999[92]
			Fruit cortex	Water	In vitro	Vero cells		Extract demonstrated antiviral activity against 3 HSV-1 strains, but was more effective on the clinical strain.	Li et al., 2004[29]
Punica protopunica	Pomegranate tree Socotran pomegranate	Punicaceae	Fruit Leaf	Water Methanol	In vitro	Vero cells		Water extract demonstrated antiviral activity against HSV-1.	Mothana et al., 2006[56]
Quercus brantii	Brant's oak	Fagaceae	Fruit	Ethyl alcohol	In vitro	BHK cells		Extract demonstrated antiviral activity against HSV-1, particularly when present during and after adsorption.	Karimi et al., 2017[148]
Rheum officinale	Chinese rhubarb	Polygonaceae	Rhizome	Water Ethanol	In vitro	Vero cells		Ethanolic extract demonstrated significant antiviral activity against HSV-1.	Hsiang et al., 2001[118]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
				Ethanolic acid Methanol					
Rheum palmatum	Chinese rhubarb	Polygonaceae	Rhizome	Water	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Kurokawa et al., 1993[33]
Rhododendron ferrugineum	Snow rose Alpen rose	Ericaceae	Aerial parts	Water	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1, preventing viral attachment and penetration.	Gescher et al., 2011[149]
Rhus aromatica	Fragrant sumac	Anacardiaceae	Root Bark	Water	In vitro	RC-37 cells		Extract demonstrated more potent antiviral activity against HSV-1 compared to HSV-2 when virions were pretreated.	Reichling et al., 2009[150]
Rhus javanica	Sumac	Anacardiaceae	Gall	Water	In vivo		BALB/c mice	Extract significantly delayed the development and progression of HSV-1 lesions.	Kurokawa et al., 1993[33]
			Gall	Water	In vitro	Vero cells		Extract demonstrated synergistic antiviral effects on HSV-1 when combined with acyclovir.	Kurokawa et al., 1995[98]
			Gall	Water	In vivo		BALB/c mice	Extract demonstrated synergistic antiviral effects on HSV-1 when combined with acyclovir.	Kurokawa et al., 1995[98]
			Gall	Water	In vivo		BALB/c mice	Extract reduced incidence of recurrence, severity of vesicles, and duration of lesions from HSV-1 infection.	Kurokawa et al., 1997[99]
			Dried herb	Water	In vivo		Guinea pigs	Extract reduced the number, severity, and prevalence of HSV-2 lesions.	Nakano et al., 1998[151]
Ribes nigrum	Blackcurrant	Grossulariaceae	Fruit	Sodium hydroxide	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-2 and 2 HSV-1 strains.	Suzutani et al., 2003[154]
Ricinus communis	Castor oil plant	Euphorbiaceae	Leaf	Ethanol	In vitro	Vero cells HeLa cells		Extract demonstrated antiviral activity against HSV-1.	Abdul et al., 1996[34]
Rinorea anguifera		Violaceae	Leaf	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Lipipun et al., 2003[28]
Rosmarinus officinalis	Rosemary	Lamiaceae	Aerial parts	Essential oil	In vitro	Vero cells		Extract demonstrated partial antiviral activity against HSV-1.	Vijayan et al., 2004[76]
			Leaf	Water	In vitro	RC-37 cells		Extract demonstrated antiviral activity against 2 HSV-1 strains and HSV-2 with treatment prior to infection, but not post-infection.	Nolkemper et al., 2006[121]
			Leaf	Ethanol	In vitro	RC-37 cells		Extract demonstrated antiviral activity against 3 HSV-1 strains.	Reichling et al., 2008[126]
Rubus eubatus	Blackberry	Rosaceae	Berry	Ethanol	In vitro	OKF6 cells		Extract demonstrated antiviral and virucidal activity against HSV-1, particularly by preventing viral adsorption and replication.	Danaher et al., 2011[152]
Rubus imperialis		Rosaceae	Leaf	Methanol	In vitro	Vero cells		Extract demonstrated antiviral activity against 2 HSV-1 strains.	Muller et al., 2007[108]
Salvia ballotiflora	Shrubby blue sage	Lamiaceae	Aerial parts	Hydromethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1 and HSV-2.	Silva-Mares et al., 2019[63]
Salvia officinalis	Sage	Lamiaceae	Leaf	Water	In vitro	RC-37 cells		Extract demonstrated antiviral activity against 2 HSV-1 strains and HSV-2 with treatment prior to infection, but not post-infection.	Nolkemper et al., 2006[121]
			Leaf	Water Ethanol	In vitro	RC-37 cells		All extracts inhibited HSV-1 and HSV-2, but ethanolic extracts were more potent than water extracts.	Schnitzler et al., 2008[153]
Salvia texana	Texas sage	Lamiaceae	Aerial parts	Hydromethanol	In vitro	Vero cells		Extract demonstrated minimal antiviral activity against HSV-1 and moderate activity against HSV-2.	Silva-Mares et al., 2019[63]
Sambucus nigra	Elderberry	Adoxaceae	Fruit	Sodium hydroxide	In vitro	Vero cells		Extract demonstrated antiviral activity against acyclovir-resistant HSV-1.	Suzutani et al., 2003[154]
Sargassum cymosum		Sargassaceae	Whole plant	Dichloromethane and methanol	In vitro	Vero cells		Extract demonstrated strong antiviral activity against acyclovir-resistant HSV-1, but not against acyclovir-resistant HSV-2.	Soares et al., 2012[69]
Sargassum ringgoldianum		Sargassaceae	Whole plant	Methanol	In vitro	Vero cells		Extract demonstrated complete plaque inhibition against 3 HSV-1 strains, but demonstrated strong cytotoxicity to cells.	Park et al., 2005[81]
		Sargassaceae	Whole plant	Methanol	In vitro	Vero cells			Park et al., 2005[81]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
Sargassum thunbergii								Extract demonstrated moderate plaque inhibition against one HSV-1 strain.	
Sasa senanensis	Senan bamboo	Poaceae	Leaf	Water	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1 and was synergistic with acyclovir.	Sakagami et al., 2016[155]
Satureja boliviana		Lamiaceae	Not specified	Ethanol Water	In vitro	HeLa cells Vero cells		Water extract demonstrated antiviral activity against HSV-1, but the upper limit of its effective range was cytotoxic.	Abad et al., 1999[51]
Schima wallichi	Needlewood tree	Theaceae	Leaf	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Lipipun et al., 2003[28]
Schinus molle	Brazilian peppertree	Anacardiaceae	Not specified	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Faral-tello et al., 2012[26]
Schinus terebinthifolia	Aroeira	Anacardiaceae	Bark	Water Hydroalcohol	In vitro	Vero cells		Both extracts demonstrated antiviral activity against HSV-1, but the 50% hydroalcoholic extract was more potent.	Moura-costa et al, 2012[60]
			Stem bark	Hydroethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against 3 HSV-1 strains.	Nocchi et al., 2016[156]
			Stem bark	Hydroethanol	In vivo		BALB/c mice	Extract demonstrated quicker healing of lesions and was comparable to acyclovir.	Nocchi et al., 2016[156]
Sebastiania brasiliensis		Euphorbiaceae	Leaf Aerial parts	Water	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Kott et al., 1998[115]
Sebastiania klotzschiana		Euphorbiaceae	Leaf Aerial parts	Water	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Kott et al., 1998[115]
Securidaca longepedunculata	Violet tree	Polygalaceae	Root	Ethanol Methanol	In vitro	GMK cells		Both extracts demonstrated antiviral activity against HSV-1.	Beuscher et al., 1994[68]
Senecio ambavilla	Ambaville	Asteraceae	Leaf Stem	Methanol	In vitro	Vero cells		Extract demonstrated strong antiviral activity against HSV-1.	Fortin et al., 2002[70]
Senecio scandens		Compositae	Whole plant	Water	In vitro	BCC-1/KMC cells		Extract demonstrated moderate antiviral activity against HSV-2.	Chiang et al., 2004[54]
Serissa japonica	Snow rose	Rubiaceae	Stem Leaf	Water	In vitro	BCC-1/KMC cells		Extract demonstrated potent antiviral activity against HSV-1 and HSV-2.	Chiang et al., 2003[43]
Sesbania punicea	Scarlet wisteria Brazilian rattlebox	Fabaceae	Not specified	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Faral-tello et al., 2012[26]
Sibbaldia micropetala	Bhui pasari jhar	Rosaceae	Whole plant	Methanol	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Taylor et al., 1996[36]
Sloanea guianensis		Elaeocarpaceae	Leaf Stem	Methanol	In vitro	Vero cells		Methanolic leaf extract demonstrated antiviral activity against one HSV-1 strain.	Muller et al., 2007[108]
Smilax gracilis		Smilacaceae	Not specified	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Faral-tello et al., 2012[26]
Solanum americanum	American black nightshade	Solanaceae	Leaf	Ethanol	In vitro	Vero cells HeLa cells		Extract demonstrated antiviral activity against HSV-1.	Abdul et al., 1996[34]
Solanum paniculatum		Solanaceae	Leaf	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Valadares et al., 2009[157]
Sophora flavescens	Shrubby sophora	Fabaceae	Root	Water Ethanol Ethanolic acid Methanol	In vitro	Vero cells		Hot water extract demonstrated significant antiviral activity against HSV-1.	Hsiang et al., 2001[118]
Spatholobus suberectus		Fabaceae	Rhizome	Water	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Kurokawa et al., 1993[33]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
Spirogyra spp.	Water silk Mermaid's tresses Blanket weed	Zygnemataceae	Whole plant	Water Ethanol Methanol	In vitro	Vero cells		All extracts demonstrated antiviral activity against HSV-1 and HSV-2, but the ethanolic extract was most potent.	Deethae et al., 2018[158]
Stephania cepharantha		Menispermaceae	Root tuber	Methanol	In vivo		BALB/c mice	Extract decreased number and development of HSV-1 lesions and increased mice survival time.	Nawawi et al., 2001[159]
Sterculia setigera	Kukkugi	Sterculiaceae	Bark	Ethanol	In vitro	HT-29 cells		Extract demonstrated complete HSV-1 inhibition.	Kudi and Myint, 1999[35]
Stizophyllum perforatum		Bignoniaceae	Leaf Stem	Ethanol	In vitro	Vero cells		Stem ethanolic extract demonstrated minimal antiviral activity against HSV-1.	Brandao et al., 2010[37]
Strychnos pseudoquina	Quina	Loganiaceae	Stem bark	Ethyl acetate	In vitro	Vero cells		Extract demonstrated antiviral and virucidal activity against HSV-2 and 2 HSV-1 strains.	Boff et al., 2016[160]
Stypopodium zonale		Dictyotaceae	Whole plant	Dichloromethane and methanol	In vitro	Vero cells		Extract demonstrated strong antiviral activity against both acyclovir-resistant HSV-1 and acyclovir-resistant HSV-2.	Soares et al., 2012[69]
Swertia chirata	Chirata	Ranunculaceae	Leaf Stem	Water	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Verma et al., 2008[161]
Symphonia globulifera	Chewstick	Clusiaceae	Bark	Methanol	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Lopez et al., 2001[27]
Symphyocladia latiuscula		Rhodomelaceae	Whole plant	Methanol Hexane Dichloromethane Ethyl acetate Butanol Water	In vitro	Vero cells		Methanolic extract demonstrated strong plaque inhibition against 2 HSV-1 strains. Dichloromethanic fraction exhibited the strongest antiviral activity.	Park et al., 2005[81]
			Whole plant	Methanol	In vitro		BALB/c mice	Extract significantly delayed the development and progression of HSV-1 lesions, increased survival time, decreased viral yields in skin, but had no effect on mortality rate.	Park et al., 2005[81]
Syzygium aromaticum	Clove	Myrtaceae	Flower bud	Water	In vivo		BALB/c mice	Extract significantly delayed the development and progression of HSV-1 lesions.	Kurokawa et al., 1993[33]
			Flower bud	Water	In vitro	Vero cells		Extract demonstrated synergistic antiviral effects on HSV-1 when combined with acyclovir.	Kurokawa et al., 1995[98]
			Flower bud	Water	In vivo		BALB/c mice	Extract demonstrated synergistic antiviral effects on HSV-1 when combined with acyclovir.	Kurokawa et al., 1995[98]
			Flower bud	Water	In vivo		BALB/c mice	Extract reduced incidence of recurrence, severity of vesicles, and duration of lesions from HSV-1 infection.	Kurokawa et al., 1997[99]
Tamarix nilotica	Nile Tamarisk	Tamaricaceae	Aerial parts	Hydroethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Soltan and Zaki, 2009[61]
Tanacetum parthenium	Feverfew	Asteraceae	Aerial parts	Hydroethanol	In vitro	Vero cells L-929 cells		Extract demonstrated antiviral activity against HSV-1 and promoted wound healing in L-929 cells.	Benassi-Zanqueta et al., 2019[162]
			Aerial parts	Hydroethanol	In vivo		BALB/c mice	Oral and topical treatment mildly improved HSV-1 lesions and effects were comparable to acyclovir.	Benassi-Zanqueta et al., 2019[162]
Tanacetum vulgare	Common tansy	Asteraceae	Aerial parts	Water Ethyl acetate	In vitro	Vero cells		Both extracts demonstrated mild antiviral activity against HSV-1.	Onozato et al., 2009[163]
			Aerial parts Rhizome	Methanol Petroleum ether Chloroform Ethyl acetate Butanol Water	In vitro	Vero cells		Petroleum ether and ethyl acetate fractions of aerial parts and the methanolic rhizome extract demonstrated strong antiviral activity against HSV-1 and HSV-2.	Alvarez et al., 2011[164]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
Terminalia arjuna	Arjuna Arjun tree	Combretaceae	Bark	Water	In vivo		BALB/c mice	Extract significantly delayed the development and progression of HSV-1 lesions.	Kurokawa et al., 1993[33]
Terminalia chebula		Combretaceae	Fruit	Water	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Kurokawa et al., 1993[33]
			Fruit	Water	In vivo		BALB/c mice	Extract significantly delayed the development and progression of HSV-1 lesions.	Kurokawa et al., 1993[33]
			Fruit	Water	In vitro	Vero cells		Extract demonstrated synergistic antiviral effects on HSV-1 when combined with acyclovir.	Kurokawa et al., 1995[98]
			Fruit	Water	In vivo		BALB/c mice	Extract demonstrated synergistic antiviral effects on HSV-1 when combined with acyclovir.	Kurokawa et al., 1995[98]
			Fruit	Water	In vivo		BALB/c mice	Extract reduced incidence of recurrence, severity of vesicles, and duration of lesions from HSV-1 infection.	Kurokawa et al., 1997[99]
			Fruit	Ethanol	In vitro	Vero cells		Extract demonstrated very potent antiviral activity against HSV-2, particularly in the early stages of infection.	Kesharwani et al., 2017[165]
Tessaria absinthioides		Asteraceae	Leaf	Essential oil	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Garcia et al., 2004[32]
Tetraclinis articulata	Sictus tree Arar tree	Cupressaceae	Not specified	Acetone Methanol	In vitro	Vero cells		Acetonic extract demonstrated antiviral activity against HSV-1 and HSV-2.	Jaeger Greer et al., 2012[46]
Tillandsia aeranthos		Bromeliaceae	Not specified	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Faral-tello et al., 2012[26]
Tillandsia usneoides	Spanish moss	Bromeliaceae	Not specified	Ethanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Faral-tello et al., 2012[26]
			Aerial parts	Dichloromethane Ethyl acetate n-Butanol	In vitro	Vero cells		All extracts demonstrated antiviral activity against 2 HSV-1 strains, but the ethyl acetate extract was most potent.	Andrighetti-Frohner et al., 2005[41]
Tithonia diversifolia	Mexican sunflower Tree marigold	Compositae	Whole plant	Water	In vitro	BCC-1/KMC cells		Extract demonstrated potent antiviral activity against HSV-1 and HSV-2.	Chiang et al., 2004[54]
Thymus capitatus	Headed savory	Lamiaceae	Aerial parts	Water Ethanol Essential oil	In vitro	Vero cells		All 3 extracts showed antiviral activity against HSV-1 and HSV-2. The strongest antiviral activity was seen with the ethanolic extract against HSV-2.	Toujani et al., 2018[166]
Thymus vulgaris	Thyme	Lamiaceae	Leaf	Water	In vitro	RC-37 cells		Extract demonstrated antiviral activity against 2 HSV-1 strains and HSV-2 with treatment prior to infection, but not post-infection.	Nolkemper et al., 2006[121]
			Leaf	Ethanol	In vitro	RC-37 cells		Extract demonstrated antiviral activity against 3 HSV-1 strains.	Reichling et al., 2008[126]
Toona sureni	Surian	Meliaceae	Leaf	Water Methanol	In vitro	Vero cells		Methanolic extract demonstrated complete HSV-1 inhibition, but also demonstrated cytotoxicity to cells.	Nawawi et al., 1999[92]
			Leaf	Methanol	In vivo		BALB/c mice	Extract delayed the appearance of local vesicles, but did not limit further development to mild zosteriform lesions, reduce survival time, or reduce mortality from HSV-1 infection.	Nawawi et al., 1999[92]
Trametes versicolor	Turkey tail	Polyporaceae	Mycelia	Sodium chloride	In vitro	RK-13 cells		Extract demonstrated antiviral activity against HSV-2.	Krupodorova er al., 2014[47]
Trichilia catigua	Catuaba	Meliaceae	Bark	Acetone-water Water Ethyl acetate	In vitro	HEp-2 cells		Acetone-water extract and water and ethyl acetate fractions demonstrated antiviral activity against HSV-1, but acetone-water extract was most potent.	Espada et al., 2015[167]
Trichilia glabra		Meliaceae	Leaf	Methanol Chloroform-methanol	In vitro	Vero cells		Ethanolic extract and chloroform-methanolic fractions demonstrated virucidal effects against HSV-1.	Cella et al., 2004[168]
Trichocalyx obovatus		Acanthaceae	Leaf Flower	Methanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Mothana et al., 2006[56]

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Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
Trixis divaricata		Asteraceae	Aerial parts	Essential oil	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Garcia et al., 2010[25]
Ulva fasciata		Ulvaceae	Whole plant	Dichloromethane and methanol	In vitro	Vero cells		Extract demonstrated strong antiviral activity against acyclovir-resistant HSV-1, but not against acyclovir-resistant HSV-2.	Soares et al., 2012[69]
Ulva pertusa	Sea lettuce	Ulvaceae	Whole plant	Methanol	In vitro	Vero cells		Extract demonstrated moderate plaque inhibition against one HSV-1 strain.	Park et al., 2005[81]
Unicaria tomentosa			Stem bark	Hydroethanol	In vitro	Vero cells		Extract demonstrated antiviral and virucidal activity against HSV-2, particularly by preventing viral adsorption.	Churqui et al., 2017[73]
			Stem bark	Hydroethanol	In vivo		C57bl/6 mice	Extract prevented HSV-2 infection when administered with the virus.	Churqui et al., 2017[73]
Usnea complanta	Marappasi	Usneaceae	Whole plant	Acetone and chloroform	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Vijayan et al., 2004[76]
Vachellia nilotica	Gum arabic tree Thorn mimosa	Fabaceae	Bark	Chloroform Methanol Water	In vitro	Vero cells		All extracts demonstrated strong antiviral activity against HSV-2, and the methanolic extract additionally demonstrated activity against acyclovir-resistant HSV-2.	Donalisio et al., 2018[169]
Ventilago denticulata	Drumstick tree	Rhamnaceae	Leaf	Ethanol	In vitro	Vero cells		Extract demonstrated similar antiviral activity against 3 HSV-1 strains.	Lipipun et al., 2003[28]
			Leaf	Ethanol	In vivo		BALB/c mice	Extract decreased size and development of skin lesions from HSV-1 infection, reduced mortality, and increased survival time.	Lipipun et al., 2003[28]
Veronica persica	Persian speedwell Bird's eye speedwell	Plantaginaceae	Aerial parts	Ethanol Methanol	In vitro	Vero cells		Ethanolic extract demonstrated moderate antiviral activity against HSV-1 and HSV-2, and the 80% methanolic fraction demonstrated strong activity against both viruses.	Sharifi-rad et al., 2018[170]
Viola yedoensis		Violaceae	Whole plant	Water	In vitro	SK-N-SH cells		Extract demonstrated antiviral activity against HSV-1.	Liao et al., 2010[171]
Virola multinervia		Myristicaceae	Resin Bark	Methanol	In vitro	Vero cells		Both resin and bark extracts demonstrated complete HSV-1 inhibition.	Lopez et al., 2001[27]
Vismia macrophylla	Kunth	Hypericaceae	Resin Bark	Methanol	In vitro	Vero cells		Resin extract demonstrated complete HSV-1 inhibition.	Lopez et al., 2001[27]
Vitex polygama		Lamiaceae	Fruit Leaf	Ethyl acetate	In vitro	HEp-2 cells		Both fruit and leaf extracts demonstrated antiviral activity against acyclovir-resistant HSV-1. Fruit extract had a stronger virucidal effect while the leaf extract was more potent post-infection.	Goncalves et al., 2001[172]
Wilbrandia ebracteata	Taiuia	Cucurbitaceae	Root	Ethyl acetate n-Butanol	In vitro	Vero cells		Both extracts demonstrated antiviral activity against 2 HSV-1 strains.	Andrighetti-Frohner et al., 2005[41]
Withania adunensis		Solanaceae	Leaf Fruit	Water Methanol	In vitro	Vero cells		Methanolic extract demonstrated antiviral activity against HSV-1.	Mothana et al., 2006[56]
Woodfordia floribunda	Fire flame bush	Lythraceae	Flower Leaf	Water	In vitro	Vero cells		Extract demonstrated complete HSV-1 inhibition.	Kurokawa et al., 1993[33]
Zanthoxylum rhoifolium	Prickly ash	Rutaceae	Bark Leaf	Water Hydroalcohol	In vitro	Vero cells		All extracts except the water bark extract demonstrated antiviral activity against HSV-1. The 50% hydroalcoholic leaf extract was most potent.	Moura-costa et al., 2012[60]
Zataria multiflora	Shirazi thyme	Lamiaceae	Aerial parts	Methanol	In vitro	Vero cells		Extract demonstrated antiviral activity against HSV-1.	Arabzadeh et al., 2013[173]
Zeyheria tuberculosa		Bignoniaceae	Leaf Stem Fruit	Ethanol	In vitro	Vero cells		Ethanolic leaf extract demonstrated moderate antiviral activity against HSV-1.	Brandao et al., 2010[37]
Zygophyllum album		Zygophyllaceae	Whole plant	Petroleum ether Acetone	In vitro	Vero cells		Acetone extract demonstrated antiviral activity against HSV-1.	Sassi et al., 2008[84]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
				Methanol Water					
Zygophyllum quatarense		Zygophyllaceae	Leaf Stem	Water Methanol	In vitro	Vero cells		Methanolic extract demonstrated antiviral activity against HSV-1.	Mothana et al., 2006[56]
Combination herb studies									
Hypericum perforatum Sambucus nigra Saponaria officinalis	St. John's Wort Elderberry Sweet William	Hypericaceae Adoxaceae Caryophyllaceae	Flower Aerial parts Root	Water	In vitro	Vero cells MRC-5 cells RK-13 cells		Herbal combination demonstrated antiviral activity against HSV-1.	Serkedjieva et al, 1990[174]
Aconitum carmichaelii Glycyrrhiza glabra Zingiberis siccatum	Shigyaku-to Si Ni Tang	Ranunculaceae Fabaceae Zingiberaceae	Tuber Root Rhizome	Saline	In vivo		BALB/c mice	Herbal combination showed the greatest antiviral activity against HSV-1 at 20mg/kg, increasing survival rate.	Ikemoto et al., 1994[175]
Aconitum carmichaelii Atractyloidis lanceae Cinnamomum verum Glycyrrhiza glabra	Kanzo-bushi-to Gan Cao Fu Zhi Tang	Ranunculaceae Asteraceae Lauraceae Fabaceae	Tuber Rhizome Cortex Root	Water	In vivo		Thermally-injured BALB/c mice	Herbal combination improved susceptibility to and mortality from HSV-1 infection.	Matsuo et al., 1994[176]
Cinnamomi cassia Ephedra sinica Glycyrrhizae uralensis Paeoniae lactiflora Pueraria pseudo-hirsuta Zingiberis officinale Zizyphi jujuba	Kakkon-to Ge Gan Tang	Lauraceae Ephedraceae Fabaceae Paeoniaceae Fabaceae Zingiberaceae Rhamnaceae	Cortex Herba Radix Radix Radix Rhizoma Fructus	Water	In vivo		BALB/c mice	Herbal combination decreased mortality, size, and severity of lesions when given prior to HSV-1 infection. Only noted difference when given during HSV-1 infection was a smaller size of lesions.	Nagasaka et al., 1995[177]
Artemisia capillaries Gardenia jasminoids Rheum officinale	Yin Chen Hao Tang	Compositae Rubiaceae Polygonaceae	Seed Fruit Rhizome	Water	In vitro	Vero cells HEp-2 cells		Herbal combination demonstrated antiviral activity against both HSV-1 and HSV-2, but effects were more potent against HSV-2.	Cheng et al., 2008[178]
Alisma plantago-aquatica Akebia quinata Angelica sinensis Bupleurum chinense Gardenia jasminoides Gentiana scabra Glycyrrhiza uralensis Plantago asiatica Rehmannia glutinosa Scutellaria baicalensis	Long Dan Xie Gan Tang	Alismataceae Lardizabalaceae Umbelliferae Umbelliferae Rubiaceae Gentianaceae Leguminosae Plantaginaceae Scrophulariaceae Labiatae	Tuber Fruit Root Root Fruit Root and rhizome Root and rhizome Seed Tuber Root	Water	In vitro	Vero cells		Herbal combination demonstrated antiviral activity against both HSV-1 and HSV-2, but effects were more potent against HSV-1.	Cheng et al., 2008[179]

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Table 1. (continued)

Plant name	Common name	Family	Parts used	Solvents used for extraction	Type of study (in vitro or in vivo)	Cell line used (for in vitro)	Sample population (for in vivo)	Outcome	Reference
Acacia catechu Lagerstroemia speciosa Phyllanthus emblica Terminalia chebula	Catechu Crepe-myrtle Indian gooseberry Myrobalan	Fabaceae Lythraceae Phyllanthaceae Combretaceae	Heart wood Leaf Fruit	Ethanol	In vitro	Vero cells Vk2/E6E7 cells		Herbal combination demonstrated antiviral activity against HSV-2 in Vero cells and did not decrease viability or integrity nor increase mutagenic behavior or inflammatory cytokines in Vk2/E6E7 cells.	Mishra et al., 2018[180]
Human Trials									
Melaleuca alternifolia	Tea tree	Myrtaceae	Leaf	Gel	In vivo		20 subjects with recurrent herpes labialis	Gel reduced duration of infection and viral load in lesions compared to placebo, but results were not statistically significant.	Carson et al., 2001[181]
Melissa officinalis	Lemon balm	Lamiaceae	Leaf	Cream	In vivo		115 subjects with HSV lesions of skin or transitional mucosa	Cream reduced expected healing time of HSV infection. No placebo or control included in the study.	Wolbling et al., 1994[182]
			Leaf	Cream	In vivo		116 subjects with HSV lesions of skin or transitional mucosa	Cream significantly reduced symptoms and HSV lesion swelling compared to placebo. Subjects' and physicians' assessments of healing were significantly greater for the cream compared to placebo.	Wolbling et al., 1994[182]
			Leaf	Cream	In vivo		66 subjects with at least 4 episodes of herpes labialis per year	Cream reduced severity of symptoms, healing time, spread of virus to neighboring cells, and symptoms of itching, burning, swelling, and erythema.	Koytchev et al., 1999[183]
Hypericum perforatum	St. John's Wort	Hypericaceae	Not specified	Cream	In vivo		149 subjects with HSV-1 or HSV-2 lesions	Topical cream, formulated with copper sulfate pentahydrate, reduced burning, stinging, pain, erythema, and vesiculation compared to acyclovir.	Clewell et al., 2012[184]
Coicis semen Elfuinga applanata Ganoderma lucidum Terminalia chebulae Trapa natans Wisteria floribunda	Coix seed - Reishi Black myrobalan Water chestnut Japanese wisteria	Gramineae - Ganodermataceae Combretaceae Trapaceae Fabaceae	Seed Fruit Fruit Fruit Fruit Bark	Water	In vivo		5 subjects with recurrent herpes labialis	Herbal combination reduced the healing time of herpes lesions compared to previous outbreaks when no treatment was used. Pain associated with outbreaks was also reduced in one patient.	Hijikata et al., 1998[185]
Coicis lachryma-jobi Elfuinga applanata Ganoderma lucidum Terminalia chebulae Trapa natans Wisteria floribunda	Job's tears - Reishi Black myrobalan Water chestnut Japanese wisteria	Poaceae - Ganodermataceae Combretaceae Trapaceae Fabaceae	Not specified	Water	In vivo		28 subjects with either chronic herpes labialis or genitalis	Herbal combination reduced mean time to relief from HSV infection.	Hijikata et al., 2007[186]
Rheum officinale Rheum palmatum Salvia officinalis	Chinese rhubarb Chinese rhubarb Sage	Polygonaceae Polygonaceae Lamiaceae	Root Leaf	Cream	In vivo		145 subjects with recurrent herpes labialis	The sage, sage-rhubarb, and acyclovir creams had similar mean time to healing and crust formation of HSV lesions. Subjects who used the sage-rhubarb cream reported less pain compared to the sage cream subjects.	Saller et al., 2001[187]

Abbreviations: HSV, herpes simplex virus; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2.

against both HSV-1 (strain KOS) and HSV-2 (strain HG52). The extract was found to have antiviral activity in plaque reduction assays with African green monkey kidney (RC-37) cells. When applied at the maximum non-cytotoxic concentration (not specified), the extract was able to reduce plaque formation by 99% for both HSV-1 and HSV-2. Moreover, the extract was added to RC-37 cells at various times throughout the HSV life cycle and compared to acyclovir. The P. sidoides extract showed antiviral effects if added prior to HSV infection or if added during HSV adsorption, compared to acyclovir that exhibited antiviral effects only during HSV replication. The authors conclude that P. sidoides may be effective if used as a topical antiviral treatment at the onset of HSV infection.

Forty-two Egyptian medicinal plants were selected by Soltan and Zaki[61] for their traditional uses for infectious diseases, and 80% aqueous ethanolic extracts of either aerial parts, seeds, or tubers were tested against HSV-1. A total of 5 plants showed antiherpetic activity. Moringa peregrina and Ephedra alata were observed to have the highest antiviral activity at concentration ranges 50-100 μg/ml (Rf 10^4) and 500-1000 μg/ml (Rf 10^4), respectively. Capparis sinaica, Tamarix nilotica, and Cyperus rotundus showed lesser virucidal activity at concentrations of 1000 μg/ml (Rf 10^4), 1000 μg/ml (Rf 10^4), and 500 μg/ml (Rf 10^2), respectively. It must be noted that all 5 plants are edible except for E. alata, therefore it may not be safe to use E. alata for human HSV-1 infections.

Moreover, Behbahani et al.[48] found a methanolic extract of Avicenna marina leaves to exhibit antiviral effects against HSV-2. This plant is native to Southern Africa and traditionally used to treat ulcers, rheumatism, and smallpox. The greatest inhibition was seen at a concentration of 20 μg/ml where the extract inhibited 80% of HSV-2 replication. The EC_{50} and SI values for the extract were determined to be 10 μg/ml and 25, respectively, and no cytotoxic effects were noted up to a concentration of 32 μg/ml.

Nauclea latifolia roots were used to make an extraction using a 1:1 mixture of dichloromethane and methanol and tested for anti-HSV-2 activity by Donalisio et al.[129] Two HSV-2 strains were used: an acyclovir-sensitive HSV-2 strain and an acyclovir-resistant HSV-2 strain. The IC_{50} values were found to be 7.17 μg/ml and 5.38 μg/ml for the acyclovir-sensitive and acyclovir-resistant HSV-2 strains, respectively. Time-of-addition experiments revealed that the greatest viral inhibition occurred when the extract was added to cells after HSV-2 infection. The authors note N. latifolia does not block viral attachment or entry into host cells. Additionally, the acyclovir-resistant HSV-2 strain was more susceptible to the extract than the acyclovir-sensitive HSV-2 strain, suggesting a potential different mechanism of action than acyclovir.

Hassan et al.[188] tested an aqueous extract of Hibiscus sabdariffa for anti-HSV-2 activity, but the extract failed to show any antiviral effects.

The most recent African plant to be investigated for its antiherpetic activity was Thymus capitatus, a Tunisian herb that has a long history of use for purposes such as flavoring food, medicines, cosmetics, and perfumes.[166] Toujani et al.[166] prepared aqueous and ethanolic extracts as well as an essential oil from aerial parts of T. capitatus and found all 3 exhibited antiviral effects against both HSV-1 and HSV-2. The EC_{50} and SI values, respectively, against HSV-1 were 23.4 μg/ml and >12.7 for the aqueous extract, 16.6 μg/ml and 3.5 for the ethanolic extract, and 17.6 μg/ml and 6.0 for the essential oil. The EC_{50} and SI values, respectively, against HSV-2 were 23.6 μg/ml and >12.6 for the aqueous extract, 2.3 μg/ml and 26.8 for the ethanolic extract, and 18.6 μg/ml and 6.9 for the essential oil. These results highlight that HSV-2 is more susceptible to the ethanolic extract of T. capitatus compared to HSV-1, while both viruses showed similar susceptibility to the aqueous extract and essential oil. This could be due to differences in susceptibility to antiviral compounds between the 2 viruses and the concentrations of these compounds in the different extracts.

Asia

Elanchezhiyan et al.[146] observed aqueous extracts of Pongamia pinnata to completely inhibit HSV-1 (strain AC) and HSV-2 (strain HV-219) replication at concentrations of 1 mg/ml and 20 mg/ml, respectively. Experiments were carried out using African green monkey kidney (Vero) cells and the seeds of the plant were used to prepare the extracts. Extracts were added to cells after viral inoculation, and complete inhibition was noted at 24 hours. Extract concentrations lower than 1 mg/ml and 20 mg/ml were less effective.

Houttuynia cordata, a traditional medicinal plant in Japan and China, was investigated for its antiviral effects against HSV-1 (strain HF) in human epithelial cervical carcinoma (HeLa) cells.[105] Hayashi et al.[105] found that a steam distillate of aerial parts of H. cordata was effective at inhibiting viral replication (EC_{50} = 0.0013% and SI >4.4). Neither plaque formation nor viral adsorption were reduced when HeLa cells were pretreated with the distillate. Yet, incubating the distillate with HSV-1 prior to infection prevented viral adsorption, revealing a direct effect on HSV-1 virions as the inhibitory mechanism of action of H. cordata.

Chen et al.[106] also tested the antiviral effects of H. cordata, but against HSV-2 (strain G ATCC-VR-734). An aqueous extract of the leaves and stems significantly prevented Vero cell death that is associated with HSV-2 infection, and an IC_{50} value of 50 μg/ml was determined. In addition, the extract significantly inhibited virus production by more than 3 and 4 logs at doses of 150 μg/ml and 450 μg/ml, respectively. The extract demonstrated inhibition of NF-| B, which is activated during HSV-2 infection and required for viral replication. Time-of-addition experiments revealed the extract was able to elicit similar antiviral effects when added to cells before, during, or just after HSV-2 infection, suggesting H. cordata acts early in viral infection.

The anti-HSV mechanism of action of H. cordata was further investigated by Hung et al.[107] Vero and 2 types of human epithelial carcinoma cells (Hep-2 and A549) were used in experiments with an aqueous extract of the plant against wild-type HSV-1 (strain F ATCC-VR733), acyclovir-resistant

HSV-1, and HSV-2 (strain G ATCC-VR734). The extract was able to inhibit all 3 HSV strains. The EC_{50} and SI values, respectively, were determined to be 0.692 mg/ml and 144.51 for wild-type HSV-1, 1.11 mg/ml and 90.09 for acyclovir-resistant HSV-1, and 0.3 mg/ml and 333.33 for HSV-2. It is interesting to note that the EC_{50} values were similar for the wild-type and acyclovir-resistant strains of HSV-1, suggesting H. cordata elicits antiviral effects through a different mechanism than acyclovir. Tests using Vero cells revealed the extract likely affects HSV virions directly, interfering with viral binding and penetration, blocking viral entry, and suppressing viral replication and gene expression. This multi-stage inhibition was also observed in HEp-2 and A549 cells. Similar to the previous study, the extract was also found to inhibit NF-kB activation. The authors conclude that H. cordata elicits anti-HSV effects through several mechanisms, which makes it a good candidate for treating HSV infections.

Moreover, Kurokawa et al.[33,98] tested a wide variety of Asian plants for anti-HSV-1 activity and reported findings in 2 studies. Hot water was used as the solvent for the plant extracts in both studies. In the first study, Kurokawa et al.[33] tested antiviral activities of 142 extracts against HSV-1 (strain 7401 H). Extracts that showed 100% of plaque inhibition without any visible cytotoxicity at a dose of 100 μg/ml were Elaeocarpus grandiflorus and Woodfordia floribunda. On the other hand, extracts that showed 100% of plaque inhibition without any visible cytotoxicity at a dose of either 300 or 500 μg/ml were Alpinia officinarum, Brainia insignis, Drynaria fortunei, Geum japonicum, Juglans mandshurica, Polygonum cuspidatum, Prunella vulgaris, Rheum palmatum, Spatholobus suberectus, and Terminalia chebula. In the second study, Kurokawa et al.[98] tested antiviral activities of 10 extracts in combination with acyclovir. Acyclovir and extracts were combined at their respective EC_{50} concentrations and tested against HSV-1 strain 7401 H. The acyclovir-extract combinations that reduced viral plaques to less than 10% of controls were G. japonicum, Rhus javanica, Syzygium aromaticum, and T. chebula. Further experiments revealed that the acyclovir-extract combination elicited stronger antiviral effects than either acyclovir or extract alone, suggesting synergistic activity. No acyclovir-extract combination was more cytotoxic to cells at concentrations lower than the extract alone. Additionally, G. japonicum, R. javanica, S. aromaticum, and T. chebula extracts were tested alone against 2 acyclovir-resistant HSV-1 strains. All 4 extracts were observed to elicit similar antiviral effects on the resistant strains compared to the wild-type strain.

Abdul et al.[34] tested ethanolic extracts of 61 plants that are commonly used in Malaysian indigenous medicine for their antiviral properties against HSV-1. The plant extracts that showed anti-HSV activity were Alternanthera sessilis, Blumea chinensis, Calotropis gigantea, Costus speciosus, Eleusine indica, Eugenia michelii, Euphorbia hirta, Freycinetia malaccensis, Hedyotis auricularia, Leea indica, Mentha arvensis, Orthosiphon aristatus, Polygonum minus, Ricinus communis, and Solanum americanum. The minimum inhibitory concentration (MIC) for these extracts ranged 0.001-0.01 mg/ml. Furthermore, assays using HeLa cell lines were performed with these plant extracts to test for cytotoxicity. Of the 15 extracts, only E. michelii, M. arvensis, F. malaccensis, and P. minus showed cytotoxicity, with CD_{50} values ranging 0.05-0.1 mg/ml.

Methanolic extracts of 21 plants native to Nepal that are traditionally used to treat bacterial, fungal, or viral infections were examined for antiviral activity against HSV-1 by Taylor et al.[36] Assays were performed in the presence of UV-A light, visible light, and darkness to allow for assessment of photosensitive constituents. Four extracts showed 100% viral inactivation at a variety of doses and light conditions: Macaranga pustulata (200 μg/ml in all 3 light conditions), Hypericum cordifolium (50 μg/ml in all 3 light conditions), Maesa macrophylla (100 μg/ml in all 3 light conditions), and Sibbaldia micropetala (200 μg/ml in all 3 light conditions and 100 μg/ml in visible light only). Additionally, 5 extracts were able to partially inhibit HSV-1 at varying doses and light conditions: Hypericum uralum (200 μg/ml in all 3 light conditions), Centipeda minima (13 μg/ml in all 3 light conditions), Coral-lodiscus lanuginosus (100 μg/ml in visible light only), Anemone obtusiloba (100 μg/ml in all 3 light conditions), and Princepia utilis (200 μg/ml in UV-A and visible light only). Most of the extracts studied exhibited no cytotoxicity up to a dose of 200 μg/ml; however, H. cordifolium, M. macrophylla, and A. obtusiloba showed cytotoxicity at this dose. Additionally, C. minima exhibited cytotoxicity at a dose of 25 μg/ml.

Padma et al.[38] observed an ethanolic extract of Annona muricata and an aqueous extract of Petunia nyctaginiflora, both at 1 mg/ml, to have total cytopathic effect against HSV-1 (strains 753166 and A-16). The stembark of A. muricata and aerial parts of P. nyctaginiflora were used to create ethanolic and aqueous extracts for both herbs. At the noted concentration of 1 mg/ml, no cytotoxicity to Vero cells was noted. The authors conclude that these 2 herbs have the potential to be used as antiherpetic drugs.

Furthermore, aqueous and methanolic extracts of 30 Indonesian medicinal plants were tested for antiviral effects against HSV-1 (strain 7401 H) by Nawawi et al.[92] At a concentration of 100 μg/ml, the following extracts inhibited 100% of plaque formation and their IC_{50} values were subsequently determined: the methanolic extracts of Eurycoma longifolia ($IC_{50} = 62$ μg/ml), Filicium decipiens ($IC_{50} = 68$ μg/ml), Garcinia mangostana ($IC_{50} = 40$ μg/ml), and Toona sureni ($IC_{50} = 37$ μg/ml); and the aqueous and methanolic extracts of Nephelium lappaceum ($IC_{50} = 62$ μg/ml and 70 μg/ml, respectively) and Punica granatum ($IC_{50} = 68$ μg/ml and 64 μg/ml, respectively). All extracts showed no cytotoxicity at 100 μg/ml except for T. sureni.

Yoosook et al.[53] tested the antiviral effects of Barleria lupulina and Clinacanthus nutans against standard HSV-2 (strain G) and 5 clinical HSV-2 isolates. Methanolic extracts were created from leaves of twigs of B. lupulina and the whole plant of C. nutans. B. lupulina was ineffective at inhibiting plaque formation in cells infected with HSV-2 strain G, but showed antiviral activity against the 5 HSV-2 isolates with EC_{50} values ranging 442.1-987.7 μg/ml. These doses are significantly below the cytotoxicity value found for the herb ($CC_{50} = 2.64$

mg/ml). Acyclovir was tested as a control and showed much greater antiviral activity against all HSV-2 strains with EC_{50} values ranging 1.9-13.6 μM. C. nutans did not exhibit any antiviral activity against plaque formation. In yield reduction assays, cells were treated with the extracts and acyclovir at various concentrations for either 8 or 24 hours. B. lupulina was able to reduce viral titers of all HSV-2 strains to 0.05-12.7% of control yields at 8 hours with doses ranging 0.25-1 mg/ml. C. nutans exhibited antiviral activity only at 24 hours, reducing viral titers to less than 2% of control yields at its highest non-cytotoxic dose (dose not specified). Treatment with 2.5 μM of acyclovir reduced virus titers to 14.2-43.9% of control yields at 8 hours compared to 0.1-5.3% at 24 hours.

C. nutans was also studied by Kunsorn et al.[71] that used n-hexane, dichloromethane, and methanol as solvents to create extracts that were tested against HSV-1 (strain KOS) and HSV-2 (strain Baylor 186). Extracts of Clinacanthus siamensis, prepared with the same solvents, were concurrently tested for anti-HSV-1 and anti-HSV-2 effects. All extracts exhibited antiviral activity to different degrees. The most potent extract against HSV-1 was the n-hexane extract of C. nutans ($IC_{50} = 32.05$ μg/ml and SI >50.36) followed by the methanolic extract of C. siamensis ($IC_{50} = 37.39$ μg/ml and SI >43.52). On the other hand, the most potent extract against HSV-2 was the n-hexane extract of C. siamensis ($IC_{50} = 46.52$ μg/ml and SI >34.53). For comparison, the IC_{50} values for acyclovir were found to be 0.09 μg/ml for HSV-1 and 0.43 μg/ml for HSV-2.

In a later study by Yoosook et al.,[66] crude water extracts of 8 Thai medicinal plants were evaluated against HSV-1 (KOS strain) and HSV-2 (Baylor 186 strain). Extracts of Centella asiatica, Mangifera indica, and Madura cochinchinensis showed antiviral activity against both viruses. EC_{50} and SI values, respectively, against HSV-1 were 362.40 μg/ml and 3.9 for C. asiatica, 23.94 μg/ml and 29.5 for M. indica, and 20.19 μg/ml and 8.8 for M. cochinchinensis. EC_{50} and SI values, respectively, against HSV-2 were 298.84 μg/ml and 4.7 for C. asiatica, 31.83 μg/ml and 22.2 for M. indica, and 68.32 μg/ml and 2.6 for M. cochinchinensis. This was compared to the efficacy of acyclovir that showed EC_{50} values of 0.14 μg/ml and 0.15 μg/ml for HSV-1 and HSV-2, respectively. Combinations of the extracts and acyclovir were also studied. The combination of C. asiatica and M. indica was shown to exert an additive effect on HSV-2, and each extract with acyclovir resulted in complementary or boosted antiviral effects if the dose of acyclovir was high enough. These results suggest that C. asiatica, M. indica, and M. cochinchinensis may be of use alone or combined for treatment of HSV infections.

Furthermore, the effect of 31 Chinese herbs known for their antipyretic and anti-inflammatory actions were studied for their actions against HSV-1 by Hsiang et al.[118] Methanolic extracts of the herbs were first tested, and those that exhibited inhibitory effects on viral plaques were subsequently made into extracts using cold water, hot water, ethanol, ethanolic acid, and methanol. Significant reduction in plaque numbers were achieved with the ethanolic extract of Rheum officinale ($EC_{50} = 0.12$ μg/ml and SI = 8.3), hot water extract of Sophora flavescens ($EC_{50} = 0.41$ μg/ml and SI = 8.4), hot water ($EC_{50} = 0.20$ μg/ml and SI = 9.1), cold water ($EC_{50} = 0.36$ μg/ml and SI = 8.4), and methanolic ($EC_{50} = 0.06$ μg/ml and SI = 12.3) extracts of Paeonia suffruticosa, and methanolic ($EC_{50} = 0.03$ μg/ml and SI = 8.0) and ethanolic acid ($EC_{50} = 0.02$ μg/ml and SI = 8.0) extracts of Melia toosendan. The authors deemed a SI of 8.0 or greater as being significant. Subsequent testing revealed greater than 95% of inhibition of viral attachment with the aqueous and methanolic extracts of P. suffruiticosa, ethanolic acid extracts of M. toosendan, and ethanolic extract of R. officinale. Also, inhibition of 65% of viral penetration was observed with methanolic extracts of P. suffruticosa and the ethanolic extract of R. officinale. The authors concluded that the studied herbs acted as antiviral agents at various stages of HSV-1 infection, therefore herpes simplex infections may be treated by different herbs at different times during the viral replication cycle.

Kuo et al.[147] tested ethanolic extracts of 7 Chinese herbs against HSV-1 (strain KOS) and found only Psychotria serpens, at a dose of 100 μg/ml, to significantly reduce plaque number to almost zero. This effect was similar to that of 10 μM of acyclovir. The IC_{50} value of the extract of P. serpens was determined to be 58.3 mg/ml. The other herbs, which showed little effect on the virus, were Ampelopsis cantoniensis, Melilotus indicus, Verbena bonariensis, Buddleia asiatica, Ruta graveolens, and Tadehagi triquetrum.

Of 8 Indonesian medicinal plants studied by Lohezic-Le Devehat et al.,[82] the methanolic extracts of Elytranthe tubaeflora and Melastoma malabathricum showed moderate anti-HSV-1 activity, defined by the authors as having SI values >4. On the other hand, the ethanolic and ethyl acetate extracts of Garcinia griffithii and the methanolic extracts of Elytranthe globosa, Elytranthe maingayi, and Piper aduncum showed modest anti-HSV-1 activity, having SI < 4. Neither methanolic extract of Vitex pubescens nor Scurrula ferruginea was active against HSV-1.

Chiang and colleagues investigated the antiviral activities of various Asian plants against HSV-1 (strain KOS) and/or HSV-2 (strain 196) in human skin basal cell carcinoma (BCC-1/KMC) cells in several studies. [40,43,57,54,131,189] The authors used hot water and/or ethanolic extracts and seemed to deem extracts with determined EC_{50} or IC_{50} values greater than about 200 μg/ml as having little to mild antiherpetic activity. Extracts that showed potent anti-HSV activity were Boussingaultia gracilis ($EC_{50} = 80.7$ μg/ml and SI = 37.6 for HSV-1),[43] Serissa japonica ($EC_{50} = 67.5$ μg/ml and SI = 23.3 for HSV-1; $EC_{50} = 92.1$ μg/ml and SI = 17.1 for HSV-2),[43] Blumea lacera ($IC_{50} = 83.2$ μg/ml and SI >12.0 for HSV-1; $IC_{50} = 43.3$ μg/ml and SI >23.1 for HSV-2),[54] Tithonia diversifolia ($IC_{50} = 94.4$ μg/ml and SI = 9.9 for HSV-1; $IC_{50} = 34.8$ μg/ml and SI = 27.1 for HSV-2),[54] and Ocimum basilicum (water extract: $EC_{50} = 90.9$ μg/ml and SI = 16.2 for HSV-1, $EC_{50} = 51.4$ μg/ml and SI = 28.6 for HSV-2; ethanolic extract: $EC_{50} = 108.3$ μg/ml and SI = 6.3 for HSV-1).[131] Extracts that exhibited moderate antiviral activity were Bauhinia variegata ($EC_{50} = 182.7$ μg/ml and SI = 7.4 for HSV-1; $EC_{50} = 117.1$ μg/ml and SI = 11.6 for HSV-2),[40] Arachis

hypogaea (EC_{50} = 191.1 μg/ml and SI = 18.3 for HSV-2),[40] Boussingaultia gracilis (EC_{50} = 194.7 μg/ml and SI = 15.6 for HSV-2),[43] Ardisia squamulosa (EC_{50} = 168.5 μg/ml and SI = 10.1 for HSV-1),[43] Crossostephium chinense (EC_{50} = 179.2 μg/ml and SI = 4.0 for HSV-2),[43] Caesalpinia pulcherrima (EC_{50} = 166.8 μg/ml and SI = 16.5 for HSV-1; EC_{50} = 193.1 μg/ml and SI = 14.2 for HSV-2),[57] Ixeris chinensis (IC_{50} = 154.6 μg/ml and SI >6.5 for HSV-1; IC_{50} = 120.7 μg/ml and SI >8.3 for HSV-2),[54] and Senecio scandens (IC_{50} = 197.6 μg/ml and SI >5.1 for HSV-2).[54] The EC_{50} and SI values of acyclovir, as comparison, ranged 0.61-7.6 μg/ml and 20.3-45.1 for HSV-1 and 0.81-4.7 μg/ml and 32.8-58.9 for HSV-2, respectively.[40,43,57,131,189] Herbs that had little to mild antiherpetic activity were Bidens pilosa,[43,54,189] Houttuynia cordata,[189] Adenanthera pavonia,[40] Bauhinia purpura,[40] Desmodium caudatum,[40] Desmodium triforum,[40] Glycine max,[40] Pisum sativum,[40] Artemisai princeps,[43] Cinnamomum camphora,[43] Jasminum sambac,[43] Basella rubra,[43] Drymaria cordata,[43] Portulaca grandiflora,[43] Rosa rugosa,[43] and Eclipta prostrata.[54]

Moreover, Lipipun et al.[28] explored the ability of 20 Thai medicinal plants to work as antivirals against 3 strains of HSV-1. Vero cells infected with wild-type HSV-1 (strain 7401 H) were treated with water, ethanolic, or chloroform plant extracts at a dose of 100 μg/ml. The extracts found to reduce plaque formation by at least 50%, therefore classified by the authors as having antiviral activity against HSV-1, were Aglaia odorata, Cerbera odollam, Harpullia arborea, Ventilago denticulata, Azadirachta indica, Protium serratum, Rinorea anguifera, Hura crepitans, Schima wallichi, and Moringa oleifera. The strongest antiviral effects were noted by the extracts of A. odorata, C. odollam, and V. denticulata that inhibited 100% of plaques at the 100 μg/ml dose. Furthermore, these 3 extracts were assessed for antiviral activity against thymidine kinase-deficient and phosphonoacetate-resistant HSV-1 strains and compared to the wild-type 7401 H strain. The use of acyclovir as a positive control showed that a higher dose of the drug was required to reduce plaque formation of the 2 resistant strains compared to wild-type HSV-1. It was observed that M. oleifera was most effective against the phosphonoacetate-resistant strain (EC_{50} = 43.5 μg/ml and SI = 20.1), and V. denticulata worked equally as well with all 3 strains (EC_{50} and SI ranged 42.0-52.0 μg/ml and 16.1-20.0, respectively). However, A. odorata was less effective with the thymidine kinase-deficient strain (EC_{50} = 24.5 μg/ml and SI = 12.7) than the wild-type (EC_{50} = 9.5 μg/ml and SI = 32.8) or phosphonoacetate-resistant (EC_{50} = 10.8 μg/ml and SI = 28.9) strains.

Tiwari et al.[49] also explored the anti-HSV-1 activity of Azardirachta indica, specifically focusing on the mechanism of action. Aqueous extracts of the plant's bark at concentrations ranging 50-100 μg/ml were observed to block entry of HSV-1 (strain KOS) into Chinese hamster ovary (CHO-K1), HeLa, Vero, and retinal pigment epithelial (RPE) cells. Experiments using different HSV-1 strains (F, G, MP, and 17) revealed A. incida was not strain-specific as its inhibitory effects were similar toward each strain. The extract blocked the attachment of HSV-1 virions to cells, and when cells were pretreated with the extract, viral glycoprotein mediated cell-cell fusion was inhibited. To note, A. incida was only shown to inhibit viral entry when HSV-1 was pretreated with the extract and not when cells were pretreated, suggesting activity is to due effects on viral particles.

Of the 21 Chinese medicinal herbs tested by Li et al.,[29] aqueous extracts of Agrimonia pilosa, Pithecellobium clypearia, and Punica granatum showed antiviral activity against different strains of HSV-1 (strain 15577). These 3 extracts showed IC_{50} values ranging 62.5-125 μg/ml and SI values ranging 4-12 against the standard strain. Additionally, the extracts' IC_{50} values ranged 62.5-125 μg/ml and 50-125 μg/ml against the acyclovir-resistant and clinical strain, respectively. While each plant extract was effective against all HSV-1 strains, A. pilosa was most effective against the acyclovir-resistant strain (IC_{50} = 100 μg/ml and SI = 5), P. clypearia against the standard strain (IC_{50} = 62.5 μg/ml and SI = 4), and P. granatum against the clinical strain (IC_{50} = 50 μg/ml and SI = 20).

Water and ethanolic extracts of Youngia japonica showed no activity against HSV-1 (strain 15577) in a study conducted by Ooi et al.[190] Conversely, Kuo et al.[130] found an ethanolic extract of Nelumbo nucifera at a dose of 100 μg/ml inhibited 100% HSV-1 plaque formation in HeLa cells. The extract's IC_{50} value was determined to be 50.0 μg/ml.

Vijayan et al.[76] found potent antiviral activity against HSV-1 from a methanolic extract of Hypericum mysorense (IC_{50} = 100 μg/ml and SI = 1.2), a methanolic extract of Hypericum hookerianum (IC_{50} = 50 μg/ml and SI = 2.4), and an acetone and chloroform extract of Usnea complanta (IC_{50} = 100 μg/ml and SI = 1.2). Virus yield reduction assays revealed H. mysorense and H. hookerianum as the only plant extracts to offer 100% protection from viral particles. Partial anti-HSV activity was noted from an alcoholic and ethyl acetate extract of Melia dubia, a methanolic extract of Cryptostegia grandiflora, and the essential oil of Rosmarinus officinalis. The authors tested a total of 18 plants from Nilgiris, but besides those mentioned, no others exhibited antiherpetic activity.

Moreover, an ethyl acetate extract of Euphorbia thymifolia was assessed for inhibitory effects on HSV-2 multiplication by Yang et al.[91] E. thymifolia is a widespread herb in Taiwan that is used traditionally for many functions including diuretic, detoxifying, antimalarial, and antidysentery. A negative correlation was observed between the concentration of the extract and the level of HSV-2 multiplication. The ethyl acetate extract was able to substantially decrease HSV-2 infectivity when administered at high concentrations including 2.0, 4.0, and 8.0 μg/ml. Increasing the temperature at which the extract was incubated with the infected cells was not observed to alter inhibitory activity; however, the longer the extract was incubated with the infected cells the more viral inhibition occurred. It was concluded that by inhibiting HSV-2 infectivity, E. thymifolia was able to successfully reduce viral multiplication.

In the same year, Yang et al. studied extracts of Phyllanthus urinaria for antiviral effects against HSV-1 (strain KOS) and HSV-2 (strain 196).[141] Extracts were made from whole plant

parts and various solvents including acetone, benzene, chloroform, ethanol, ethyl acetate, n-hexane, and methanol. At a dose of 10 μg/ml, moderate HSV-1 plaque inhibition was observed from the acetone (31.4%), ethanolic (40.4%), and methanolic (41.3%) extracts. However, these 3 extracts, at the same dose, inhibited greater than 90% of HSV-2 plaques. The IC_{50} and SI values, respectively, against HSV-2 were determined to be 4.3 μg/ml and 3.5 for the acetone extract, 5.0 μg/ml and 4.0 for the ethanolic extract, and 4.0 μg/ml and 4.1 for the methanolic extract. For comparison, acyclovir at a dose of 0.05 μg/ml inhibited close to 90% of HSV-1 and HSV-2 plaques. Time-of-addition experiments showed that HSV-2 was suppressed the most when extracts were added to cells just after viral infection and effects were greatly reduced if added pre- or post-viral infection. The authors also tested whether lowering the incubation time or temperature affected the HSV-2 virucidal activity of the 3 extracts and found that it did not affect it significantly.

Tan et al.[138] tested other plants from the genus Phyllanthus, including Phyllanthus urinaria, against HSV-1 and HSV-2. Whole plant aqueous extracts of P. amarus, P. niruri, P. urinaria, and P. watsonii were tested. All extracts inhibited viral replication of both HSV-1 and HSV-2 with IC_{50} and SI values ranging 11.9-39.5 μg/ml and 12.7 to >33.6, respectively. Of the 4 extracts, P. urinaria demonstrated the highest SI against both viruses (>33.6 for both). It was also found that the extracts exhibited more potent antiviral effects on HSV-1 than HSV-2. Moreover, time-of-addition experiments found that all 4 extracts inhibited viral replication most effectively when introduced to cells at inoculation or post-infection, but not when introduced pre-infection.

Moderate anti-HSV-1 and anti-HSV-2 activity of a methanolic extract of Ophirrhiza nicobarica was observed by Chattopadhyay et al.[132] At a concentration of 300 μg/ml, the maximum nontoxic concentration, the extract completely inhibited plaque formation of both viruses. Pretreatment of the cells with the extract prior to viral infection did not decrease viral penetration or adsorption, nor did pretreatment of the virus reduce infectivity.

Mothana et al.[56] tested hot aqueous and methanolic extracts of 25 plant species gathered from the island Soqotra in Yemen against HSV-1 (strain KOS). The strongest antiviral effects were noted by the methanolic extracts of Boswellia elongata (SI not reported), Buxus hildebrandtii (SI = 71.4), and Euryops arabicus (SI not reported), each demonstrating an IC_{50} value of 0.35 μg/ml. The methanolic extract of Cissus subaphylla also showed promising anti-HSV-1 activity with an IC_{50} of 0.7 μg/ml (SI not reported). For comparison, the IC_{50} value of acyclovir was calculated as 0.7 μg/ml. Experiments were recreated with tenfold higher viral counts, and the extracts of B. elongata and B. hildebrandtii maintained their strong antiviral effects. Other methanolic extracts that showed inhibition of HSV-1 were Boswellia ameero, Cassia socotrana, Cissus hamaderohensis, Commiphora parvifolia, Dracaena cinnabari, Exacum affine, Fagonia luntii. Jatropha unicostate, Kalanchoe farinacea, Pulicaria stephanocarpa, Trichocalyx obovatus, Withania adunensis, and Zygophyllum quatarense with IC_{50} values ranging 1.5-25 μg/ml. Additionally, the hot aqueous extracts of Dorstenia socotrana, P. stephanocarpa, and Punica protopunica were active against HSV-1, but were less potent with IC_{50} values of 32.1 μg/ml, 50 μg/ml, and 5.8 μg/ml, respectively.

Furthermore, Aloe vera was studied by Zandi et al.[30] for its effect against HSV-2 infection by administering a crude hot glycerine extract to infected Vero cells at different times during infection. The extract was found to elicit complete cytopathic effects on HSV-2 at a concentration of 700 μg/ml when added at viral inoculation, and the IC_{50} and SI values were determined to be 428 μg/ml and 7.56, respectively. When the extract was added after the viral attachment stage, a dose of 850 μg/ml entirely prevented the cytopathic effect of HSV-2. The IC_{50} and SI values were determined to be 536 μg/ml and 6.04, respectively.

The anti-HSV-1 activities of the Indian medicinal plant Swertia chirata were examined by Verma et al.[161] Water extracts using dried powder of the leaves and stems of the plant were prepared to a total concentration of 1 g/ml. Subsequent dilutions and treatment to cells showed that the extract inhibited plaque formation by more than 70% at a dilution of 1:64. Adding the extract at 4, 8, and 24 hours after infection showed the greatest reduction in infected cells at 4 hours. Additionally, no genetic material amplification was found at 12, 24, 48, or 72 hours after simultaneous HSV-1 infection and S. chirata treatment.

Kuo et al.[116] investigated the antiviral activity of a methanolic extract of Lobelia chinensis against HSV-1 (strain KOS) in HeLa cells. The extract was found to inhibit plaque formation, demonstrating IC_{50} and SI values of 139.2 μg/ml and approximately 22.5, respectively. Time-of-addition experiments revealed the extract is effective if added in the window of 0-8 hours post-infection. Additionally, experiments revealed that L. chinensis is able to block HSV-1 replication, likely by impairing DNA synthesis.

Three different extracts of Cedrus libani, commonly known as Cedar of Lebanon, were observed to have antiviral activity against HSV-1 (strain F) by Loizzo et al.[65] The extracts tested were as follows: ethanolic extract of the plant's leaves, ethanolic extract of the plant's cones, and essential oil from the plant's bark. The 3 extracts demonstrated similar antiviral effects with IC_{50} and SI values ranging 0.44-0.66 mg/ml and 1.74-2.91, respectively. For comparison, the IC_{50} value and therapeutic index of acyclovir was found to be 3.77 μM and >27, respectively.

Wang et al.[137] investigated the antiviral effect of an ethanolic extract of the bark of Phellodendron amurense, a herb that is considered as one of the 50 fundamental herbs in China. The extract's maximum non-cytotoxic dose was determined as 44.12 μg/ml and was tested at different stages during HSV-1 infection. Pretreatment of cells with the extract only inhibited about 10% of HSV-1 plaques, but pretreatment of HSV-1 resulted in 74% inhibition of plaque formation. Addition of the extract during the viral adsorption and replication inhibited plaques by 10-15%. Acyclovir was also tested and found to inhibit over 90% of plaques only when added during viral

replication. These results suggest that P. amurense elicits effects prior to viral infection and acyclovir elicits effects after infection.

Two other Chinese medicinal herbs, Radix isatidis and Viola yedoensis, were tested for antiviral activity against HSV-1 by Liao et al.[171] Experiments were conducted with infection of the KOS strain of HSV-1 into human neuroblastoma (SK-N-SH) cells and treatment with 600 μg/ml of aqueous extracts of the root of R. isatidis and the whole plant of V. yedoensis. Only V. yedoensis showed inhibition of viral replication. Antiviral effects were similar when the cells were pretreated with the extract 6 hours before infection and treatment to cells 4 hours post-infection. The authors suggested that the mechanism of action is likely not one of direct inactivation of HSV-1.

Aqueous and ethanolic extracts of Cajanus cajan, commonly known as pigeon pea, exhibited antiviral effects against both HSV-1 (strain KOS) and HSV-2 (strain HG52).[58] Zu et al.[58] found both viruses to be more susceptible to the ethanolic extract (IC_{50} = 0.022 μg/ml and SI = 618.2 for HSV-1; IC_{50} = 0.10 μg/ml and SI = 136.0 for HSV-2) compared to the aqueous extract (IC_{50} = 14.93 μg/ml and SI >15 for HSV-1; IC_{50} = 2.33 μg/ml and SI >100 for HSV-2). The ethanolic extract showed greater antiviral activity than acyclovir (IC_{50} = 0.59 μg/ml and SI >55.9 for HSV-1; IC_{50} = 0.62 μg/ml and SI >53.2 for HSV-2). Time-response assays showed 90% plaque inhibition after a treatment duration of 10 minutes with the ethanolic extract and 60 minutes with the aqueous extract. Additionally, the extracts were added at different times during viral infection. Both extracts significantly reduced plaque formation by 95-99% only when either HSV-1 or HSV-2 was pretreated with the extract. When the extracts were added during HSV-2 adsorption, plaque formation was inhibited by about 45-60%. Acyclovir was antiviral when added post-infection, during viral intracellular replication. These results suggest that C. cajan elicits its antiviral effects directly on HSV virions.

Arabzadeh et al.[173] observed a methanolic extract of Zataria multiflora to significantly inhibit HSV-1 (strain KOS) plaque formation at doses below its maximum non-toxic concentration (1000 μg/ml). When the extract was added to cells during viral adsorption at doses of 800 μg/ml, 500 μg/ml, and 250 μg/ml, inhibition of 100%, 93.2%, and 86.2%, respectively, of HSV-1 plaques was observed. Additionally, the extract was added to cells at 1, 2, and 3 hours after viral infection, and 100% plaque inhibition was observed with all doses, which ranged 250-1000 μg/ml.

Moreover, a methanolic extract of Achyranthes aspera was investigated for antiviral effects against HSV-1 (strain F) and HSV-2 (strain G) by Mukherjee et al.[24] The extract inhibited HSV plaque formation in a dose-dependent manner with 100% inhibition of HSV-1 and HSV-2 noted at 112.5 μg/ml and 120 μg/ml, respectively. The EC_{50} and SI values, respectively, of the extract were determined to be 64.4 μg/ml and 10.2 for HSV-1 and 72.8 μg/ml and 9.0 for HSV-2. For comparison, acyclovir was found to have EC_{50} and SI values, respectively, of 2.1 μg/ml and 61.9 for HSV-1 and 2.9 μg/ml and 44.8 for HSV-2. Time-of-addition experiments revealed that A. aspera elicits its antiviral effects post-infection for both viruses with little inhibition noted before or at the time of infection.

The ability of Camellia sinensis, Nerium oleander, and Echium amoenum to prevent HSV-1 (strain KOS) multiplication was explored by Farahani et al.[59] The plants were individually extracted using a decoction method to yield aqueous extracts, and Hep-2 cells were used to test for cytotoxicity. It was observed that N. oleander was toxic to cells at all concentrations and therefore was not used in the antiviral assays. Antiviral activity of the other 2 extracts were measured at 1, 2, and 3 hours post-treatment. Significant antiviral effects of C. sinensis were observed at one (IC_{50} = 20 μg/ml and SI = 50) and 2 (IC_{50} = 60 μg/ml and SI = 16.7) hours post-treatment, but activity was decreased by the third hour (IC_{50} = 480 μg/ml and SI = 2.1). E. amoenum was found to be antiviral during the first hour (IC_{50} = 350 μg/ml and SI = 2.9), but less so than C. sinensis. It was concluded that C. sinensis is an effective treatment to inhibit HSV-1 multiplication within 1 hour.

Cho et al.[83] found an aqueous extract of Epimedium koreanum to inhibit HSV multiplication in both mouse macrophages (RAW264.7) and human embryonic kidney (HEK293 T) cells. The type of HSV virus used in the experiments was not specified. The virus was more susceptible to the extract in mouse macrophages (EC_{50} = 0.62 μg/ml and SI = 23.5) than in human embryonic kidney cells (EC_{50} = 1.41 μg/ml and SI = 5.9). At an extract dose of 1 μg/ml, E. koreanum was able to reduce viral titers 2-fold in both RAW264.7 and HEK293 T cells when compared to control.

Pedilanthus tithymaloides demonstrated strong antiviral activity against HSV-2 (strain G), 2 HSV-2 clinical isolates, and a thymidine kinase-deficient strain of HSV-2.[134] Ojha et al.[134] found that EC_{50} values for a methanolic extract of the plant ranged 48.5-52.6 μg/ml for the 4 viral strains with SI values of 8.29-9.00. The extract inhibited 99% of HSV-2 multiplication at a dose of 86.5 μg/ml by 2-4 hours post-infection. Acyclovir was tested as a control and shown to have EC_{50} values of 2.6-2.8 μg/ml and SI values of 46.00-49.53 for strain G and one of the clinical isolates. Further testing revealed the extract was able to inhibit NF-êB, which is activated during HSV-2 infection and required for viral replication.

Indigofera heterantha, a common plant in the western Himalayan region, was tested for antiviral activity against HSV-2 (strain G) by Kaushik et al.[110] Hydromethanolic extracts of the root, twig, and stem of the plant were separately prepared. The root extract exhibited the strongest antiviral activity of the 3 extracts with IC_{50} and SI values of 284.2 μg/ml and 13.3, respectively. A subsequent study by the authors showed the extract elicits its effect early in the viral replication cycle by blocking HSV-2 attachment, adsorption, and entry into host cells.[191]

Furthermore, He et al.[39] observed an ethanolic extract of the fungus Antrodia camphorata to have antiviral activity against HSV-1 (strain F) and HSV-2 (strain G). Although not nearly as potent as acyclovir, A. camphorata was found to inhibit viral plaque formation with IC_{50} values of 61.2 μg/ml and

57.5 μg/ml for HSV-1 and HSV-2, respectively. In addition, the SI values for the extract were determined as 7.92 for HSV-1 and 8.43 for HSV-2. For comparison, the IC_{50} and SI values, respectively, for acyclovir were determined as 2.1 μg/ml and 61.9 for HSV-1 and 2.9 μg/ml and 44.8 for HSV-2.

A methanolic extract of Euphorbia spinidens was tested for its ability to act as an antiviral against HSV-1 (strain KOS) by Karimi et al.[90] It was observed that the extract was able to inhibit HSV-1 in a dose-dependent manner, but was not as effective as treatment with acyclovir. The EC_{50} and SI values, respectively, were determined to be 0.34 μg/ml and 14.9 for E. spinidens and 0.028 μg/ml and >178.6 for acyclovir. Time-of-addition experiments revealed that application of the extract at a concentration of 5 mg/ml was most effective at inhibiting the virus within the first 2 hours of its life cycle, demonstrating a total of 70% inhibition. The authors conclude that the extract of E. spinidens may inhibit HSV-1 adsorption and early stages of viral replication.

Karimi et al.[148] also tested anti-HSV-1 activity of Quercus brantii. A crude extract of the plant's acorns was prepared using ethyl alcohol, and effects against HSV-1 (strain KOS) were examined in baby hamster kidney (BHK) cells. The extract exhibited antiviral activity against HSV-1 (IC_{50} = 4.3 μg/ml and SI = 48.4), but was not more potent than acyclovir (IC_{50} = 1.3 μg/ml and SI = 136.5). Additional experiments found that the greatest viral inhibition occurred when the extract was present both during and after adsorption.

Various extracts of Ficus religiosa, commonly known as sacred fig or bodhi tree, showed antiviral activity against HSV-2 (strain MS) and an acyclovir-resistant HSV-2 strain.[95] Ghosh et al.[95] prepared several extracts using either the leaves or bark of the plant with water, methanol, ethyl acetate, or chloroform as solvents. Extracts from the bark showed more potent antiviral activity against the regular strain compared to leaf extracts. Most notable were the water (EC_{50} = 9.76 μg/ml and SI = 156.8) and chloroform (EC_{50} = 6.75 μg/ml and SI = 119.9) bark extracts. These extracts were not as strong as acyclovir, which showed an EC_{50} value of 0.64 μg/ml and a SI of >468. Against the acyclovir-resistant strain, the water bark extract showed the most potent antiviral activity (EC_{50} = 6.28 μg/ml and SI = 243.6). These values suggest that the water bark extract elicited more potent antiviral effects against acyclovir-resistant HSV-2 compared to a wild-type HSV-2. Further testing revealed inhibition of HSV-2 by the water bark extract occurred by inactivating virions prior to infection while the chloroform bark extract elicited its effect by inhibiting viral attachment and/or entry into cells.

Sakagami et al.[155] investigated the antiviral activity of an alkaline water extract of Sasa senanensis leaves against HSV-1 (strain F). They observed the extract to have anti-HSV activity with an SI of 6-7. The extract was also tested in combination with acyclovir, which showed a synergistic effect.

Very potent anti-HSV-2 activity was observed by a 50% ethanolic extract of the fruits of Terminalia chebula by Kesharwani et al.[165] The extract demonstrated an IC_{50} of 0.01 μg/ml and a SI of over 40,000 against HSV-2 (strain G ATCC-VR-734), which made it significantly more potent than acyclovir (IC_{50} = 29.04 μg/ml and SI = 12.1). Pretreatment of the virus with the extract showed significant viral inhibition. This effect was attributed to the extract's ability to inhibit viral attachment and penetration into host cells. Conversely, the extract was less effective when added to cells post-infection.

A hydromethanolic extract of Hemidesmus indicus root was observed to inhibit both HSV-1 and HSV-2 replication to a similar degree.[104] Bonvicini et al.[104] tested antiviral activity when cells were pretreated with the extract, when the extract was added to cells at and post-infection, and when virions were pretreated with the extract. When the extract was added to cells at the time of infection, the EC_{50} values of the extract were determined as 66.8 μg/ml and 70.6 μg/ml for HSV-1 and HSV-2, respectively. With treatment post-infection, the extract's EC_{50} values were determined as 91.3 μg/ml and 86.1 μg/ml for HSV-1 and HSV-2, respectively. No effect on viral replication was observed when cells were pretreated with the extract. Inhibitory effects were markedly stronger when virions were pretreated with the extract. These results indicate that H. indicus is able to inhibit HSV throughout the infection cycle, but effects are more potent pre-infection. Further pre-infection testing revealed the extract specifically inhibits viral attachment. Viral entry is also inhibited by the extract, but only at higher concentrations. Interestingly, the extract's inhibitory effects were stronger in the second round of infection compared to the first.

Moreover, a chloroform fraction of an ethanolic extract of Arisaema tortuosum leaves demonstrated antiherpetic activity as investigated by Ritta et al.[44] Initially, cytotoxicity of A. tortuosum leaves and tubers were assessed using separate ethanolic extracts. The ethanolic extract of the leaves was found to be less toxic and was further fractionated with n-hexane, chloroform, ethyl acetate, and n-butanol. All fractions were found to be highly toxic except for the chloroform fraction, which was assessed for antiviral effects against HSV-1, HSV-2, and an acyclovir-resistant strain of HSV-2. HSV-2 (EC_{50} = 0.53 μg/ml and SI = 758) and acyclovir-resistant HSV-2 (EC_{50} = 0.86 μg/ml and SI = 467.4) were more susceptible to the chloroform extract compared to HSV-1 (EC_{50} = 2.64 μg/ml and SI = 12). The authors note that the chloroform extract was observed to act as a direct virucidal agent as well as inhibit viral attachment, adsorption, and replication.

Park et al.[81] investigated antiviral effects of methanolic extracts of 5 varieties of marine algae against wild-type (strain 7401 H), thymidine kinase-deficient (strain B2006), and acyclovir and phosphonoacetic acid-resistant HSV-1 strains. All extracts were tested at a dose of 100 μg/ml, and Sargassum ringgoldianum inhibited 100% plaque formation of all 3 HSV-1 strains, but exhibited strong cytotoxicity to Vero cells. Symphyocladia latiuscula demonstrated moderate cytotoxicity, inhibited 100% plaque formation against wild-type HSV-1, and 82.74% against acyclovir and phosphonoacetic acid-resistant HSV-1; however, thymidine kinase-deficient HSV-1 plaques were only inhibited by 38.1%. The IC_{50} value of S. latiuscula was determined as 56.7 μg/ml (HSV-1 strain not specified).

Moderate plaque inhibition was also noted against acyclovir and phosphonoacetic acid-resistant HSV-1 with the extracts of Sargassum thunbergii, Ecklonia stolonifera, and Ulva pertusa, demonstrating 55.99%, 47.79%, and 40.67% inhibition, respectively. S. thunbergii and U. pertusa showed no cytotoxicity, while E. stolonifera was mildly cytotoxic to Vero cells. The methanolic extract of S. latiuscula was successively fractionated into 5 fractions using the following order of solvents: hexane, dichloromethane, ethyl acetate, butanol, and water. The dichloromethanic fraction showed the strongest anti-HSV-1 activity with an IC_{50} value of 7.73 μg/ml (HSV-1 strain not specified).

Another marine algae, Cystoseira myrica, was studied by Zandi et al.[77] for antiviral activity against HSV-1 (strain KOS). A hot water extract of the whole plant was prepared and sterilized by 2 methods, filtration and autoclaving. When the extracts were added to cells at the same time of viral inoculation, the IC_{50} and SI values, respectively, were determined to be 99 μg/ml and 33.4 for the filtered extract and 125 μg/ml and 28.2 for the autoclaved extract. The extracts were less effective when added 2 hours post-inoculation, demonstrating IC_{50} and SI values, respectively, of 143 μg/ml and 23.1 for the filtered extract and 162 μg/ml and 21.7 for the autoclaved extract.

Lastly, Deethae et al.[158] created aqueous, ethanolic, and methanolic extracts from the freshwater green algae Spirogyra and investigated antiviral activity against HSV-1 (strain F) and HSV-2 (strain G). Firstly, effects were measured when extracts were added to cells before, during, and after viral attachment. All 3 extracts exhibited their strongest antiviral effects when added to cells during attachment, with HSV-1 being more susceptible to the ethanolic extract (IC_{50} = 164.20 μg/ml and SI = 2.17) and HSV-2 to the methanolic extract (IC_{50} = 75.03 μg/ml and SI = 3.34). Moreover, both HSV-1 and HSV-2 virions, when treated with extracts prior to infection, were most strongly inhibited by the methanolic extract. In terms of effects on viral replication, the extracts were able to inhibit HSV yields by 30 hours post-infection. The methanolic extract exhibited the greatest inhibitory effects on HSV-1, and the aqueous extract exhibited the greatest inhibitory effects on HSV-2. When comparing all viral stages tested, the most potent anti-HSV activity was observed during viral attachment.

Central America/Caribbean

Del Barrio and Parra[139] assessed the antiviral activity of an aqueous extract of the leaves and stems of Phyllanthus orbicularis, a plant native to Cuba, against HSV-2 in human foreskin fibroblast cells. The extract demonstrated EC_{50} and SI values of 25.7 μg/ml and 26.03, respectively. Direct treatment of HSV-2 virions resulted in a 2 log10 reduction in viral titers with treatment of 5-25 μg/ml of P. orbicularis extract and a 2.75 log10 reduction with 50-75 μg/ml of the extract. The authors suggest that P. orbicularis may elicit its antiherpetic effects by inhibiting virions, either directly or by blocking their entry into host cells.

Subsequently, Fernandez Romero et al.[140] made the stems and leaves of P. orbicularis into 5 successive extract fractions using the following order of solvents: diethyl ether, chloroform, butanol, 50% ethanol, and an acetic acid/water combination. The butanolic and acetic acid fractions demonstrated significant virucidal activity against acyclovir-sensitive HSV-1 and acyclovir-resistant HSV-1, each in human foreskin fibroblasts and Vero cells. When added to cells at the time of viral infection, the butanolic extract demonstrated EC_{50} and SI values, respectively, of 30.4-31.3 μg/ml and 21.6-22.8 against acyclovir-sensitive HSV-1 and 32.8-42.5 μg/ml and 15.5-21.8 against acyclovir-resistant HSV-1. The acetic acid extract was not as potent, demonstrating EC_{50} and SI values, respectively, of 32.5-35.9 μg/ml and 10.3-11.6 against acyclovir-sensitive HSV-1 and 29.4-30.7 μg/ml and 11.3-13.5 against acyclovir-resistant HSV-1. Additionally, extracts were added to virions prior to infection, which showed greater antiviral effects. The acetic acid extract elicited more potent effects against both acyclovir-sensitive HSV-1 (EC_{50} = 0.47-0.53 μg/ml and SI = 705-785) and acyclovir-resistant HSV-1 (EC_{50} = 0.40-0.68 μg/ml and SI = 491-1040) compared to the butanolic extract (EC_{50} = 0.74-1.93 μg/ml and SI = 371-895 for acyclovir-sensitive HSV-1; EC_{50} = 1.15-1.51 μg/ml and SI = 474-572 for acyclovir-resistant HSV-1). The authors conclude that the butanolic and acetic acid extracts of P. orbicularis may reduce viral adsorption, attachment, or penetration into host cells. They also conclude that the SI values of these 2 extracts were 10-20 times higher than that of the aqueous extract of P. orbicularis used in the study by del Barrio and Parra.[139]

Europe

Much of the research on European Lamiaceae family herbs is focused on Melissa officinalis. Dimitrova et al.[120] explored prophylactic and therapeutic effects of 4 extracts of M. officinalis on HSV-1 (strain DA) using the solvents 50% ethyl alcohol, 50% ethanol, ethyl acetate, and water. When incubated with HSV-1 virions, complete viral inactivation was noted by 3 hours with the water extract and by 12 hours with the non-aqueous extracts. Furthermore, the non-aqueous extracts were added to rabbit kidney (RK) cells pre- and post-infection, but all 3 extracts failed to inhibit viral reproduction.

Additionally, Schnitzler et al.[122] investigated the antiviral effects of M. officinalis essential oil on HSV-1 (strain KOS) and HSV-2 (strain HG). The essential oil was diluted in up to 1% ethanol. Plaque reduction assays revealed that at a concentration of 0.002% oil, there was a 98.8% reduction of HSV-1 and a 97.2% reduction of HSV-2 titres. At higher doses, the viral infectivity was almost completely absent. The IC_{50} and SI values, respectively, were calculated to be 0.0004% and 7.5 for HSV-1 and 0.00008% and 37.5 for HSV-2. When HSV-1 and HSV-2 were pretreated with M. officinalis oil at its maximum non-cytotoxic concentration (0.002%), viral infectivity was significantly reduced. However, when the treatment was applied to the viruses during viral adsorption, a moderate reduction in plaque formation of 64.8% and 39.9% for

HSV-1 and HSV-2, respectively, was seen. Plaque formation was not affected when RC-37 cells were treated with the essential oil prior to or during infection. The essential oil is highly lipophilic, which the authors proposed as a mechanism by which the active constituents in the oil can be used as a direct antiviral for topical use in humans.

Mazzanti et al.[123] found that a hydroethanolic extract of M. officinalis elicited significant antiviral effects on HSV-2 after viral penetration. The extract was first tested for cytotoxicity and showed no impairment to cells up to a concentration of 1 mg/ml. When Vero cells were treated with the extract at a dose of 0.5 mg/ml post-infection, the cytopathic effect was reduced by 60%, which was the maximum effect observed. However, incubation of the extract with HSV-2 virions did not reduce viral penetration. The authors suggest that M. officinalis does not bind to HSV-2 to prevent entry into host cells, but elicits its effects after penetration.

Research on the antiviral effects of M. officinalis continued to be explored by Astani et al.[124] by investigating an aqueous extract of M. officinalis for antiviral activity against HSV-1 (strain KOS). Pretreatment of virions with the extract demonstrated an IC_{50} and SI of 0.4 μg/ml and 875, respectively, and >99% of viral inactivation was seen at a concentration of 15 μg/ml. Furthermore, the extract inhibited viral attachment to RC-37 cells by 98% at 7.5 μg/ml, a concentration 20 times lower than its maximum non-cytotoxic concentration (150 μg/ml). The authors conclude that since M. officinalis demonstrated both viral inactivation and inhibition of viral attachment, the plant is a good candidate for use as a prophylactic for HSV infections.

Nolkemper et al.[121] examined the antiviral effects of aqueous extracts from different species in the Lamiaceae plant family, including extracts from M. officinalis, Mentha piperita, Prunella vulgaris, Rosmarinus officinalis, Salvia officinalis, and Thymus vulgaris. All extracts showed inhibitory effects when virions were treated with the extracts pre-infection, but effects were more potent against HSV-1 (strain KOS) compared to HSV-2 (strain HG). From strongest to weakest antiherpetic activity, the extracts were M. piperita (IC_{50} = 0.041 μg/ml and SI = 2610 for HSV-1; IC_{50} = 0.227 μg/ml and SI = 471 for HSV-2), M. officinalis (IC_{50} = 0.025 μg/ml and SI = 2200 for HSV-1; IC_{50} = 0.027 μg/ml and SI = 2037 for HSV-2), T. vulgaris (IC_{50} = 0.065 μg/ml and SI = 954 for HSV-1; IC_{50} = 0.077 μg/ml and SI = 805 for HSV-2), P. vulgaris (IC_{50} = 0.229 μg/ml and SI = 546 for HSV-1; IC_{50} = 2.114 μg/ml and SI = 59 for HSV-2), S. officinalis (IC_{50} = 0.777 μg/ml and SI = 113 for HSV-1; IC_{50} = 1.359 μg/ml and SI = 65 for HSV-2), and R. officinalis (IC_{50} = 0.646 μg/ml and SI = 98 for HSV-1; IC_{50} = 1.055 μg/ml and SI = 60 for HSV-2). Time-of-addition experiments revealed all extracts elicited their strongest antiviral effects when virions were pretreated, and none of the extracts demonstrated an ability to inhibit viral replication if treated post-infection. After treatment of an acyclovir-resistant strain of HSV-1 with maximum non-cytotoxic concentrations of each extract, it was observed that M. piperita and S. officinalis were able to decrease viral infectivity by 85% and 97%, respectively. The authors proposed that aqueous extracts of various species in the Lamiaceae family are able to inhibit HSV adsorption, including strains known to be resistant to pharmaceutical antiviral treatment. As such, these plants may be beneficial as a topical therapeutic treatment to prevent recurrent HSV infections.

Moreover, Schnitzler et al.[153] found aqueous extracts and multiple ethanolic extracts (20%, 40%, 60%, and 80%) of Salvia officinalis to be antiviral against HSV-1 (strain KOS) and HSV-2 (strain HG). Extracts were made from S. officinalis specimens from 2 geographic locations: the authors' garden and the Swabian Mountains. When RC-37 cells were pretreated with the extracts, the greatest HSV-2 plaque reduction was seen with the 20% ethanolic extracts of S. officinalis specimens from the garden (94%) and Swabian Mountains (99%). Effects on HSV-1 were significantly weaker. When virions were pretreated with an extract, viral plaques were reduced by 90% and 99% for HSV-1 and HSV-2, respectively, regardless of the location of origin. Each garden extract as well as the aqueous and 40% ethanolic mountain extracts demonstrated stronger antiviral activity against HSV-2 (IC_{50} = 0.02-3.20 μg/ml and SI = 197-18,345) compared to HSV-1 (IC_{50} = 0.03-11.18 μg/ml and SI = 56-5463). Conversely, the 20%, 60%, and 80% ethanolic mountain extracts had greater effects on HSV-1 (IC_{50} = 0.12-0.48 μg/ml and SI = 1135-3755) compared to HSV-2 (IC_{50} = 0.25-0.64 μg/ml and SI = 865-1802).The authors conclude that the ethanolic extracts were more antiviral than the aqueous extracts, and those made of S. officinalis from the garden had a greater antiviral effect. Therefore, the collection location may play a part in the ability of S. officinalis to act as an antiherpetic treatment.

Subsequently, Reichling et al.[126] prepared ethanolic extracts of 4 common medicinal plants from the Lamiaceae family and investigated their antiviral activities against HSV-1. The plants tested were Prunella vulgaris, Mentha piperita, Rosmarinus officinalis, and Thymus vulgaris. Two extracts of each plant were prepared using 20% ethanol and 80% ethanol as solvents and tested against acyclovir-sensitive HSV-1 (strain KOS) and acyclovir-resistant HSV-1 (strains Angelotti and 1246/99). A series of dilutions of all extracts were done and tested for viral infectivity. All dilution extracts were effective, even low concentrations of 0.01% almost completely reduced viral infectivity. M. piperita extracts were the most effective against wild-type HSV-1, demonstrating IC_{50} and SI values, respectively, of 0.06 μg/ml and 7040 for the 20% ethanolic extract and 0.05 μg/ml and 5632 for the 80% ethanolic extract. The other extracts demonstrated IC_{50} values ranging 0.08-0.82 μg/ml and SI values ranging 90-4530. Moreover, when the extracts were tested against acyclovir-resistant HSV-1, all 80% ethanolic extracts demonstrated complete plaque reduction of both strains. Time-of-addition experiments revealed when host cells were pretreated with the extracts, the 80% ethanolic extracts of P. vulgaris and M. piperita were the only extracts that significantly reduced viral infectivity. When the virus was pretreated, the 20% ethanolic extract of M. piperita and 80% ethanolic extracts of P. vulgaris, M. piperita, and T. vulgaris were

effective at entirely reducing viral infectivity. The other extracts were effective at reducing plaques by more than 75%. When the extracts were added during viral adsorption, the 80% ethanolic extracts of P. vulgaris and M. piperita fully suppressed viral infectivity while all other extracts, except the 80% ethanolic extract of R. officinalis, reduced plaque formation by more than 50%. The authors conclude that the 80% ethanolic extracts of M. piperita and P. vulgaris show a dual antiherpetic mechanism of action, and hence are promising candidates for treatment of HSV infections.

Another study tested the antiviral activity of M. piperita essential oil against HSV-1 (strain KOS) and HSV-2 (strain HG52).[127] Schuhmacher et al.[127] found the essential oil, diluted in ethanol, was able to reduce HSV-1 plaque formation by 82% and HSV-2 plaque formation by 92% when virions were pretreated with 0.01% of the oil for 1 hour. The IC_{50} values for M. piperita against HSV-1 and HSV-2 were calculated as 0.002% and 0.0008%, respectively. When HSV-1 virions were incubated with the essential oil for 3 hours, plaques were reduced by 99%. Time-of-addition experiments revealed the greatest antiviral effects with pretreatment of the viruses with the essential oil and little antiviral activity with pretreatment or post-treatment of host cells. Additionally, pretreatment with the oil, at a concentration of 0.01%, inhibited acyclovir-resistant HSV-1 by 99%. The authors suggest M. piperita elicits antiviral effects by blocking viral adsorption.

Lastly, Omidian et al.[125] investigated the antiviral effects of a hot water extract of M. piperita at different stages of HSV-1 replication. The extract partially prevented HSV-1 infection when host cells were pretreated (EC_{50} = 62.70 mg/ml and SI = 1.79) and partially inhibited HSV-1 adsorption (EC_{50} = 26.65 μg/ml). Addition of the extract after viral adsorption showed viral particles to be completely inactive within 2 hours, and HSV-1 yield was inhibited 30 hours post-infection.

Many other European plants that do not belong to the Lamiaceae family have been studied for their antiviral effects. Extracts of Geranium sanguineum were tested by Serkedjieva and Ivancheva[97] for their antiviral abilities against HSV-1 (strain KOS) and HSV-2 (strain G) in Vero and human embryonic skin-muscle (E6SM) cells. Five extracts were made with aerial root parts from the early plant and ethanol, methanol, or hydroethanol; overground parts and methanol; and aerial root parts from the late plant and methanol. The strongest antiviral effect was observed by the hydroethanolic extract (EC_{50} = 5.4 μg/ml and SI = 17.8) and the weakest by the methanolic overground extract (EC_{50} = 12.1 μg/ml and SI = 5.6). The hydroethanolic extract demonstrated a dose-dependent viral inhibition against HSV-1 and was further tested for virucidal action against HSV-2. HSV-2 showed to be more susceptible to the extract (SI = 27.7) compared to HSV-1. Also, time-of-addition experiments revealed that the hydroethanolic extract only elicits significant antiviral effects when added to cells post-infection, but not when added to cells pre-infection or during viral adsorption or penetration.

Subsequently, Serkedjieva[145] studied the red algae Polysiphonia denudata for its antiviral effect against 3 HSV-1 strains (KOS, McIntyre, and Kupka) and HSV-2 (strain GC25927). A water extract showed stronger antiherpetic effects against HSV-1 (EC_{50} = 0.18-0.42 μg/ml and SI = 24.8-47.7) compared to HSV-2 (EC_{50} = 1.2 μg/ml and SI = 8.7). The antiviral effect differed between the HSV strain and cell type used. For example, the lowest EC_{50} of 0.18 mg/ml (SI = 47.7) was observed in Vero cells with the Kupka strain of HSV-1, whereas the highest EC_{50} of 1.2 mg/ml (SI = 8.7) was observed in E6SM cells with the GC25927 strain of HSV-2. The antiviral effect was dose-dependent and at higher concentrations, specifically an MIC_{90} of 6.5 mg/ml, the water extract was able to act extracellularly and prevent viral adsorption. Time-of-addition experiments demonstrated that the extract had inhibitory effects when added at viral adsorption or post-infection.

Serkedjieva[67] assessed an additional red algae, Ceramium rubrum, for its antiviral effects against HSV-1 (strain Kupka) in Vero cells, and HSV-1 (strain KOS) and HSV-2 (strain GC25927) in E6SM cells. HSV-1 strain KOS was most susceptible to the C. rubrum water extract (EC_{50} = 0.5 mg/ml and SI = 10.8), showing dose-dependent direct virucidal activity. The extract was less potent against HSV-1 strain Kupka and HSV-2, demonstrating EC_{50} and SI values, respectively, of 1.1-1.2 mg/ml and 4.9-5.2.

Moreover, dry aqueous extracts of Rhus aromatica, made from the plant's roots and bark, were studied by Reichling et al.[150] for antiherpetic activity against HSV-1 (strain KOS) and HSV-2 (strain HG52). R. aromatica did not significantly decrease infection in cells exposed to virions prior to treatment with the plant extract, however, the extract was shown to significantly decrease plaque formation when incubated with virions pre-infection (IC_{50} = 0.0005% and SI = 5400 for HSV-1; IC_{50} = 0.0043% and SI = 628 for HSV-2). HSV-1 was more susceptible to the extract, and when virions were incubated with the extract at a non-cytotoxic dose of 0.0025% for 1 minute, HSV-1 plaques were reduced by 90%.

Lazreg Aref et al.[94] made 5 different extracts from the latex of Ficus carica and the solvents hexane, ethyl acetate, methanol, chloroform, and hexane-ethyl acetate. None of the extracts showed cytotoxic effects to Vero cells at concentrations up to 100 mg/ml, except 100 mg/ml of the chloroform extract. The hexane and hexane-ethyl acetate extracts showed greatest inhibition of HSV-1 by preventing viral penetration, adsorption, and intracellular replication at all concentrations tested. Specifically, the concentrations of these 2 extracts ranged from 78 μg/ml to 100 mg/ml.

Gescher et al.[149] observed an aqueous extract made from the aerial parts of Rhododendron ferrugineum to prevent HSV-1 (strain 17 syn^+) attachment and penetration into host cells. The extract completely interfered with viral attachment and penetration at concentrations greater than 1 μg/ml and 25 μg/ml, respectively. When virions were pretreated with the extract, antiviral effects corresponded to an IC_{50} of 7.4 μg/ml and SI of 63.9. The authors suggest that R. ferrugineum directly interacts with the viral envelope to prevent attachment and penetration into host cells.

Sarkar et al.[112] studied the mycelia of the mushroom Lentinus edodes for antiviral activity against HSV-1 (strain F). L. edodes was cultured, extracted, and filtered with the end product being named JLS-S001. This extract was observed to block the release of HSV-1 particles from cells (EC_{50} = 20 μg/ml, SI = 40). When cells were pretreated with the extract, viral adsorption was not observed to be prevented.

L. edodes, along with other mushrooms, were evaluated for antiherpetic activity by Santoyo et al.[55] Water and methanolic extracts were prepared of mushrooms Boletus edulis, L. edodes, and Pleurotus ostreatus. Water extracts exhibited greater virucidal activity than methanolic extracts, but overall effects were low. At a concentration of 3.75 mg/ml, HSV-1 (strain KOS) was inhibited by 50%, 25%, and 15% with the water extracts of L. edodes, B. edulis, and P. ostreatus, respectively, while all methanolic extracts showed 50% inhibition at a concentration of 18.75 mg/ml. Time-of-addition experiments showed that when cells were pretreated with the extracts, viral infection was inhibited by all 3 water extracts by approximately 60% and 90% at concentrations of 75 μg/ml and 100 μg/ml, respectively. The methanolic extracts at concentrations of 100 μg/ml inhibited viral infectivity by 40-50%. The water extracts were also more potent at blocking viral adsorption, demonstrating a 60% and 80% reduction in viral infectivity at concentrations of 50 μg/ml and 75 μg/ml, respectively. Lastly, viral replication was inhibited in a dose-dependent manner more strongly by the water extracts. The IC_{50} and SI values, respectively, for the water extracts were determined to be 27.04 μg/ml and 14.21 for L. edodes, 35.12 μg/ml and 13.96 for B. edulis, and 26.69 μg/ml and 15.15 for P. ostreatus. Although methanolic extracts were less effective at preventing infection of pretreated cells, preventing viral adsorption, and inhibiting viral replication, they were still more effective than control. In terms of mechanism of action. The authors speculate the mushroom extracts block viral attachment or adsorption at initial HSV-1 infection and further inhibit intracellular viral replication.

In another study by Santoyo et al.,[78] pressurized liquid extraction was utilized to create hexane, ethanol, and water extracts with the microalgae Haematococcus pluvialis and Dunaliella salina and evaluated for antiviral activity against HSV-1 (strain KOS). When H. pluvialis extracts were added to virally-infected cells, inhibition of intracellular replication was greatest with the ethanolic extract (IC_{50} = 99.59 μg/ml and SI = 7.39) compared to the hexane (IC_{50} = 189.58 μg/ml and SI = 3.57) and aqueous (IC_{50} = 133.98 μg/ml and SI = 12.01) extracts. D. salina extracts showed slightly weaker activity, with the aqueous extract (IC_{50} = 137.53 μg/ml and SI = 11.48) exhibiting stronger antiviral effects compared to the hexane (IC_{50} = 168.81 μg/ml and SI = 2.88) and ethanolic (IC_{50} = 152.73 μg/ml and SI = 4.07) extracts. Time-of-addition experiments revealed the extracts were more effective when cells were treated before infection compared to addition at the time of infection. The ethanolic extract of H. pluvialis was the most effective, showing an 85% reduction in HSV-1 infectivity at a dose of 75 μg/ml with pretreatment, but a 75% reduction at a dose 150 μg/ml with simultaneous addition. The extracts were also tested for virucidal activity, but all extracts exhibited IC_{50} values greater than 10 mg/ml, which the authors concluded as having virtually no virucidal activity.

Furthermore, Civitelli et al.[128] compared the antiherpetic activity of Mentha suaveolens essential oil against HSV-1 (strain F) to that of the essential oil from Melaleuca alternifolia. The IC_{50} and SI values, respectively, were found to be 5.1 μg/ml and 67 for M. suaveolens essential oil and 13.2 μg/ml and 44 for M. alternifolia essential oil. These values suggest greater antiviral capabilities of M. suaveolens compared to M. alternifolia. Interestingly, when each essential oil was combined with acyclovir, additive antiviral effects were observed. Additionally, each extract was shown to inhibit intracellular viral metabolism, but not to prevent viral adsorption.

Glycyrrhiza glabra was tested by Ghannad et al.[100] for its ability to prevent viral adsorption and delay viral incubation of HSV-1. The greatest antiviral activity was seen when Vero cells were pretreated with an aqueous extract of G. glabra and incubated with HSV-1 for only 1 hour. Additionally, cells were treated with HSV-1, incubated for 1 hour, washed, and treated with a non-cytotoxic dose of the extract after 1, 4, 8, and 12 hours. The most significant results, compared to control, were seen from treatment after hours 1 and 12. The authors speculate that the antiviral capacity of G. glabra comes from either direct viral inhibition or prevention of the viral attachment to host cells. The authors also suggest that G. glabra may interfere with viral gene expression due to results implying the extract was able to delay viral replication.

Fukuchi et al.[101] studied the ability of aqueous Glycyrrhiza glabra extracts of different pH values to exhibit antiviral activity against HSV-1 (strain F). The neutral water extracts (EC_{50} = 650 to 740 μg/ml and SI = 2.0 to >4.6) showed greater antiviral activity compared to the alkaline extracts (EC_{50} = 600 to >3000 μg/ml and SI = <1 to 3.2). An alkaline extract of Sasa senanensis was used as a positive control as the authors demonstrated its anti-HSV activity in a previous study. S. senanensis out-performed all extracts of G. glabra in the context of preserving cell viability after HSV-1 infection (EC_{50} = 0.033-0.048 μg/ml and SI = 4.5-11.4). Overall, G. glabra has some potential to act as an antiherpetic treatment, but may not be the most promising botanical available.

A total of 24 different plant species were tested for antiviral activity against HSV-1 and HSV-2 by Sokmen et al.,[192] but all failed to show any effects. The plants studied were Allium macrochaetum subsp. macrochaetum, A. macrochaetum subsp. tuncelianum, A. pustulosum, A. flavum, A. scorodoprosum, A. chrysanthemum, A. dictyoprosum, Rhus coriaria, Bupleurum sulphureum, Cannabis sativa var. sativa, Helianthemum ledifolium, Ecbalium elaterium, Phlomis kurdica, Sideritis libanotica, Thymus fallax, Linum usitatissimum, Urtica dioica, Peganum harmala, Hypericum scabrum, H. Capitatum, Achillea biebersteinii, Pimpinella anisum, and Nigella sativa.

North America

Opuntia streptacantha is a cactus found in Mexico that has been safely used to treat mild cases of diabetes in humans. Ahmad

et al.[133] studied the antiviral effects of O. streptacantha against HSV-2 (strain 3345), using extracts of dried powder, acetone, ether, and chloroform. Different concentrations of the extract were added to baby hamster kidney cells (BHK-21) immediately after viral adsorption. A concentration of 3.5 mg/ml reduced viral replication by 2.3 $\log_{10}$, and at 15 mg/ml, viral replication ceased entirely. Also, at a concentration of 15 mg/ml, viral protein synthesis was completely inhibited, but no effects on cellular protein synthesis were observed. More potent effects on viral replication were seen with pretreatment of cells 24 hours prior to viral inoculation, which inhibited replication by 2.6 $\log_{10}$ at a concentration of 3.5 mg/ml. Similar reductions were noted with pretreatment of cells 48 hours pre-infection. Additionally, human cervical cells were inoculated with HSV-2 then incubated with the plant extract or placebo for 2 days. When the extract was delivered at a concentration of 15 mg/ml, the viral replication was reduced by 3.5 $\log_{10}$. Lastly, humans were given either 3 or 6 grams of O. streptacantha for 30 days to assess toxicity. No adverse events were reported from human ingestion of the extract after 30 days.

Binns et al.[79] made extracts from the roots of 8 different species of Echinacea plants using 70% ethanol and assessed their antiviral activity against HSV-1. Some extracts were further fractionated with n-hexane and/or ethyl acetate. Antiviral assays included exposure to visible and UV-A light to ensure activation of any compounds that may be photosensitizers. The greatest inhibitory activity was elicited by the ethanolic extract of E. pallida var. Sanguinea with a MIC of <0.026 mg/ml and the n-hexane fraction of E. purpurea root with a MIC of 1.56 mg/ml. Additionally, ethanolic extracts of E. atrorubens var atrorubens and E. pallida var angustifolia and the n-hexane fractions of E. pallida var. angustifolia, E. pallida var. pallida, and E. pallida var. tennesseensis each had an MIC of <1 mg/ml.

The antiviral activity of E. pallida was also studied by Schneider et al.[80] against HSV-1 (strain KOS) and HSV-2 (strain HG52) using a hydroethanolic extract and the plant's pressed juice. Aerial parts were used to make extracts with 20%, 40%, 60%, and 80% aqueous ethanol as well as a pressed juice that was subsequently mixed with 96% ethanol as a preservative. All hydroalcoholic extracts showed dose-dependent antiviral activity, but the most significant antiviral activity was found from the pressed juice ($IC_{50} = 0.001\%$ and SI = 22,700 for HSV-1; $IC_{50} = 0.0002\%$ and SI = 113,500 for HSV-2). The IC_{50} values against HSV-1 for the 20%, 40%, 60%, and 80% ethanolic extracts were 0.03% (SI = 506), 0.001% (SI = 8400), 0.005% (SI = 1100), and 0.007% (SI = 514), respectively. Additionally, the IC_{50} values against HSV-2 for the 20%, 40%, 60%, and 80% ethanolic extracts were 0.007% (SI = 2171), 0.01% (SI = 840), 0.006% (SI = 916), and 0.004% (SI = 900), respectively. Time-of-addition experiments showed that the pressed juice was highly effective against HSV virions both intra- and extracellularly, while the hydroethanolic extracts affected virions extracellularly.

Furthermore, Lavoie et al.[75] tested Cornus canadensis for its antiviral actions against HSV-1 (strain ATCC-VR733). The extracts were made from dried stems and leaves via decoction or infusion with 3 different solvents each: water, ethanol, and 1:1 of water and ethanol. Viral absorption was best prevented by the simultaneous addition of HSV-1 and the water: ethanol infusion as well as the water decoction, both demonstrating an EC_{50} of 9 μg/ml. Direct viral inhibition was seen with both the decoctions and infusions of either the water or water: ethanol extracts, EC_{50} ranging 11-17 μg/ml. No extracts were observed to elicit antiviral effects when cells were pretreated nor when added during viral replication, defined by the authors as having EC_{50} values >50 μg/ml. Therefore, C. canadensis is most effective when used during or after the initial stages of the viral infection.

Recently, Silva-Mares et al.[63] screened a variety of plants for antiherpetic activity. Methanol or 1:9 of water: methanol extracts were created from the leaves, aerial parts, or cortex of Juglans mollis, Persea americana, Hamelia patens, Clematis drummondii, Salvia texana, and Salvia ballotaeflora. Also, ethyl acetate and ethyl ether extracts were created from the roots of Ceanothus coeruleus and Chrysactinia mexicana, respectively. The extracts were added after viral infection had been established in the Vero cells. The greatest antiviral activity was observed from the extract of S. ballotaeflora against both HSV-1 and HSV-2 with IC_{50} values of 31 μg/ml and 16 μg/ml, respectively. This was followed by the extract of J. mollis with IC_{50} values of 76 μg/ml and 126 μg/ml against HSV-1 and HSV-2, respectively. The SI values toward HSV-1 and HSV-2, respectively, were >26.3 and >15.8 for J. mollis and 7.5 and 14.6 for S. ballotaeflora. SI values toward HSV-1 and HSV-2, respectively, for the other species studied were as follows: 5.0 and <3.4 for P. americana; >4 and >9.4 for H patens, 1.9 and 7.5 for S texana, 5.45 and 3.8 for C. coeruleus, >11.7 and >5.8 for C. mexicana, and >4.3 and >7.8 for C. drummondii.

Another recent study by Zaharieva et al.[102] assessed a hydromethanolic extract of Graptopetalum paraguayense for antiviral activity against strains of HSV-1 and HSV-2. The extract was found to be antiviral toward wild-type strains of HSV-1 (EC_{50} = 0.0001 mg/ml, SI = 25,000) and HSV-2 (EC_{50} = 0.01 mg/ml, SI = 250), and acyclovir-resistant strains of HSV-1 (EC_{50} = 0.001 mg/ml, SI = 2,500) and HSV-2 (EC_{50} = 0.1 mg/ml, SI = 25). Interestingly, the extract had greater antiherpetic action than acyclovir in all 4 strains tested.

Oceania

Schnitzler et al.[87] compared the antiherpetic effect of tea tree oil, from Melaleuca alternifolia, to that of eucalyptus oil, from Eucalyptus globulus. Tea tree oil ($IC_{50} = 0.0009\%$ and SI = 6.7 for HSV-1; $IC_{50} = 0.0008\%$ and SI = 7.5 for HSV-2) demonstrated more potent antiviral activity than eucalyptus oil ($IC_{50} = 0.009\%$ and SI = 3.3 for HSV-1; $IC_{50} = 0.008\%$ and SI = 3.75 for HSV-2). Additionally, tea tree oil had significantly greater virucidal activity when virions were pretreated, eliminating over 90% of each HSV strain at non-cytotoxic concentrations. Eucalyptus oil showed 58% and 75% reduction in viral titers of HSV-1 and HSV-2, respectively. Time-of-addition

experiments revealed that both oils have the ability to impact viral adsorption, but not after viral penetration. The authors conclude that oils from either M. alternifolia or E. globulus have potential to be effective topical treatments for HSV infections.

Another 3 species from the Melaleuca family, M. ericifolia, M. leucadendron, and M. armillaris, were studied for the ability of their essential oils to act against HSV-1.[119] Farag et al.[119] observed a 99% virucidal effect with M. armillaris, a 92% virucidal effect with M. leucadendron, and a 91.5% virucidal effect with M. ericifolia. The authors explain that the variation in plaque reduction could be due to the different make up of each plant's essential oils as well as the time of year the leaves were collected.

Moreover, Reichling et al.[113] investigated antiviral effects of the essential oil of Leptospermum scoparium, commonly known as Manuka oil, against both HSV-1 (strain KOS) and HSV-2 (strain HG52). Manuka oil, which is commercially used as an anti-infective oil in New Zealand, was diluted with ethanol to a final ethanol concentration of 1% for all assays. L. scoparium essential oil inhibited plaque formation for both viruses in a dose-dependent manner when virions were pretreated with the oil. The IC_{50} and SI values, respectively, were determined to be 0.96 μg/ml and 40 for HSV-1 and 0.58 μg/ml and 66.2 for HSV-2. Furthermore, manuka oil was added at the non-cytotoxic concentration of 28.8 μg/ml to HSV-treated cells at different stages of the viral infection cycle. Pretreatment of cells with the oil prior to viral infection did not reduce plaque formation. However, pretreatment of viruses prior to infection reduced infectivity by 99.5% and 98.9% for HSV-1 and HSV-2, respectively. Manuka oil was less effective as the viral life cycle progressed. Therefore, L. scoparium essential oil has the potential to be effective as a prophylactic for HSV infection rather than a treatment.

South America

Hayashi et al.[74] observed a chloroform and ethanolic extract from dried leaves and twigs of Cordia salicifolia to have antiviral activity against HSV-1 (strain HF). The ED_{50} and SI values were found to be 0.85 μg/ml and 261, respectively, when the extract was added post-infection. Time-of-addition experiments showed the extract inhibited viral penetration and replication, but not attachment, and had a direct virucidal effect on HSV-1 virions. A clinically relevant finding was that the extract exhibited 99% inhibition of HSV-1 when added between 3 hours pre-infection to 8 hours post-infection.

Pacheco et al.[45] assessed aqueous and hydroalcoholic extracts of 36 species of Chilean plants for antiviral activity against HSV-1 (strain F) and HSV-2 (strain 333). Hydroalcoholic extracts of Cassia stipulaceae (IC_{50} = 80 μg/ml) and Illinita sp. (IC_{50} = 40 μg/ml) were found to have antiviral activity against HSV-1. Antiviral activity against HSV-2 was observed from the hydroalcoholic extracts of Aristotelia chilensis (IC_{50} = 40 μg/ml), Drimys winteri (IC_{50} = 35-80 μg/ml), and Elytropus chilensis (IC_{50} = 100 μg/ml) and the aqueous extract of Luma apiculata (IC_{50} = 100 μg/ml).

Aqueous extracts of the leaves and aerial parts of plants native to Argentina were prepared and assessed for antiviral activity against HSV-1 (strain F) by Kott et al.[115] The plants tested were Polygonum punctatum, Lithraea molleoides, Sebastiania brasiliensis, Myrcianthes cisplatensis, and Sebastiania klotzschiana. All extracts were found to have an antiviral effect except for M. cisplatensis. The greatest viral inhibition was observed by S. klotzschiana with an EC_{50} of 39 μg/ml. Other observed EC_{50} values ranged 51-169 μg/ml. The maximal non-cytotoxic concentrations were found to be 450 μg/ml for P. punctatum and 250 μg/ml for L. molleoides, S. brasiliensis, and S. klotzschiana.

Ethanolic and aqueous extracts of Baccharis genistelloides, Baccharis rubricaulis, Ambrosia arborescens, Phoradendron crassifolium, Rumex obtusifolius, Plantago australis, and Satureja boliviana, plants native to Bolivia, were tested by Abad et al.[51] for antiviral effects against HSV-1. Ethanolic extracts demonstrated high cytotoxicity, for example, the ethanolic extract of B. rubricaulis was cytotoxic at concentrations as low as 5 μg/ml. Only aqueous extracts were observed for antiviral effects, however, their maximum non-cytotoxic concentrations were at the upper limit of their effective concentration ranges The aqueous extracts that demonstrated inhibition of HSV-1 were S. boliviana, B. genistelloides, and P. crassifolium. Concentrations that were observed to show antiherpetic effects were 10-125 μg/ml, 25-50 μg/ml, and 125-500 μg/ml for S. boliviana, B. genistelloides, and P. crassifolium, respectively.

Subsequently, Abad et al.[52] assessed 10 plants from South America for anti-HSV-1 activity. Aqueous and ethanolic extracts of Baccharis trinervis, Baccharis teindalensis, Eupatorium articulatum, Eupatorium glutinosum, Tagetes pusilla, Neurolaena lobata, Conyza floribunda, Phytolacca bogotensis, Phytolacca rivinoides, and Heisteria acuminata were tested. At concentrations of 50-200 μg/ml, the aqueous B. trinervis extract was able to inhibit 80-100% of viral replication. Two other extracts were observed to inhibit viral replication, but demonstrated cytotoxicity at concentrations that closely paralleled effective concentrations. These extracts were the ethanolic H. acuminata extract and the aqueous E. articulatum extract, which inhibited less than 60% of viral replication at concentrations ranging 125-250 μg/ml.

Aerial parts from Achyrocline flaccida were made into an aqueous extract and tested against radiolabeled HSV-1 (strain F) by Garcia et al.[193] The extract was observed to inhibit >95% viral adsorption when 200 μg/ml was applied during infection, but had no inhibitory effect when applied as a pretreatment to cells. Through the use of radiolabeled virions, it was observed that penetration was reduced by 50% with a concentration of 200 μg/ml of the extract.

Goncalves et al.[172] used an acyclovir-resistant strain of HSV-1 to assess the antiherpetic activity of leaf and fruit ethyl acetate extracts of Vitex polygama. Maximum non-cytotoxic concentrations were determined as 25 μg/ml and 50 μg/ml for

the leaf and fruit extracts, respectively, and used for all testing. Both extracts were observed to inhibit HSV-1 when cells were pretreated. The leaf extract showed 73.7% inhibition while the fruit extract showed 85.2% inhibition. Additionally, the leaf extract was able to disrupt intracellular activity by 60.2% while the fruit extract had a direct virucidal effect by inhibiting 73.1% of virions. Neither extract could prevent HSV-1 attachment to host cells. As such, the leaf extract would likely be more applicable to use during HSV infection, whereas the fruit extract may have more of an effect when used to prevent infection.

Methanolic extracts of 24 plants traditionally used for skin infections from various regions within Columbia were tested for ability to inhibit HSV-1 by Lopez et al.[27] A total of 13 extracts demonstrated complete inhibition of viral cytopathic effects. These included extracts from Vismia macrophylla (MIC = 5.5 μg/ml), Symphonia globulifera (MIC = 25 μg/ml), Eschweilera rufifolia (MIC = 8 μg/ml), Byrsonima verbascifolia (MIC = 6.5 μg/ml for root bark extract; MIC = 2.5 μg/ml for leaf extract), Iryanthera megistophylla (MIC = 10 μg/ml), Virola multinervia (MIC = 11.5 μg/ml for resin extract; MIC = 17 μg/ml for bark extract), Myrteola nummulari (MIC = 10.5 μg/ml), Polygonum punctatum (MIC = 20 μg/ml), Adiantum latifolium (MIC = 11.5 μg/ml), Ampelozizyphus amazonicus (MIC = 22 μg/ml), and Duroia hirsuta (MIC = 10.5 μg/ml). Of these extracts, the most notable was the B. verbascifolia leaf extract, which completely inhibited HSV-1 activity at a low concentration of 2.5 μg/ml.

Moreover, Betancur-Galvis et al.[89] made petroleum ether, dichloromethane, ethanolic and/or water extracts from 10 Columbian medicinal plants from the Euphorbia genus and assessed antiherpetic activity against HSV-2. The species assessed were E. cestrifolia, E. cotinifolia, E. tirucalli, E. arenaria, and E. pulcherrima, E. heterophyla, E. cyatophora, E. graminea, E. cf. cotinifolia, and Euphorbia sp. Additional water-methanol (20:80) extracts were made from fresh parts of E. tirucalli and E. cotinifolia. Strong antiviral activity was seen from the hydromethanolic extracts of the leaves and stems of E. tirucalli (IC_{50} = 140.2 mg/ml and SI >7.13) and E. cotinifolia (IC_{50} = 104.6 mg/ml and SI >9.56), and moderate antiviral activity was seen from the ethanolic extracts of the stems of E. cotinifolia (IC_{50} = 75.6 mg/ml and SI = 1.59), E. cestrifolia (IC_{50} = 160.1 mg/ml and SI = 1.41) and E. tirucalli (IC_{50} = 64.3 mg/ml and SI = 3.46) and the dichloromethane extracts of the leaves of E. cotinifolia (IC_{50} = 36.8 mg/ml and SI = 4.08) and E. cestrifolia (IC_{50} = 59.8 mg/ml and SI = 2.83). The greatest inhibitory effects were observed from the hydromethanolic extracts of E. tirucalli and E. cotinifolia. It is important to note that these 2 extracts were not found to be cytotoxic at any dose studied, but their inhibitory action was lower than that of acyclovir (IC_{50} = 2.8 mg/ml and SI = 31,600). The authors believe that the antiviral activity of E. tirucalli and E. cotinifolia is acceptable and that these plants are good candidates for further research.

Significant inhibitory and virucidal action against acyclovir-resistant HSV-1 was observed from a 1:1 sodium chloride: glycerol extract of the seeds of Licania tomentosa by Miranda et al.[114] The ED_{50} and SI values of 9 μg/ml and 851, respectively, were calculated. Further experiments were conducted at the extract's maximum non-cytotoxic concentration, which was determined as 625 μg/ml. Viral inhibition of 90% was observed when the cells were pretreated with the extract for 3-4 hours at 37°C prior to infection, but the extract was cytotoxic if cells were pretreated at 4°C. When the extract was added to acyclovir-resistant HSV-1 directly, 59% of virions were inactivated. Addition of the extract after viral attachment resulted in 92.7% inhibition, but addition 2 hours post-infection only inhibited 74.4% of the virus.

Garcia et al.[25] assessed virucidal activity of essential oils from various medicinal plants found in Argentina. Viral inactivation of HSV-1 (strain F) was observed from the essential oils of Aloysia gratissima (IC_{50} = 65 ppm and SI = 2.31),[32] Artemisia douglasiana (IC_{50} = 83 ppm and SI = 3.77),[32] Eupatorium patens (IC_{50} = 125 ppm and SI = 2.35),[32] Tessaria absinthioides (IC_{50} = 105 ppm and SI = 2.50),[32] Lepechinia floribunda (IC_{50} = 20.3 ppm and SI = 3.80),[25] Lantana grisebachii (IC_{50} = 26.1 ppm and SI >19.16),[25] Lantana camara (IC_{50} = 43.3 ppm and SI = 2.48),[25] Eupatorium catarium (IC_{50} = 47.9 ppm and SI = 10.09),[25] Eupatorium arnottianum (IC_{50} = 52.1 ppm and SI = 7.61),[25] and Trixis divaricata (IC_{50} = 37.8 ppm and SI = 4.22).[25] Since L. grisebachii essential oil showed the strongest virucidal activity, the authors tested it against HSV-2 (strain G) and acyclovir-resistant HSV-1 (strain Field). The oil was found to elicit virucidal effects against both viruses with IC_{50} and SI values, respectively, of 44.3 ppm and >11.29 against HSV-2 and 79.7 ppm and >6.27 against acyclovir-resistant HSV-1.

A methanolic extract of the leaves of Trichilia glabra was made by Cella et al.[168] and further fractionated with different proportions of chloroform-methanol ranging from 100:0-90:10. The extracts exhibited virucidal activity against HSV-1 (strain F) in a dose-dependent manner. At a dose of 0.25 mg/ml, the 95:5 and 90:10 chloroform-methanolic fractions reduced viral titers by 2.4 $\log_{10}$ and 1.5 $\log_{10}$, respectively. Additionally, 33% reduction of HSV titers was observed with 0.27 mg/ml of the 95:5 chloroform-methanolic fraction, 0.35 mg/ml of the 90:10 chloroform-methanolic fraction, and 0.5 mg/ml of the methanolic extract.

A total of 51 aqueous and hydroethanolic extracts from plants native to Southern Brazil were tested for antiviral activity against HSV-1 by Montanha et al.[31] Extracts were tested against HSV-1 strain KOS, and those that exhibited anti-HSV activity were subsequently tested against the HSV-1 strains ATCC-VR733 and 29-R/acyclovir-resistant. The aqueous extracts of Ilex brevicuspis (5 mg/ml), Ilex theezans (0.25 mg/ml), and Maytenus ilicifolia (1.25 mg/ml) and the hydroethanolic extracts of Aloysia gratissima (1.25 mg/ml), Baccharis megapotamica (0.0048 mg/ml), and M. ilicifolia (0.5 mg/ml) inhibited 100% of viral cytopathic effects at their determined maximum tolerated concentrations. The hydroethanolic extracts of Baccharis erioclada (0.25 mg/ml), Glechon marifolia (0.625 mg/ml), and Glechon spathulata (0.25 mg/ml)

inhibited 100% of viral cytopathic effects at half of their maximum tolerated concentrations. The aqueous extract of B. eriocladа (0.312 mg/ml) and the hydroethanolic extract of Baccharis uncinella (0.312 mg/ml) inhibited 100% of viral cytopathic effects at a quarter of their maximum tolerated concentrations. Additionally, complete inhibition of cytopathic effects from HSV-1 strain ATCC-VR733 was observed from the aqueous extracts of I. brevicuspis (5 mg/ml), I. theezans (0.25 mg/ml), B. eriocladа (0.625 mg/ml), and M. ilicifolia (1.25 mg/ml) and the hydroethanolic extracts of B. eriocladа (0.5 mg/ml), M. ilicifolia (0.5 mg/ml), G. marifolia (0.625 mg/ml), G. spathulata (0.25 mg/ml), and A. gratissima (1.25 mg/ml). Lastly, the extracts that showed complete inhibition cytopathic effects of the 29-R/acyclovir-resistant HSV-1 strain were the aqueous extract B. eriocladа (1.25 mg/ml) and the hydroethanolic extracts of B. eriocladа (0.5 mg/ml), B. uncinella (1.25 mg/ml), and G. spathulata (0.25 mg/ml).

Furthermore, 15 medicinal plants from Argentina were assessed for antiherpetic activity against HSV-1 (strain F) and HSV-2 (strain G) by Ruffa et al.[85] Extracts were prepared with methanol, and the methanolic extract was subsequently dried, dissolved in hot water, and lyophilized to create an infusion. Only the methanolic extract and infusion of Juglans australis (methanolic: EC_{50} = 96.0 μg/ml and SI = 5.9 for HSV-1; infusion: EC_{50} = 65.3 μg/ml and SI = 8.1 for HSV-1, EC_{50} = 114.1 μg/ml and SI = 4.3 for HSV-2) and the methanolic extract of Eriobotrya japonica (EC_{50} = 183.2 μg/ml and SI = 2.4 for HSV-1, EC_{50} = 146.1 μg/ml and SI = 3.0 for HSV-2) were found to be antiherpetic. Only the infusion of J. australis showed effective antiviral activity as defined by the authors as a SI > 8 against HSV-1.

Andrighetti-Frohner et al.[41] made hydroethanolic extracts that were subsequently extracted with dichloromethane, ethyl acetate, and n-butanol using 6 medicinal plants from the Brazilian Atlantic Tropical Forest. The plants studied were Cuphea carthagenensis, Lippia alba, Tillandsia usneoides, Bromelia antiacantha, Araucaria angustifolia, and Wilbrandia ebracteata, and the HSV-1 strains used to test antiviral activity were wild-type strain KOS and 29-R/acyclovir-resistant strain. The most potent extracts were the ethyl acetate extracts of C. carthagenensis (EC_{50} = 2 μg/ml and SI = 90) and T. usneoides (EC_{50} = 3 μg/ml and SI = 65) against strain KOS. Other extracts that showed activity against strain KOS were the dichloromethane extracts of C. carthagenensis (EC_{50} = 4 μg/ml and SI = 49) and T. usneoides (EC_{50} = 10 μg/ml and SI = 18), the ethyl acetate extracts of A. angustifolia (EC_{50} = 35 μg/ml and SI = 9) and W. ebracteata (EC_{50} = 62 μg/ml and SI = 4), and the n-butanolic extracts of A. angustifolia (EC_{50} = 13 μg/ml and SI = 11), C. carthagenensis (EC_{50} = 31 μg/ml and SI = 12), T. usneoides (EC_{50} = 3 μg/ml and SI = 8), and W. ebracteata (EC_{50} = 125 μg/ml and SI = 1). The acyclovir-resistant strain was most strongly affected by W. ebracteata, demonstrating EC_{50} and SI values, respectively, of 25 μg/ml and 10 for the ethyl acetate extract and 12 μg/ml and 10 for the n-butanolic extract. Other extracts that showed activity against strain 29-R/acyclovir-resistant were the n-butanolic extracts of L. alba (EC_{50} = 2 μg/ml and SI = 8) and the dichloromethane, ethyl acetate, and n-butanolic extracts of T. usneoides (EC_{50} = 26 μg/ml and SI = 7, EC_{50} = 23 μg/ml and SI = 8, EC_{50} = 12 μg/ml and SI = 2, respectively).

Eight South American plant extracts were assessed for antiviral activity against HSV-1 strains KOS and 29-R/acyclovir-resistant by Muller et al.[108] Extracts were prepared with water, ethanol, 40% hydroethanol, or methanol. Antiherpetic activity, defined by the authors as a SI >7, was exhibited toward HSV-1 strain KOS by the aqueous extract of Ilex paraguariensis (EC_{50} = 80.0 μg/ml and SI = 15.8) and the methanolic extracts of Rubus imperialis (EC_{50} = 70.0 μg/ml and SI = 19.8) and Lafoensia pacari (EC_{50} = 60.0 μg/ml and SI = 19.0). Additionally, antiherpetic activity against strain 29-R/acyclovir-resistant was observed by the aqueous extracts of I. paraguariensis (EC_{50} = 100.0 μg/ml and SI = 12.6) and Passiflora edulis (EC_{50} = 89.9 μg/ml and SI = 17.8) and the methanolic extracts of R. imperialis (EC_{50} = 90.0 μg/ml and SI = 15.4) and Sloanea guianensis (EC_{50} = 140.0 μg/ml and SI = 10.0).

I. paraguariensis was also studied by Luckemeyer et al.[109] A hydroethanolic extract of the plant's leaves was prepared and further partitioned into butanol, aqueous residual, butanol residual, and ethyl acetate fractions. The extract and fractions were observed for antiherpetic action against HSV-1 (strain KOS) and HSV-2 (strain 333). The extract and all fractions, except for the aqueous residual fraction, showed antiherpetic activity against both strains, with the strongest inhibitory action observed from the ethyl acetate fraction (IC_{50} = 6.6 μg/ml and SI = 188.7 against HSV-1; IC_{50} = 7.1 μg/ml and SI = 264.7 against HSV-2). Additionally, the hydroethanolic extract showed strong inhibition toward HSV-2 (IC_{50} = 14.1 μg/ml and SI = 171.3) and HSV-1 (IC_{50} = 22.2 μg/ml and SI = 68.9). For comparison, acyclovir was also tested and demonstrated an IC_{50} of 0.5 μg/ml and a SI >2000 against HSV-1 as well as an IC_{50} of 1.2 μg/ml and SI >833.4 against HSV-2. Through other experiments in this study, the authors were able to show that the ethyl acetate fraction can prevent viral attachment and penetration into host cells and can reduce lateral spread of virions.

Valadares et al.[157] observed an ethanolic extract of Solanum paniculatum leaves to have antiviral activity against HSV-1. The extract demonstrated an EC_{50} of approximately 298 μg/ml and a SI of 1.4. For comparison, acyclovir was also tested and was found to have an EC_{50} of 40 μg/ml.

Moreover, 34 ethanolic extracts of 18 species of Brazilian medicinal plants were tested against HSV-1 by Brandao et al.[37] A total of 30 extracts were found to be non-cytotoxic at reasonable or ideal doses, and 10 of these were found to exhibit some antiherpetic activity. Extracts that showed moderate effects were Arrabidaea formosa (leaves: EC_{50} = 82.2 μg/ml and SI >6.1; stems: EC_{50} = 90.2 μg/ml and SI >5.5) and Zeyheria tuberculosa (leaves: EC_{50} = 81.8 μg/ml and SI = 2.1). Low activity was observed by Anemopaegma setilobum (leaves: EC_{50} = 138.1 μg/ml and SI >1.4; stems: EC_{50} = 168.2 μg/ml and SI >3.0), Arrabidaea craterophora (stems: EC_{50} = 188.1 μg/ml and SI = 1.9), A. formosa (fruit: EC_{50} = 148.5 μg/ml and SI >3.4), Arrabidaea pulchra (leaves:

$EC_{50} = 232.1$ μg/ml and SI >2.2), Arrabidaea sceptrum (stems: $EC_{50} = 375.3$ μg/ml and SI >1.3), and Stizophyllum perforatum (stems: $EC_{50} = 338.7$ μg/ml and SI >1.5).

Faral-tello et al.[26] created ethanolic extracts from 24 South American plants and 4 South American algal species and tested for antiviral activity against HSV-1 (strain F). None of the algal species offered inhibitory action toward HSV-1, however, 14 of the plant extracts demonstrated viral inhibition. These plants were Achyrocline satureioides, Bauhinia candicans, Chenopodium ambrosioides, Limonium brasiliense, Margyricarpus pinnatus, Phyllanthus niruri, Polygonum punctatum, Psidium incanum, Psidium luridum, Schinus molle, Sesbania punicea, Smilax gracilis, Tillandsia aeranthos, and Tillandsia usneoides. EC_{50} values of these plant extracts ranged 50-1500 μg/ml, and the highest SI values calculated were from P. niruri (42.37), P. incanum (14.89), and L. brasiliense (4.58). These 14 extracts were also tested for ability to directly inactivate HSV-1 virions at their respective maximum non-cytotoxic concentrations, and 6 showed virucidal activity, which was defined by the authors as inactivating $\geq$90% of viral particles. These extracts were C. ambrosioides, L. brasiliense, M. pinnatus, S. gracilis, T. aeranthos, and T. usneoides.

Thirty-six varieties of marine algae from Brazil were investigated for antiherpetic activity against acyclovir-resistant HSV-1 and HSV-2 by Soares et al.[69] Extracts were prepared using either dichloromethane and methanol in a 1:1 ratio or dichloromethane alone and added to Vero cells at determined maximum non-cytotoxic concentrations at the same time as viral infection. Strong antiviral activity against acyclovir-resistant HSV-1, defined as greater than 90% percent inhibition of viral titers, was exhibited by the dichloromethanic and methanolic extracts of Laurencia dendroidea (97.5% inhibition at 3.1 μg/ml), Hypnea spinella (92% inhibition at 200 μg/ml), Lobophora variegata (92% inhibition at 6.2 μg/ml), Stypopodium zonale (96.8% inhibition at 50 μg/ml), Sargassum cymosum (98.2% inhibition at 50 μg/ml), Ulva fasciata (99.9% inhibition at 200 μg/ml), and Codium decorticatum (99.9% inhibition at 200 μg/ml) as well as the dichloromethanic extract of Penicillus capitatus (93.0% inhibition at 250 μg/ml). Moreover, strong antiviral activity against acyclovir-resistant HSV-2 was exhibited by the dichloromethanic and methanolic extracts of Chondracanthus acicularis (92.4% inhibition at 100 μg/ml) and Stypopodium zonale (95.8% inhibition at 50 μg/ml) as well as the dichloromethanic extract of Penicillus capitatus (96% inhibition at 250 μg/ml). Cytotoxicity was not noted by the extracts that exhibited strong anti-HSV activity ($CC_{50} > 200$ μg/ml), except the extract of L. dendroidea ($CC_{50} = 48.2$ μg/ml).

Moura-Costa et al.[60] assessed aqueous and hydroalcoholic (50% and 70%) extracts from 6 Brazilian plants against HSV-1. The plants studied were Campomanesia eugenioides, Luehea paniculata, Ocimum gratissimum, Cordia americana, Schinus terebinthifolius, and Zanthoxylum rhoifolium. All extracts, except the aqueous extracts of C. americana and Z. rhoifolium bark, showed anti-HSV-1 activity. The hydroalcoholic extracts (EC_{50} and SI ranged 1.4-26 μg/ml and 6.9-21.3, respectively) were observed to have greater antiviral effects compared to the aqueous extracts (EC_{50} and SI ranged 0.6-20 μg/ml and 13-62, respectively). The highest SI values observed were from the 70% hydroalcoholic extracts of C. eugenioides (52) and C. americana bark (55) and the 50% hydroalcoholic extracts of O. gratissimum,[190] C. americana leaves,[82] S. terebinthifolius (>48), and Z. rhoifolium leaves .[146]

S. terebinthifolia was also tested by Nocchi et al.[156] for antiherpetic activity against the HSV-1 KOS strain, 29-R/acyclovir-resistant strain, and a clinical strain. A crude hydroethanolic extract of the plant demonstrated EC_{50} and SI values, respectively, of 10.20 μg/ml and >49 against strain KOS, 13.9 μg/ml and >35.9 against strain 29-R, and 14.2 μg/ml and >34.9 against the clinical strain. Further testing revealed the extract elicited its antiviral effects by inhibiting viral attachment and penetration when the extract was added during the adsorption and infection viral stages. However, little effects were noted on viral infectivity when virions were pretreated with the extract. Interestingly, the extract showed to have a synergistic effect with acyclovir when the 2 were tested in combination.

Furthermore, Petronilho et al.[64] found a hydroethanolic extract of Cecropia glaziovii leaves to inhibit viral replication of the HSV-1 strain 29-R/acyclovir-resistant. This extract demonstrated an EC_{50} of 40 μg/ml and SI of 50, suggesting strong viral inhibitory capacity.

Silva Junior et al.[96] found a dichloromethane extract from the roots of Gallesia gorazema to elicit 93% viral inhibition of HSV-1 at its maximum non-cytotoxic concentration of 100 μg/ml, but had no effect against HSV-2. An ethanolic extract from the leaves of Gallesia gorazema was also tested, but failed to demonstrate any antiherpetic activity against HSV-1 or HSV-2.

A crude extract of Trichilia catigua bark was prepared using 7:3 acetone: water and further partitioned with water or ethyl acetate by Espada et al.[167] Antiviral and virucidal activity as well as inhibition of viral adsorption of HSV-1 were investigated. The crude extract ($IC_{50} = 4.59$ μg/ml and SI >87) demonstrated stronger antiviral activity than the aqueous fraction ($IC_{50} = 12.5$ μg/ml and SI >32) or ethyl acetate fraction ($IC_{50} = 11.1$ μg/ml and SI >35.97). Time-of-addition experiments revealed the extract and fractions were most effective when added to cells at the time of infection. Greater inhibition of viral adsorption was seen with the ethyl acetate fraction, demonstrating 96.45% inhibition at 100 μg/ml. Moreover, 100% direct viral inhibition was elicited by 100 μg/ml, 50 μg/ml, and 25 μg/ml of the crude extract, aqueous fraction, and ethyl acetate fraction, respectively. The crude extract was also found to act as an antagonist to acyclovir while the 2 fractions acted synergistically.

Boff et al.[160] assessed the antiviral actions of an ethyl acetate extract from the stem bark of Strychnos pseudoquina against HSV-2 strain 333, and HSV-1 strains KOS and 29-R/acyclovir-resistant. When extract and virus were administered simultaneously to cells, the extract demonstrated IC_{50} and SI values, respectively, of 5.29 μg/ml and 10.16 for HSV-1 strain KOS and 6.55 μg/ml and 8.21 for HSV-2. When the extract was administered post-infection, it demonstrated IC_{50} and SI

values, respectively, of 22.2 μg/ml and 3.84 for HSV-1 strain KOS, 17.62 μg/ml and 3.05 for HSV-1 strain 29-R, and 8.64 μg/ml and 6.22 for HSV-2. Time-of-addition experiments revealed the extract had antiherpetic activity during viral adsorption ($IC_{50} = 1.96$ μg/ml and SI = 27.43 for HSV-1 strain KOS; $IC_{50} = 6.02$ μg/ml and SI = 8.92 for HSV-2), post-adsorption ($IC_{50} = 3.12$ μg/ml and SI = 17.23 for HSV-1; $IC_{50} = 3.15$ μg/ml and SI = 17.07 for HSV-2), and penetration ($IC_{50} = 7.33$ μg/ml and SI = 7.34 for HSV-1; $IC_{50} = 4.47$ μg/ml and SI = 12.03 for HSV-2). Pretreatment of cells with the extract inhibited HSV-2 replication ($IC_{50} = 7.56$ μg/ml and SI = 7.11), but had no effect on HSV-1 replication.

Antiviral activity against HSV-2 (strain 333) of hydroethanolic extracts of Equisetum giganteum, Croton lechleri, Uncaria tomentosa, and Copaifera reticulata was investigated by Churqui et al.[73] Viral plaques were reduced by 100% by extracts of E. giganteum, U. tomentosa, and C. reticulata at a concentration of 100 μg/ml and the C. lechleri extract at 30 μg/ml. IC_{50} values for the E. giganteum, U. tomentosa, C. reticulata, and C. lechleri extracts were found to be 18 μg/ml, 28 μg/ml, 50 μg/ml, and 10 μg/ml, respectively, and SI values were calculated as >55.56, >35.71, 10, and >100, respectively. All extracts demonstrated virucidal effects and prevented viral adsorption, but were not effective at inhibiting viral replication or preventing infection with pretreatment of cells.

An aqueous extract from Baccharis anomala was studied by Venturi et al.[50] for its effect on ATCC-VR733 and 29-R/acyclovir-resistant strains of HSV-1. The aqueous extract demonstrated EC_{50} and SI values, respectively, of 0.0088 mg/ml and 49.14 against the wild-type strain and 0.065 mg/ml and 66.53 against the 29-R strain. Additionally, pretreatment of cells with the extract did not prevent HSV infection, therefore the extract likely does not act by inhibiting viral attachment.

Aerial parts of Tanacetum parthenium were used to create a hydroethanolic extract that was tested against HSV-1 (strain KOS) in Vero and mouse fibroblast (L-929) cells by Benassi-Zanqueta et al.[162] The extract encouraged wound healing in L-929 cells, demonstrating a fivefold increase in wound healing at 48 hours and a 3-fold increase at 72 hours compared to control. In addition, the extract inhibited viral replication in Vero cells, demonstrating EC_{50} and SI values of 3.1 μg/ml and 18.1, respectively.

Most recently, Fahmy et al.[86] found a methanolic extract of Erythrina speciosa leaves that was further partitioned with ethyl acetate to inhibit HSV-1, demonstrating EC_{50} and SI values, respectively, of 94 μg/ml and 2.65.

Multiple Geographic Locations

The antiviral activity of Macrocystidia cucumis mycelia was assessed against HSV-1 (strain F) in BHK-21 cells by Saboulard et al.[117] The mycelia were grown in a culture broth and were found to possess antiviral activity, specifically, a decrease in expression of the HSV-1 antigen after 21 days of cultivation. This activity was maintained when the culture broth was diluted up to 64-fold, and there was no cytotoxicity observed. The authors proceeded to isolate the active compound from this broth and determined it to be a novel nucleoside analogue. This compound was found to have a MIC of 0.72 μg/ml against HSV-1.

Pan et al.[111] assessed an aqueous extract of another mushroom, Inonotus obliquus, for antiviral activity against HSV-1. The extract was found to have an IC_{50} value of 12.29 μg/ml and a SI of > 80, and primarily acted through prevention of viral entry.

Furthermore, a variety of mushrooms were assessed for antiviral activity against HSV-2 (strain BH) in RK-13 cells by Krupodorova et al.[47] The mushrooms were cultured as biomass and the mycelia were made into aqueous extracts using a 0.9% sodium chloride solution. Four species were found to inhibit HSV-2 replication, namely Fomes fomentarius ($EC_{50} = 0.62$ mg/ml and SI = 40.32), Pleurotus ostreatus ($EC_{50} = 0.155$ mg/ml and SI = 80.64), Auriporia aurea ($EC_{50} = 0.155$ mg/ml and SI = 161.29), and Trametes versicolor ($EC_{50} = 0.077$ mg/ml and SI = 324.67).

Chiang et al.[144,143] tested aqueous extracts of Plantago major and Plantago asiatica against HSV-1 (strain KOS) and HSV-2 (strain 196) in BCC-1/KMC cells. Both P. asiatica ($EC_{50} = 1318$ μg/ml and SI = 46.5)[143] and P. major ($EC_{50} = 843$ μg/ml and SI = 2.2)[144,143] demonstrated antiviral activity against HSV-2, but neither extract was active against HSV-1. The authors described the observed antiviral activity as weak, therefore P. major and P. asiatica are likely poor candidates for further HSV research.

An extract of Sambucus nigra was assessed for antiherpetic activity against HSV-1 (strain VR-3), acyclovir-resistant HSV-1 (strain VRTK-), and HSV-2 (strain UW-268) by Suzutani et al.[154] The extract's antiviral effects were compared to that of an extract of Ribes nigrum, called Kurokarin. The S. nigra extract was shown to have a SI of 2.14 against acyclovir-resistant HSV-1, but SI <1 against the other 2 strains. The SI values of Kurokarin were determined to be 1.19 against wild-type HSV-1, 2.19 against acyclovir-resistant HSV-1, and 1.72 against HSV-2. Both extracts offered more potent viral inhibition against acyclovir-resistant HSV-1 compared to the wild type HSV-1.

Ozcelik et al.[142] created 15 lipophilic extracts from Pistacia vera using n-hexane and different plant parts (seed, kernel, leaf, stem, branch, and shell skins) and assessed for antiviral effects against HSV (type not specified) Inhibition of viral cytopathic effects was observed from 6 of the 15 extracts. The most effective extracts were those made from the plant's fresh kernels, skins of processed woody shells, and unripe seeds, each with MIC <0.00006 μg/ml.

Moreover, Eugenia caryophyllus flower buds were extracted by Tragoolpua et al.[88] with ethanol and assessed against HSV-1 (strain F and 5 isolates) and HSV-2 (strain G and 5 isolates). The extract had similar antiviral activity against HSV-1 strain F ($ED_{50} = 72.8$ μg/ml and SI = 1.55) and HSV-2 strain G ($ED_{50} = 74.4$ μg/ml and SI = 1.52). HSV-1 isolates and HSV-2 isolates that also showed activity had similar

antiviral effects (ED_{50} = 62.0-73.1 μg/ml and SI = 1.54-1.82; ED_{50} = 42.6-52.9 μg/ml and SI = 2.13-2.65, respectively). Both HSV-1 strain F and HSV-2 strain G were completely inactivated after exposure to the extract for 3 hours at a concentration of 78.1 μg/ml. Additionally, when administered 30 hours after infection, the extract was able to inhibit 10-27% of replication of HSV-1 and HSV-1 isolates and 16-35% of replication of HSV-2 and HSV-2 isolates.

Onozato et al.[163] observed aqueous and ethyl acetate extracts of Tanacetum vulgare to exhibit antiherpetic activity against HSV-1. The ethyl acetate extract (EC_{50} = 40 μg/ml and SI = 3.9) showed slightly more potent effects than the aqueous extract (EC_{50} = 55 μg/ml and SI = 2.2). Further experiments were conducted with an isolated compound, and the authors concluded that T. vulgare most likely exhibits antiviral activity by interfering with HSV-1 replication.

T. vulgare was also studied by Alvarez et al.[164] The plant's aerial parts and rhizomes were extracted with methanol and aerial part extracts were fractionated with petroleum ether, chloroform, ethyl acetate, butanol, and water. The chloroform fraction was found to be cytotoxic and therefore was not assessed for antiviral capacity. Each extract/fraction was investigated against HSV-1 and HSV-2. The greatest antiviral effects were observed by the petroleum ether (EC_{50} = 69.9 μg/ml and SI = 3.37 for HSV-1; EC_{50} = 61.16 μg/ml and SI = 3.85 for HSV-2) and ethyl acetate (EC_{50} = 95.7 μg/ml and SI = 2.03 for HSV-1; EC_{50} = 59.4 μg/ml and SI = 3.27 for HSV-2) fractions and the methanolic rhizome extract (EC_{50} = 295.8 μg/ml and SI = 3.68 for HSV-1; EC_{50} = 500.0 μg/ml and SI = 2.18 for HSV-2). A strong antiviral effect was observed when petroleum ether or ethyl acetate extracts were added up to 6 hours after initial infection. The methanolic rhizome extract showed viral inhibition when added up to 2 hours after initial infection. Additionally, the ethyl acetate and petroleum ether extracts were able to inhibit >80% viral adsorption when added at concentrations of 50 μg/ml.

Yarmolinsky et al.[93] studied the ethanolic extracts of Ficus benjamina (leaf, fruit, stem) and Lilium candidum (leaf, petal, bulb) for antiviral effect on HSV-1 (strain ATCC-VR-735) and HSV-2. Leaf extracts of both plants showed strong viral inhibition toward both viruses, while the other extracts failed to show significant effects. The most pronounced effects were observed when the extracts were added simultaneously with the virus, rather than being added to cells post-infection. The leaf extract of F. benjamina (SI = 980 for HSV-1; SI ~800 for HSV-2) was found to have a greater SI for both viruses than acyclovir (SI ~700 for HSV-1; SI ~300 for HSV-2), and significantly greater than the leaf extract of L. candidum (SI = 87.5 for HSV-1; SI = 35 for HSV-2). Both extracts were also found to be synergistic with acyclovir.

A total of 31 medicinal plants were extracted with acetone and methanol by Jaeger Greer et al.,[46] and each extract was tested against HSV-1 (McIntyre strain) and HSV-2 (strain 333). Extracts from 8 plants varied in 10-98% inhibition of plaque formation at concentrations ranging 0.025-0.2 mg/ml. These extracts were the acetonic extracts of Atractylis macrophylla, Clematis cirrhosa, Gnaphalium chilense, Hymenoclea salsola, Kalanchoe pinnata, Lithospermum officinale, Psilostrophe cooperi, and Tetraclinis articulata and the methanolic extracts of H. salsola and K. pinnata. The acetonic extract of K. pinnata offered the safest antiviral effect with 95% and 98% inhibition of HSV-1 and HSV-2, respectively, at a concentration of 0.2 mg/ml, without being cytotoxic at this concentration. In subsequent experiments, the acetonic extract of K. pinnata demonstrated an EC_{50} of 0.025 mg/ml and SI of 50 for both HSV-1 and HSV-2. Although not as potent, the methanolic extract of K. pinnata demonstrated an EC_{50} of 0.05 mg/ml and SI of 19 for HSV-1 and EC_{50} of 0.2 mg/ml and SI of 4.75 for HSV-2. Another notable SI was demonstrated by the acetonic extract of A. macrophylla (EC_{50} = 0.05 mg/ml and SI = 5) against HSV-2.

Furthermore, Danaher et al.[152] found an ethanolic extract of Rubus eubatus berries to elicit direct virucidal effects and prevent viral adsorption and replication of HSV-1 (strain 17^{+}) in oral epithelial (OKF6) cells. Specifically, 56 μg/ml of extract was able to reduce viral yield by 99%. When the extract was added 1 hour post-infection, a concentration of 280 μg/ml was required to significantly reduce viral yields. Additionally, the extract was not found to be cytotoxic at high concentrations.

A hydroethanolic extract of Arctium lappa fruits was shown to have antiviral effects against HSV-1 (strain ATCC-VR733) by Dias et al.[42] All tested concentrations of the extract (3.125-400 μg/ml) were non-cytotoxic, and the extract showed a dose-dependent reduction in viral loads. At 400 μg/ml, A. lappa prevented cellular damage from viral infection and showed similar, although slightly better, antiviral capacity to 50 μg/ml of acyclovir.

Various plant parts from Peganum harmala were used to create extracts with a combination of solvents (hexane, dichloromethane, ethyl acetate, methanol, and ethanol) that were assessed by Benzekri et al.[135] for antiviral activity against HSV-2. Only the seed extract demonstrated viral inhibition (IC_{50} = 161 μg/ml and SI = 13.19). Time-of-addition experiments showed that the seed extract offered direct virucidal activity (IC_{50} = 49 μg/ml and SI = 43.46) and interfered with viral adsorption and lysis, but it did not protect pretreated cells from viral infection.

Donalisio et al.[169] found Vachellia nilotica bark extracts prepared with methanol (EC_{50} = 4.71 μg/ml and SI = 30.6), water (EC_{50} = 10.2 μg/ml and SI = 18.6), and chloroform (EC_{50} = 12.3 μg/ml and SI = 15.4) exhibited antiviral activity against HSV-2 (strain ATCC-VR540). Acyclovir was also tested and demonstrated EC_{50} and SI values of 3.17 μg/ml and >468, respectively. Against an acyclovir-resistant strain of HSV-2, the methanolic extract showed antiviral activity (EC_{50} = 6.71 μg/ml and SI = 21.5), suggesting a different mechanism of action compared to acyclovir. Additionally, the methanolic extract was observed to reduce viral load when added during infection, but only mildly reduce viral load when added after infection. The methanolic extract did not prevent infection in pretreated cells.

Lastly, an ethanolic extract of Veronica persica was tested by Sharifi-Rad et al.[170] for antiviral effects on HSV-1 and HSV-2. The extract was able to reduce viral load in a dose-dependent manner when added after infection. The SI was found to be 65 for HSV-1 and 45 for HSV-2. The ethanolic extract was further fractionated with 0%, 20%, 40%, 60%, 80%, and 100% methanol. The most notable antiviral effect was observed by the 80% methanolic fraction (IC_{50} = 0.62 μg/ml and SI = 451.6 for HSV-1; IC_{50} = 0.73 μg/ml and SI = 383.5 for HSV-2), whereas all other fractions demonstrated SI <4. It should be acknowledged that the SI values achieved by the 80% methanolic fractions were greater than those observed by acyclovir (SI = 320 for HSV-1; SI = 300 for HSV-2). Moreover, time-of-addition experiments revealed that the greatest viral inhibition occurred when cells were treated with the 80% methanolic fraction at inoculation and again post-infection. Single treatment at or post-infection demonstrated weaker effects. Additionally, the 80% methanolic fraction demonstrated synergistic antiviral effects with acyclovir.

Single Herbs In Vivo

Dimitrova et al.[120] investigated the antiviral effects of 4 extracts of Melissa officinalis on HSV-1 (strain DA) infection in rabbits. Extracts were prepared with either 50% ethyl alcohol, 50% ethanol extract, ethyl acetate, or water. Rabbits were infected with HSV-1 into their eyes and treated 1 of the 4 extracts, 8 or 9 times a day at 1-hour intervals. Tear secretions were taken from each rabbit daily for 7 days and analyzed. No differences were found between treated and control rabbits for any outcome measure. The authors were unable to demonstrate antiviral effects of M. officinalis extracts in vivo.

A wide variety of aqueous Asian plant extracts were tested by Kurokawa et al.[33,98,99] in 3 studies for their ability to delay development of lesions and prolong survival time of female BALB/c mice infected with HSV-1 (strain 7401 H). Many of these extracts were previously found by the authors to exhibit antiviral effects against HSV-1 in vitro, either alone or in combination with acyclovir. In the first study, Kurokawa et al.[33] cutaneously inoculated mice with HSV-1 and aqueous plant extracts were orally administered at a dose of 1-10 mg in a volume of 0.25 ml/mouse once at 8 hours prior to inoculation and then 3 times daily for 10 days after inoculation. The extracts of Alpinia officinarum, Caesalpinia sappan, Geum japonicum, Paeonia suffruticosa, Phellodendron amurense, Polygala tenufolia, Punica granatum, Rhus javanica, Syzygium aromaticum, Terminalia arjuna, and Terminalia chebula significantly delayed the development and progression of herpes lesions. The only extract to prolong mean survival time was Phellodendron amurense.

In the second study, Kurokawa et al.[98] tested the antiviral activities of 4 aqueous extracts of G. japonicum, R. javanica, S. aromaticum, and T. chebula each in combination with acyclovir. Extracts were dosed at 250 mg/kg and acyclovir at 2.5 mg/kg. The combination of acyclovir with G. japonicum, S. aromaticum, and T. chebula showed to significantly delay the development and progression of herpes lesions and/or mean survival time compared to acyclovir or extract alone. The combination of acyclovir with R. javanica did not show significant antiviral effects compared to acyclovir or extract alone. No significant toxicity was found for any of the combinations tested. Additionally, the 4 extracts and acyclovir were tested on viral yields in the skin and brain of mice. The extracts showed 2.5-20 times greater antiviral activity in the brain than skin. On the other hand, acyclovir was observed to elicit stronger anti-HSV effects in the skin than the brain. The combination of acyclovir with each of the extracts exhibited stronger antiviral effects than acyclovir or extract alone, and these effects were stronger in the brain than skin.

In the third study, Kurokawa et al.[99] tested hot water extracts of G. japonicum, R. javanica, S. aromaticum, and T. chebula for their ability to prevent recurrent HSV-1 infection in BALB/c mice that were infected with the virus 4 months prior and exposed to ultraviolet irradiation. The extracts, or water as control, were administered orally to the mice 3 times per day for 10 days at a total dose of 750 mg/kg/day. The UV irradiation began on day six. The extracts were shown to reduce incidence of recurrence, reduce the severity of vesicles, and decrease the duration of lesions if they occurred. The prophylactic treatment also reduced the ability to detect viral DNA in the trigeminal ganglion or pinna of the mice. The strongest prophylactic response was observed in mice treated with the S. aromaticum extract.

Nakano et al.[151] also investigated the antiviral effects of R. javanica and its prophylactic ability with recurrent HSV-2 (strain Ito-1262) herpes genitalis in guinea pigs in a crossover study. First, female guinea pigs were intravaginally infected with HSV-2 and monitored for 1.5 months until lesions healed. After primary infection was alleviated, guinea pigs were given an aqueous extract of R. javanica or water for 2 months. R. javanica was administered through drinking water at an average dose of 625 mg/kg/day. After 2 months, there were notable decreases in the number of vesicles, time to heal, and severity of lesions. The second part of the crossover design was conducted once secondary infection was cleared. Guinea pigs that received placebo treatment were administered R. javanica for 2 to 3 months, and those that previously received R. javanica were given either water or a new extract of T. chebula for the same duration. Both extracts were dosed on average at 625 mg/kg/day. In guinea pigs who received R. javanica followed by water, infection was not immediately triggered by discontinuation of the extract. However, treatment with R. javanica reduced the number, severity, and prevalence of lesions. The authors note that by maintaining similar results after crossover, R. javanica potentially provided prophylactic relief from recurrent HSV-2 infection.

Furthermore, Nawawi et al.[92] investigated the antiherpetic effects of methanolic extracts of 7 Indonesian medicinal plants in BALB/c mice. The plants studied were Eurycoma longifoli, Filicium decipiens, Garcinia mangostana, Melaleuca leucadendron, Nephelium lappaceum, Punica granatum, and Toona sureni. Extracts were dissolved in 2% dimethyl sulfoxide and

orally administered to mice 8 hours before HSV-1 (strain 7401 H) inoculation and 3 times daily post-inoculation. All extracts were able to significantly delay the appearance of vesicles in the local region, but only M. leucadendron and N. lappaceum were able to both limit further development to mild zosteriform lesions and reduce mortality when compared to control. Specifically, N. lappaceum completely inhibited development of mild zosteriform lesions and was the only extract to exhibit similar antiherpetic activity as acyclovir (0.1 mg/mouse was given as comparison). The authors conclude that N. lappaceum has the potential to be used as an anti-HSV-1 treatment in humans.

A later study by Nawawi et al.[159] explored the efficacy of a methanolic extract of the root tubers of Stephania cepharantha at fighting off HSV-1 (strain 7401 H) infection in BALB/c mice. After cutaneously infecting mice with HSV-1, the extract was orally administered at 125 or 250 mg/kg of body weight. The extract led to a decrease in the number and development of vesicles and an increase in survival time of mice.

Lipipun et al.[28] assessed the water, ethanolic, or chloroform extracts of Aglaia odorata, Moringa oleifera, Ventilago denticulata, Cerbera odollam, and Willughbeia edulis for antiherpetic properties in female BALB/c mice. The mice were shaved and cutaneously infected with wild-type HSV-1 (strain 7401 H) and administered an extract orally in a dose of 250 mg/kg 8 hours prior to infection and then every 8 hours for 5 days. The size and development of skin lesions was significantly reduced in mice that were treated with A. odorata, M. oleifera, and V. denticulata. New female BALB/c mice were then virally infected and given either 5 mg/kg of acyclovir or 250 mg/kg of either A. odorata, M. oleifera, or V. denticulata every 8 hours for 2 weeks. All 3 plant extracts significantly reduced the development of vesicles in the local region, but only M. oleifera reduced mortality of the mice and increased survival times. The antiviral activities of A. odorata, M. oleifera, and V. denticulata were comparable to that of acyclovir.

Moreover, Park et al.[81] found a methanolic extract of Symphyocladia latiuscula to significantly delay the appearance and limit further progression of HSV-1 infection in female BALB/c mice. Mice were inoculated with wild-type HSV-1 (strain 7401 H) and orally administered the extract at a dose of 0.5 mg/mouse 4 hours pre-inoculation and then 3 times a day for 6 to 10 days post-inoculation. The extract significantly delayed the appearance of local vesicles and further progression to mild zosteriform lesions compared to control. Although survival time increased with the extract compared to control, the mortality rate was 100% in both groups. Further experiments evaluated viral yields in the skin and brain of mice treated with the extract at 3 and 6 days post-inoculation. At both 3 and 6 days post-infection, the extract significantly reduced viral yields in the skin, but not in the brain.

The therapeutic effect of Carissa edulis extract in BALB/c mice infected with wild-type HSV-1 (strain 7401 H), wild-type HSV-2 (strain Ito-1262), or acyclovir-resistant 7401 H HSV-1 was investigated by Tolo et al.[62] The extract was previously found by the authors to exhibit antiviral effects against HSV-1 and HSV-2 in vitro. Mice were treated post-infection with 250 mg/kg of the extract 3 times a day for 1 week. Onset of infection was significantly delayed by 2 days in both the wild-type and acyclovir-resistant HSV-1 infected mice. Delay of onset of infection in wild-type HSV-2 mice was not significantly different from control. Notably, the delay in onset of infection in wild-type HSV-1 infected mice was similar to the delay observed with treatment with acyclovir. Additionally, a longer survival time and lower mortality rate was observed in wild-type HSV-1 infected mice treated with the herbal extract compared to control.

A methanolic extract of Lobelia chinensis demonstrated antiviral effects against HSV-1 infection in BALB/c mice by Kuo et al.[116] The extract was previously found by the authors to exhibit anti-HSV-1 activity in vitro, likely by blocking viral DNA synthesis. Mice were inoculated with HSV-1 (strain KOS) and treated orally with either 20 or 50 mg/kg of the extract or 60 mg/kg of acyclovir 3 times a day for 7 days. No differences were observed in the development of lesions in mice treated with 20 mg/kg of extract and control. However, lesions completely disappeared in mice treated with 50 mg/kg of the extract or acyclovir, suggesting both are effective at preventing lesion formation. Further experiments revealed L. chinensis disrupts HSV-1 replication in mice, likely by reducing viral DNA expression. The extract was found not to have any toxic effects on the liver or kidneys of mice treated with the extract.

Kaushik et al.[110] tested the therapeutic effect of a hydromethanolic extract of Indigofera heterantha on HSV-2 infection in BALB/c mice. The authors had previously found the extract to demonstrate antiviral activity in vitro by blocking HSV-2 attachment, adsorption, and entry into host cells. The extract was formulated into a cream to be used for topical application at the genital region of mice. Mice were vaginally inoculated with HSV-2 (strain G) and administered 375, 750, or 1500 mg/kg of cream 3 times a day for 5 days, starting at 30 minutes post-infection. Treatment with 375 and 1500 mg/kg of cream resulted in 100% survival for the mice, and treatment with 750 mg/kg resulted in 87.5% survival. In terms of effects on lesion formation, clinical symptoms, and extravaginal disease, only treatment with 1500 mg/kg showed 100% reduction. Further experiments tested the prophylactic ability of the extract cream. Treatment with 125 mg/kg and 500 mg/kg at 2 and 4 hours pre-infection resulted in 100% survival and significant reductions in lesion scores. The authors conclude that I. heterantha has the potential to both treat and prevent genital herpes infection.

Nocchi et al.[156] investigated the anti-HSV activity of a crude hydroethanolic extract of Schinus terebinthifolia in female BALB/c mice. The extract was previously found by the authors to exhibit antiviral effects against HSV-1 in vitro by inhibiting viral attachment and penetration. Mice were infected with HSV-1 (strain KOS) and either given no treatment, 2% crude extract, 5% crude extract, or acyclovir cream 5 times per day for 10 days. The lesions developed more slowly and cleared up more quickly on mice who were treated with the crude extract

versus no treatment. Additionally, the authors report no statistically significant differences between the lesions in mice treated with crude extract versus acyclovir. It is important to acknowledge that the authors also verified an absence of genotoxicity from the crude extract on bone marrow of the rodents.

Hydroethanolic extracts of Equisetum giganteum, Croton lechleri, Uncaria tomentosa, and Copaifera reticulata were investigated by Churqui et al.[73] against HSV-2 infection in female C57bl/6 mice. The extracts were previously found by the authors to exhibit antiviral effects against HSV-2 (strain 333) in vitro by preventing viral adsorption. When each of the extracts were administered simultaneously with the virus to mice, HSV infection was successfully prevented by all 4 extracts via viral inhibition.

Mostly recently, Benassi-Zanqueta et al.[162] studied the anti-HSV-1 activity of oral and topical administrations of a hydroethanolic extract of Tanacetum parthenium in BALB/c mice. The extract was previously found by the authors to exhibit antiviral effects against HSV-1 (strain KOS) in vitro. Oral administration was given once daily and mice were administered either no treatment, control treatment, acyclovir at 10 mg/kg body weight, hydroethanolic extract at 4 mg/kg body weight, or hydroethanolic extract at 8 mg/kg body weight. Topical administration was given 4 times a day and mice were administered either no treatment, control treatment, 5% acyclovir, 2.5% hydroethanolic extract, or 5% hydroethanolic extract. Both arms were carried out for 10 days. The hydroethanolic extract was determined not to be genotoxic nor irritating. Oral and topical treatment with the extract or acyclovir was found to yield similar results, but improvement of HSV lesions was mild compared to inactive treatments.

Herbal Combinations In Vitro

Serkedjieva et al.[174] prepared an aqueous extract from 100 g Sambucus nigra, 70 g Hypericum perforatum, and 40 g Saponaria officinalis and investigated the herbal combination's antiviral effects against HSV-1 (McIntyre strain). The extract was assessed for cytotoxicity in human fetal lung fibroblast (MRC-5) cells and a maximum tolerated concentration was determined to be 250 μg/ml. At a concentration of 200 μg/ml, the extract showed virucidal effects to a 0.01/ml viral dose, but the ability to inactivate virions was only seen at a 0.1/ml viral dose. Moreover, MRC-5 and rabbit kidney (RK-13) cells were infected with HSV-1 and incubated with the extract or control for 24 hours. The extract at a concentration of 250 ug/ml was tested in MRC-5 cells, and concentrations of 100, 150, or 200 ug/ml were tested in RK-13 cells. There was a 2.4 log difference and a 1-3 log difference between control and treatment viral titres in MRC-5 and RK-13 cells, respectively.

Cheng et al.[178,179] investigated the antiherpetic activity of 2 traditional Chinese medicinal formulas in 2 studies. In the first study, Cheng et al.[178] prepared an aqueous extract of Yin Chen Hao Tang, which consisted of 108 g Artemisia capillaries, 36 g Gardenia jasminoids, and 36 g Rheum officinale. The extract was tested against HSV-1 (strain KOS) and HSV-2 (strain 196 and strain G) and found to inhibit both viruses to different degrees. The IC_{50} and SI values against HSV-1 ranged 145.5-150.1 μg/ml and 5.7-6.0, respectively. Antiviral activity was more potent against the HSV-2 strains, with IC_{50} and SI values ranging 19.6-29.4 μg/ml and 28.9-43.4, respectively. Time-of-addition experiments revealed antiviral effects of the extract on HSV-2 were only noted when the extract was added simultaneously with the virus to cells or added 2 hours post-infection and presence maintained for 48 hours. In addition, pretreatment of HSV-2 virions with the extract showed to inhibit viral infectivity, and this inactivation was observed to be irreversible.

In the second study, Cheng et al.[179] made an aqueous extract of Long Dan Xie Gan Tang, which consisted of the following 10 Chinese herbs and weights: 32 g Alisma plantago-aquatica, 16 g Akebia quinata, 16 g Angelica sinensis, 32 g Bupleurum chinense, 16 g Gardenia jasminoides, 32 g Gentiana scabra, 16 g Glycyrrhiza uralensis, 16 g Plantago asiatica, 16 g Rehmannia glutinosa, and 16 g Scutellaria baicalensis. The extract showed to inhibit both HSV-1 (strain KOS) and HSV-2 (strain 196) in a dose-dependent manner, but HSV-1 was more susceptible to the extract. The IC_{50} and SI values, respectively, were determined to be 257.5 μg/ml and 15.8 against HSV-1 and 494.6 μg/ml and 8.2 against HSV-2. Additionally, HSV-2 virions were pretreated with the extract and a decrease in viral infectivity was observed. The authors conclude that Long Dan Xie Gan Tang likely inactivates herpes viruses directly, which is a different mechanism of action than acyclovir.

An aqueous extract of Chui-Uren-Chien, another traditional Chinese medicine formula that is considered to be immunomodulatory, was tested for anti-HSV-1 activity by Liao et al.[171] The extract was prepared from 7.5 g Panax ginseng, 11.25 g Astragalus membranaceus, 7.50 g Glycyrrhiza uralensis, 3.75 g Cimicifuga foetida, and 11.25 g Atractylodes macrocephala. HSV-1 (strain KOS) inhibition was not noted when the extract, at a dose of 600 μg/ml, was treated to virally infected SK-N-SH cells.

Lastly, Mishra et al.[180] investigated the ability of a herbal gel formulation to act as an antiviral on HSV-2 (strain G ATCC-VR-734). The gel was previously studied on ulcers caused by HIV-1, and the authors propose that there is a strong link between ulcers caused by HIV-1 and HSV-2. The gel contained 50% ethanolic extracts of Acacia catechu, Lagerstroemia speciosa, Terminalia chebula, and Phyllanthus emblica. The use of this gel formulation resulted in a greater decrease in HSV-2 attachment (IC_{50} = 46.55 μg/ml and SI = 68.30) and penetration (IC_{50} = 54.94 μg/ml and SI = 57.87) than seen when treating infected cells with acyclovir. When cells were treated post-infection, acyclovir (IC_{50} = 0.065 μg/ml SI = 69,082) had significantly greater inhibition than the formulation (IC_{50} = 469.05 μg/ml and SI = 6.78). However, when testing virucidal activity, the gel formulation (IC_{50} = 27.26 μg/ml and SI = 116.63) was significantly more potent on virions than acyclovir (IC_{50} = 124.50 μg/ml and SI = 3.61). Moreover, physiological effects were

explored by applying the gel to normal human vaginal mucosa (Vk2/E6E7) cells. The gel did not decrease viability of local vaginal flora or the integrity of vaginal keratinocytes. It also did not increase mutagenic behavior or secretion of inflammatory cytokines. The authors conclude that these results are more applicable to patient care than results from non-human cell lines.

Herbal Combinations In Vivo

Ikemoto et al.[175] investigated the antiviral activity of Shigyaku-to in mice and tissue culture cells. Shigyaku-to is the Japanese name for the traditional Chinese herbal medicine Si Ni Tang, which is a combination of Glycyrrhiza glabra, Zingiberis siccatum, and Aconitum carmichaelii at a ratio of 3:2:1. It has been traditionally used for thousands of years in China to treat a variety of infections. To test the antiviral activity of this herbal combination, mice were infected with lethal amounts of HSV-1 (strain KOS) and treated with various doses of Shigyaku-to (1.25-80mg/kg). The strongest antiviral activity was seen with a dose of 20mg/kg where 74% of mice survived infection compared to 100% mortality of mice treated with saline control. Moreover, when infected mice were inoculated with whole spleen cells from uninfected mice treated with Shigyaku-to, survival rate was significantly higher compared to non-inoculated controls. Shigyaku-to's antiviral mechanism was investigated in Vero cells, but the herbal combination did not show any virucidal or virostatic activities in vitro. The authors suggest that the antiviral mechanism of this herbal combination may be due to stimulation of the body's antiviral functions in mice.

Another traditional Chinese herbal formula, Kanzo-bushi-to, was studied for antiviral effects in thermally-injured BALB/c mice by Matsuo et al.[176] Kanzo-bushi-to is the Japanese name for the Chinese formula Gan Cao Fu Zhi Tang. The authors chose to use thermally-injured mice because they are approximately 100 times more susceptible to herpes infection than non-thermally-injured mice. A hot water extract was made from Kanzo-bushi-to, which is a combination of Aconitum carmichaelii, Atractyloidis lanceae, Cinnamomum verum, and Glycyrrhiza glabra at a ratio of 2:12:7:4. Mice were thermally injured and 1 day later were inoculated with HSV-1 (strain KOS). The extract was administered intraperitoneally on days one and 4 post-injury at a dose of 5 mg/kg. The extract significantly reduced the mortality rate of mice, demonstrating a rate of 10% compared to 95% in controls. Further experiments showed that $CD8^+$ ST-cell activities were reduced in mice treated with the extract. This is an important finding because an increase in $CD8^+$ ST cell activity is involved in the increased susceptibility to infection of thermally-injured mice. Additionally, an accelerated generation of Contra-ST-cells was observed in mice treated with the extract, which likely explains the reduction in $CD8^+$ ST cell activity. The authors conclude that an aqueous extract of Kanzo-bushi-to reduced the susceptibility to HSV-1 infection in thermally-injured mice by expanding the generation of Contra-ST-cells

Lastly, Nagasaka et al.[177] studied a Chinese herbal combination called Kakkon-to for its antiherpetic properties. Kakkon-to, which is the Japanese name for the Chinese formula Ge Gan Tang, is a mixture of 24 g Pueraria pseudo-hirsuta radix, 12 g Ephedra sinica herba, 12 g Zizyphi jujuba fructus, 9 g Cinnamomi cassia cortex, 9 g Paeoniae lactiflora radix, 6 g Glycyrrhizae uralensis radix, and 3 g Zingiberis officinale rhizoma. A hot water extract of the herbal mixture was prepared and female BALB/c mice were orally given either 300mg/kg of the extract or water 4 hours pre-infection. Mice were subjected to cutaneous HSV infection by inoculation with HSV-1 strain 7401 H and treated with the same 300mg/kg of extract or water every 8 hours for 7 days. Mice treated with Kakkon-to showed 33% mortality compared to 100% mortality in those untreated. Additionally, the size and severity of lesions significantly decreased in mice treated with Kakkon-to versus those untreated. To study the antiviral effect on an established HSV-1 infection, separate female mice were inoculated with HSV-1 strain 7401 H and were either treated with 330mg/kg Kakkon-to at zero or 18 hours post-infection or were non-treated controls. The appearance of skin lesions was significantly reduced in the treatment groups compared to controls. However, the lesions developed along the same course from vesicular to ulcerated lesions in all groups. The only noted difference was smaller lesion sizes in treated mice regardless of treatment time. The authors concluded that Kakkon-to acted as both a therapeutic and prophylactic agent against HSV-1 cutaneous infection.

Human Trials

The effect of Melaleuca alternifolia oil gel on recurrent herpes labialis was studied via a randomized, placebo-controlled, investigator-blinded trial conducted by Carson et al.[181] Participants were not blinded to their treatment due to the unique smell of M. alternifolia oi, and 20 participants with a history of recurrent herpes labialis were recruited. Treatment was either a 6% M. alternifolia oil aqueous gel or placebo gel. Participants were instructed to apply the gel 5 times daily as close to onset of infection as possible. Those treated with M. alternifolia oil gel had a shorter duration of infection (9 days) compared to participants treated with placebo (12.5 days), and the viral load present in lesions was lower in those treated with M. alternifolia oil gel than with placebo. However, both groups had similar results for HSV presence (via PCR) and time to crust formation. Study results were not statistically significant, which the authors owe to the small population studied. However, Melaleuca alternifolia oil has potential to be a cost effective alternative topical treatment for herpes labialis infections.

Two human trials, carried out by Wolbling et al.,[182] demonstrated the antiviral effects of Melissa officinalis on HSV lesions. Lomaherpan cream containing 1% dried extract of M. officinalis was tested. The first trial tested the cream on HSV lesions without the use of a placebo-control group. The trial was conducted at 3 dermatology clinics on a total of 115 patients with HSV lesions of the skin or transitional mucosa for

not more than 72 hours. Subjects were instructed to apply the cream to lesions 5 times daily until lesions completely healed. Lesions completely healed by day 4, 6, and 8 in 60%, 87%, and 96% of subjects, respectively. The authors believed the cream reduced healing time as HSV lesions naturally heal within 10 to 14 days. The second trial was a randomized, double-blind, placebo-controlled study of 116 patients with HSV lesions with the same inclusion criteria as the trial before. A cream that did not contain M. officinalis was used as placebo. Subjects were instructed to apply the cream to lesions 2 to 4 times daily for a period of 5 to maximum 10 days. Clinical symptoms between the treatment and placebo groups were not statistically different at baseline. On day two, significant reductions in symptoms and lesion swelling was noted in the treatment compared to the placebo group. On day five, complete resolution of symptoms was noted by 24 subjects in the treatment group compared to 15 subjects in the placebo group. Subjects' and physicians' assessments of healing were significantly greater for the treatment group compared to the placebo group. The trial provided evidence for the use of M. officinalis as a treatment for HSV lesions. The antiviral effect was found to be most significant if treatment was commenced as early as possible during the course of infection.

Koytchev et al.[183] also assessed the antiviral activity of M. officinalis on HSV infections in a randomized, double-blind, placebo-controlled trial. The study included 66 patients based on the criteria of at least 4 episodes of herpes labialis per year. A cream was created to have 1% active ingredient, described as the dried extract of M. officinalis at a 70:1 concentration. Subjects were given either the treatment or a placebo cream and instructed to apply the cream to lesions 4 times daily for a duration of 5 days. Symptom scores were measured on the second day of treatment because most symptoms in patients with recurrent herpes labialis have the greatest severity around this time. Treatment with the M. officinalis cream resulted in significantly lower scores of symptom severity compared to placebo. The authors report that the M. officinalis cream resulted in a shortened healing time, decreased spread of virus to neighboring cells, and reduced symptoms such as itching, burning, swelling and erythema. Additionally, it is speculated that the M. officinalis cream may elongate the asymptomatic stage in individuals with recurrent herpes labialis.

Furthermore, the efficacy of Echinacea purpurea at reducing the frequency and severity of herpes genitalis was studied by Vonau et al.[194] using a placebo-controlled, double blind, crossover trial with 50 participants. The strain of HSV present in each participant was confirmed and found to be a mix of HSV-1 and HSV-2. The extract used was a marketed compound called Echinaforce, made of the plant and root of E. purpurea. Treatment with placebo or 800 mg bid orally of the extract was given for 6 months followed by 6 months of treatment with the opposite arm. There was no significant difference found between E. purpurea or placebo at preventing or reducing the frequency of recurrence of herpes genitalis. Additionally, there were no significant differences between pain scores, duration of infection, or neutrophil count between placebo or extract.

Clewell et al.[184] explored the effect of a topical formulation of Hypericum perforatum and copper sulfate pentahydrate compared to that of topical 5% acyclovir on HSV lesions. The formulation is marketed as Dynamiclear and aims to treat HSV lesions with a one-time application. The authors explain that Dynamiclear would be a more cost-effective treatment compared to the topical 5% acyclovir as the latter requires multiple applications. A total of 149 participants with active HSV-1 or HSV-2 lesions between the ages of 18-55 were randomized to receive either a single treatment of Dynamiclear or topical 5% acyclovir for 14 days. Participants reported their symptoms and physical exams were evaluated on days 1, 2, 3, 8, and 14. The Dynamiclear group had lower reports of burning or stinging sensation and decreased ratings of acute pain, erythema, and vesiculation compared to the acyclovir group. In fact, the acyclovir group was 4 times more likely to have vesiculation than those treated with Dynamiclear. It is important to note that the Dynamiclear treatment was not associated with any adverse events or toxicity.

The therapeutic antiviral effects of 2 herbal combinations were assessed by Hijikata et al.[185,186] in 2 trials. In the first trial, Hijikata et al.[185] prepared an aqueous extract to contain a daily dose of 4 g Coicis semen, 2 g Elfuinga applanata, 4 g Ganoderma lucidum, 2 g Terminalia chebulae, 2 g Trapa natans, and 2 g Wisteria floribunda. One male and 4 females, aged 31-60 years, with recurrent herpes labialis were treated orally with the extract, either taking a single, double, or triple daily dose. For all 5 patients, use of the herbal combination extract significantly reduced the healing time of herpes lesions compared to previous outbreaks when no treatment was used. Lesions crusted and resolved within a few days compared to resolving within approximately 2 weeks with no treatment. In addition, pain associated with outbreaks was significantly reduced for one patient with use of the extract.

In the second trial, Hijikata et al.[186] prepared an aqueous extract that was subsequently dried to a powder to contain a daily dose of 2 g Wisteria floribunda, 2 g Trapa natans, 2 g Terminalia chebulae, 4 g Coicis lachryma-jobi, 4 g Ganoderma lucidum, and 2 g Elfuinga applanata. Study participants had recurrent HSV infections for at least 1 year and had been treated by external medical professionals without improvement. The study recruited 15 patients with herpes genitalis and 13 patients with herpes labialis. Patients were instructed to take a double daily dose of the herbal combination on days one and 2 of infection and a single daily dose for subsequent days until complete relief. At baseline, the mean time to relief from infection was 10.9 ± 6.3 days for herpes genitalis and 7.8 ± 4.3 days for herpes labialis. After treatment with the herbal combination, the mean time to relief was reduced to 4.9 ± 1.3 days for herpes genitalis and 4.0 ± 1.1 days for herpes labialis. Both reductions were statistically significant. The authors concluded that treatment with this herbal combination provided fast and effective relief from recurrent HSV infections.

Lastly, Saller et al.[187] conducted a double-blind, randomized, comparative trial to assess the efficacy of 2 herbal creams on herpes labialis lesions. The first cream contained

sage extract from leaves of Salvia officinalis, and the second cream contained sage extract and rhubarb extract from the roots of Rheum palmatum and Rheum officinale. The reference treatment was Zovirax, which contained acyclovir (50 mg/g). All subjects were provided a topical treatment. A total of 145 subjects participated in the trial and were split into 3 treatment groups so that 64 received the rhubarb-sage cream, 40 received the sage cream, and 41 received the Zovirax cream. Participants' HSV status was assessed by the amount of swelling present and pain associated with lesions. Mean time to healing for the sage, sage-rhubarb, and Zovirax cream groups was 7.1, 6.7, and 6.5 days, respectively, and mean time to crust formation was 7.8, 7.2, and 6.3 days, respectively. Mean time to healing and crust formation were not statistically different between treatments. Additionally, the participants who used the rhubarb-sage extract cream reported less pain than those using the sage extract cream. This study provides a basis of knowledge that herbal remedies, specifically the combination of rhubarb and sage, may be as effective as current pharmacological topical therapies for the treatment of HSV lesions.

Identified Constituents

A wide variety of phytochemicals and constituents can be found within medicinal plants. Several studies within this review have identified constituents found in their plants of interest. Compounds isolated from multiple antiviral plants included phenolic acids[56,90,108,136-138,174,180] such as cichoric acid,[79,80] gallic acid,[92,138,150,180] rosmarinic acid,[63,120,121,123,124,126,153,173,182,187] caffeic acid,[94,109,120,121,124,126,153,182] catechinic acid,[72] coumaric acid,[94,124,153] ferulic acid,[94,120] carnosic acid,[153] chlorogenic acid,[109,162,182] atomaric acid,[69] and caffeoyl acids.[108] Flavonoids were identified,[24,41,56,70,82,90,95,97,101,107,108,121,126,132,136-138,148,150,160,163,174,180] specifically luteolin,[44,48, 94,121,126,134,153,164,172] quercetin,[57,83,102,106,172] quercitrin,[106] apigenin,[44,121,126,131,153] rutin,[57, 109,138] myricetin,[57] and kaempferol.[102] Other constituents included alkaloids,[56,24,41,49,95,107,129,132, 135,158,159] tannins,[29, 56,70,75,82,92, 95, 97, 138,141, 148,165,150,174,180,190] xanthones,[66,82] saponins,[41,95,100,101,108,109,129,174] sesquiterpenes,[78] halogenated sesquiterpenes,[69] sesquiterpene lactones,[162,163] monoterpenes,[131,65,166] triterpenoids,[24,41,56,57,66,70,95,96,131,132, 158,150] sterols,[24,41,56,96,132,166,180] phenols,[78] bromophenols,[81] coumarins,[41,136] lignans,[42,112] aldehydes,[105,104,166] alkanes,[78] polysaccharides,[30,49, 55,68,78,83,100,158,171] carbohydrates,[112] protein,[112] ketones,[82,105] triacylglycerols,[69] fatty acids,[69,78] carboxylic acids,[39] hydroxyanthracene.[187] Lastly, constituents identified in antiviral essential oils were bicyclogermacrene,[25] germacrene-D,[25] spathulenol,[25] β-caryophyllene,[25] piperitenone,[25] α–copaene,[25] eugenol,[119] 1,8-cineole,[119] 1,8-cineole,[119] terpinen-4-ol,[119] flavesone,[113] leptospermone,[113] citral a,[122] caryophyllen,[122] citral b,[122] citronellal,[122] β-cubeben,[122] menthylheptenon,[122] caryophyllenoxid,[122] and ocimen.[122]

Limitations

This review has several limitations. First of all, the use of different outcome measures among the studies reviewed poses a challenge to compare results. Several studies calculated SI values of plant extracts against herpes simplex virus infections, while others only reported their CC_{50}, TD_{50}, IC_{50}, and/or ED_{50} values. Furthermore, some of the studies reviewed reported none of these outcome measures. Reporting the CC_{50} or TD_{50} with the IC_{50} or ED_{50} is important to be able to fully evaluate the therapeutic potential of an extract and compare potential between extracts. For example, if an extract has a high ED_{50}, but a low CC_{50}, it will be cytotoxic to cells before it shows significant antiviral activity, and this will correspond to a low SI. On the other hand, a low ED_{50} with a high CC_{50} would give an extract a high safety profile, as it would elicit antiviral effects before any signs of cytotoxicity, which would correspond to a high SI. In some studies, missing SI values could be calculated, but in others, this was not possible if only the CC_{50}/TD_{50} or IC_{50}/ED_{50} was reported. In these cases, efficacy is open to interpretation.

Secondly, SI ranges or cut-off values that represent mild, moderate, or strong antiviral activity varied among studies. A possible reason for this discrepancy could be the dose of virus used in the studies. For example, an extract demonstrating an SI of 20 may be considered as having strong antiviral activity by one group of authors, while another group may classify it as having moderate effects. This, paired with varying doses of HSV-1 and HSV-2 virions administered to cells, makes it difficult to compare the absolute antiviral effects of extracts.

Thirdly, comparing the absolute antiviral effect of botanicals between studies is challenging because extracts were prepared with different solvents as well as type and amount of plant material. The antiviral activity of a plant is due to its active constituents. Without knowing what these constituents are, their polarity, and which part of the plant they are contained in, it is difficult to determine the ideal method of extraction. As such, plants which have antiviral potential may be found to not possess effects if its extract was prepared with a solvent that was not ideal to extract its active constituents.

Lastly, the majority of the studies conducted on botanicals were done in vitro. While many show promising anti-HSV activity, the results cannot be extrapolated to how the botanicals would perform clinically. The low number of human clinical trials limits conclusions that can be made on the efficacy of various botanicals on HSV prevention and treatment. Therefore, more in vivo research is needed in the form of randomized clinical trials.

Conclusion

Herpes simplex virus affects many individuals around the world as it is easily transmitted from person-to-person due to viral shedding in the absence of symptoms.[1] While HSV infection is not fatal, it is recurrent and as such it can negatively affect an individual's quality of life. There is no cure for HSV,

therefore management strategies are important to prevent and treat HSV outbreaks. The efficacy of current treatments has begun to falter, as seen by emerging viral resistance to nucleoside analogues.[12] Research has studied the ability of various botanicals to fight HSV infections and possibly uncover higher efficacy treatments than currently utilized. HSV may be less likely to develop resistance to botanicals because their various active constituents have various mechanisms of action, for example by targeting viral attachment, penetration, DNA replication, gene expression, or by directly inactivating virions. This gives botanicals a potential benefit over the conventional therapy for HSV, acyclovir, which specifically targets viral replication. Additionally, results suggest that combination therapies have the potential to elicit greater benefits over single therapies. Future research should include human clinical trials that study the combination of botanicals that demonstrate anti-HSV activity in vitro.

Authors' Note

AG, LB, and CP designed the research; AG and LB conducted this research; AG and LB wrote the first draft of the manuscript and all authors contributed to revisions and approved the final version of the manuscript. No ethical approval was required or obtained for this research.

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