SIMPLIX Ingredient Research Summary

There is ample evidence suggesting that diet and nutrition play significant roles in modulating risk factors associated with HSV infections. In recent years, there has been an increasing emphasis on the impact of micronutrients in respiratory health, particularly concerning HSV viruses. To explore this, we conducted a comprehensive review of existing literature up until 2024, aiming to elucidate the effects of micronutrients, minerals, and vitamins on the course of HSV infections. Our review encompassed studies primarily focused on evaluating dietary supplements. Various natural compounds and micronutrients have shown potential in bolstering immunity and the body's reponse to HSV infections at different stages, from initial exposure to the development of symptoms. Healthcare providers should be well-versed in this research and incorporate these findings into their counseling sessions with patients. Furthermore, there is a need for further meticulously designed investigations to provide precise guidelines for clinical practice in the prevention and management of HSV infections.

Ingredient	Data for Ingredient	Reference		
Lysine	A clinical study tested the effectiveness of oral L-lysine monohydrochloride in preventing and treating recurrent herpes simplex (HSV) infection. Participants took 1000mg L-lysine tablets three times daily for six months, while others received a placebo. The L-lysine group experienced an average of 2.4 fewer HSV infections, with reduced severity of symptoms and faster healing times compared to the placebo group.	https://pubmed.ncbi.nlm.nih.gov/3115841/		
	A study surveyed 1543 subjects over six months to evaluate lysine supplementation's impact on herpes infection. On average, subjects consumed 936 mg of lysine daily. Results indicated that 84% reported lysine prevented recurrence or reduced infection frequency. Symptoms were described as severe or intolerable by 79% without lysine, dropping to 8% with lysine. Without lysine, 90% reported healing in six to 15 days, whereas with lysine, 83% said lesions healed in five days or less. Overall, 88% considered lysine supplementation effective for treating herpes infection.	https://academic.oup.com/jac/article-abstract/12/5/489/827083?login=false		
	The study investigated long-term lysine supplementation for recurrent herpes simplex labialis. Twenty-six volunteers received 1,000 mg of lysine daily for 12 months. Results showed fewer lesions in the lysine group compared to controls. Serum lysine levels above 165 nmol/ml correlated with reduced recurrence rates	https://www.sciencedirect.com/science/article/abs/pii/0030422084900306		
	This study investigated the clinical effects of 630 mg of L-lysine monohydrochloride, a natural viral inhibitor, on recurrent aphthous ulcer (RAU) etiology, potentially linked to herpes simplex virus (HSV). Thirty patients were divided into placebo and lysine treatment groups. After two months of therapy, significant reductions in ulcer number and recurrence were observed in the lysine group.	https://www.researchgate.net/profile/Cafer_Eroglu/publication/267202860_Clinical_success_of_lysine_in_association_with_serumal_and_salivary_presence_of_HSV-1_in_patients_with_recurrent_aphthous_ulceration/links/54b244b30cf28ebe92e19525.pdf		
	A study involving 45 patients with recurrent herpes infections revealed that daily lysine doses ranging from 312 to 1200 mg of lysine accelerated recovery and reduced recurrence rates. Tissue culture studies indicated that lysine dominance over arginine inhibited viral replication and reduced cytopathogenicity of herpes simplex virus, while an arginine-dominant environment enhanced viral replication.	https://karger.com/drm/article-abstract/156/5/257/344358/A-Multicentered-Study-of-Lysine-Therapy-in-Herpes		
	Results showed limited effectiveness in preventing herpes simplex lesions at doses below 1 g/day, unless combined with low-arginine diets. Higher doses (>3 g/day) improved patients' subjective experience of the disease.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6419779/#:~:text=Results,subjective%20experience%20of%20the%20disease.		
	In a clinical study involving forty-one patients, oral ingestion of 1,248 mg of L-Lysine monohydrochloride per day demonstrated a reduction in the recurrence rate of herpes simplex attacks and decrease the severity of symptoms during recurrences.	https://pubmed.ncbi.nlm.nih.gov/6435961/		
	In vitro tests examined the anti-HSV-1 activity of Andrographolide (AD), 14-deoxyandrographolide (DAD), and 3,19-isopropylideneandrographolide (IPAD) isolated from Andrographis paniculata. IPAD showed significant inhibition of HSV-1 replication, particularly in the early stage, confirmed by gene expression analysis. This suggests IPAD's potential as an anti-HSV-1 agent.	https://pubmed.ncbi.nlm.nih.gov/21486208/		

Andrographis	An analogue of andrographolide, 3,19-isopropylideneandrographolide (IPAD), exhibits inhibitory effects on wild-type herpes simplex virus serotype 1 (HSV-1) replication. Non-cytotoxic concentrations of IPAD (20.50 μM) completely inhibit cytopathic effect (CPE) formation induced by HSV wild types and HSV-1 DRs post-viral entry into cells, with anti-HSV activities including inhibition of viral DNA and protein synthesis.	https://link.springer.com/article/10.1186/s12906-015-0591-x		
	Andrographis paniculata extracts showed antiviral activity against influenza A (H3N2) and herpes simplex virus-1 (HSV-1).	https://www.nature.com/articles/s41598-023-46249-y		
	A diterpenoid lactone compound, 3,19-isopropylideneandrographolide (IPAD), derived from Andrographis paniculata (Burm. f.) Nees, has demonstrated inhibitory effects on herpes simplex virus type 1 (HSV-1) infection at the post-entry step.	https://www.sciencedirect.com/science/article/abs/pii/S0166354216301760		
	The study explored anti-HSV-1 activities of andrographolide and its analogues. Three analogues showed significant pre-infection activity, while 3,19-isopropylideneandrographolide exhibited absolute inhibition of HSV-1 replication post-infection. Andrographolide displayed moderate inhibitory activities of 34.48% and 56.90% for pre- and post-infection.	https://pubmed.ncbi.nlm.nih.gov/21259187/		
Zinc	Twenty patients with frequent episodes received systemic zinc sulphate (22.5mg bid) treatment for specified months over a year. Results revealed a notable decrease in herpetic lesions to less than four episodes annually, each lasting less than seven days on average (with an average of 3 episodes and duration of 5.7 days per episode). These findings suggest that systemic zinc sulphate may effectively reduce both the frequency and duration of recurrent herpes labialis episodes.	https://pubmed.ncbi.nlm.nih.gov/16011612/		
	Zinc sulfate, when added to the medium of herpes simplex virus-infected BSC-1 cells at concentrations of 0.1 mM and 0.2 mM, exhibited significant inhibitory effects on the synthesis of infectious virus progeny. At 0.1 mM, it inhibited virus synthesis by 95 to 96%, while at 0.2 mM, inhibition reached 99.8%.	https://journals.asm.org/doi/abs/10.1128/aac.8.3.377		
	Clinical isolates of herpes simplex virus (HSV) were tested for inactivation using zinc salts in a standard plaque assay. Treatment with 50 mM zinc gluconate for 2 hours resulted in >98% inactivation of seven out of ten isolates (five HSV-1 and five HSV-2). Zinc lactate treatment showed >97% inactivation for nine isolates. Concentration dependency was observed, with 100% inactivation for HSV-1 at 50 mM zinc gluconate or zinc lactate, and 30% inactivation for HSV-2 at the same concentration of zinc gluconate. Zinc lactate at 50 mM showed over 92% inactivation for HSV-2. The pH range of 6.1 to 7.6 did not affect zinc salt inactivation, showing 99.7 to 100% efficacy with a 2-hour treatment of 50 mM zinc salt.	https://journals.asm.org/doi/full/10.1128/jcm.38.5.1758-1762.2000		
	This report describes the use of a combined traditional cell culture and quantitative real-time PCR method to assess the antiviral effect of zinc sulfate (ZnSO4) on herpes simplex virus (HSV)-infected Vero cells. Results indicate that treatment with 0.3 mM ZnSO4 significantly inhibits virus replication, with at least a 68-fold reduction in virus progeny (MOI 0.001). Furthermore, the IC50 value suggests that the most effective concentration of ZnSO4 is 0.23 mM.	https://link.springer.com/article/10.1007/s12011-019-01728-0		
	HSV DNA polymerase, isolated from infected cells, was almost completely inhibited by 0.1 mM zinc acetate in vitro. Conversely, cellular DNA polymerases α and β remained resistant to 0.3 mM zinc acetate. This indicates a selective inhibitory effect of zinc ions on the viral DNA polymerase, potentially explaining the inhibition of HSV replication.	https://pubmed.ncbi.nlm.nih.gov/203099/		
	Plaque reduction assays investigated the impact of ascorbic acid supplementation on herpes simplex viral diseases. Ascorbic acid showed meaningful reductions in HSV-1 infections. Specifically, treatment with 50 μM ascorbate reduced infections to 10.77% ±4.25%, and at 500 μM to 3.06%±1.62%.	https://www.koreamed.org/SearchBasic.php?RID=2001248		

Vitamin C	A water-soluble bioflavonoid-ascorbic acid complex was evaluated in treating fifty cases of recurrent herpes labialis. Dosages included 600 mg of each component administered three times daily for twenty cases, and 1,000 mg of each five times daily for another twenty. Ten cases received a lactose placebo. Treatment lasted for 3 days post-symptom recognition. The complex notably reduced vesiculation and vesicular membrane disruption, especially when initiated during the prodromal stage. Symptom remission occurred in an average of 4.2 +/- 1.7 days with the 600 mg dosage. No adverse reactions were reported.	https://pubmed.ncbi.nlm.nih.gov/339141/		
	Suspensions of herpes simplex virus types 1 and 2, cytomegalovirus, and parainfluenzavirus type 2 were effectively inactivated within 24 hours when treated with 1 mg/ml (5.05 mM) of copper-catalyzed sodium ascorbate at 37°C.	https://journals.asm.org/doi/abs/10.1128/jcm.24.4.527-531.1986		
	In a clinical pilot study, 48 healthy patients with active HSV-1 lesions (age: 4-61 years; mean: 31+/-16 years) received 1 mg of lignin-ascorbic acid tablet or solution orally three times daily for a month. Patients starting treatment within 48 hours of symptom onset did not develop characteristic lesions, while those starting later experienced shorter cold sore durations and reduced symptoms. The majority reported decreased symptom severity and recurrence episodes after treatment/	https://pubmed.ncbi.nlm.nih.gov/20023248/		
Melissa officinalis	Melissa officinalis extract directly interacted with resistant viral particles, with low IC50 values (0.13 and 0.23 µg/mL) and high selectivity indices (2692 and 1522). Both extract and rosmarinic acid inhibited HSV-1 attachment. The extract also hindered virus penetration by 80% and 96% for sensitive and resistant strains, respectively.	https://pubmed.ncbi.nlm.nih.gov/24817544/		
	A systematic review showcases that Melissa was more effective than Acyclovir and placebo in reducing the lesion pain and size of recurrent herpes infection.	https://publish.kne-publishing.com/index.php/jids/article/view/6886		
	This study examined the antiviral activity of an aqueous extract of Melissa officinalis and phenolic compounds (caffeic acid, p-coumaric acid, and rosmarinic acid) against HSV-1 in vitro. While no antiviral effect was observed when drugs were added to HSV-1-infected cells, the Melissa extract showed potent virucidal activity against HSV-1, even at a low concentration of 1.5 µg/ml, compared to 100 times higher concentrations required for phenolic compounds. Additionally, both the Melissa extract and rosmarinic acid inhibited HSV-1 attachment to host cells in a dose-dependent manner.	https://karger.com/che/article-abstract/58/1/70/67076/Melissa-officinalis-Extract-Inhibits-Attachment-of?redirectedFrom=fulltext		
	Aqueous extracts from various plants of the Lamiaceae family, including lemon balm (Melissa officinalis), peppermint (Mentha x piperita), prunella (Prunella vulgaris), rosemary (Rosmarinus officinalis), sage (Salvia officinalis), and thyme (Thymus vulgaris), were investigated for their antiviral activity against Herpes simplex virus (HSV). In vitro tests on RC-37 cells demonstrated high antiviral activity against HSV-1, HSV-2, and an acyclovir-resistant strain of HSV-1 (ACVres). The extracts significantly reduced plaque formation by over 90% for HSV-1 and HSV-2 and over 85% for ACVres at non-cytotoxic concentrations.	https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-2006-951719		
	Lemon balm hydroalcoholic extract was found to be non-toxic to VERO cells up to a concentration of 800 µg/ml and inhibited the growth and development of HSV-1 in a dose-dependent manner in VERO cells. Treatment during and after virus infection showed more significant antiviral effects than pre-infection treatment.	https://www.sid.ir/paper/315606/en		
	The study investigated the impact of Melissa officinalis L. volatile oil components on Herpes simplex virus type 2 (HSV-2) replication in HEp-2 cells. Up to 100 µg/ml, the volatile oil showed no toxicity to HEp-2 cells, but toxicity was observed at higher concentrations. Non-toxic concentrations exhibited antiviral activity against HSV-2, indicating the presence of an anti-HSV-2 substance in the M. officinalis L. extract.	https://www.sciencedirect.com/science/article/abs/pii/S094471130400100X		

	In this study, Melissa officinalis L. essential oil (MEO) was loaded into glycerosomes (MEO-GS) for anti-herpetic activity against HSV type 1. MEO-GS exhibited a high encapsulation efficiency of approximately 63% for citral and 76% for β-caryophyllene. The release of MEO from glycerosomes was less than 10% within 24 hours. Furthermore, MEO-GS demonstrated potent anti-HSV type 1 activity in vitro without causing cytotoxic effects, suggesting their potential as a stable and effective anti-herpetic formulation.	https://www.mdpi.com/1420-3049/25/14/3111		
	Melissa officinalis, traditionally used for various ailments, including Herpes simplex lesions, was tested against HSV-2 in vitro. The extract reduced HSV-2 cytopathic effect at non-toxic concentrations (0.025-1 mg/mL), with maximum inhibition of 60% at 0.5 mg/mL.	https://pubmed.ncbi.nlm.nih.gov/19023806/		
Sulfated Polysaccharides	Protein-bound polysaccharides from Ganoderma lucidum were tested for antiviral activity against HSV-1 and HSV-2. The acidic polysaccharide showed stronger effects than the neutral one, with an EC50 of 300–520 μg/ml, demonstrating 50% inhibition, directly targeting the viruses by inhibiting attachment and penetration into cells.	https://www.sciencedirect.com/science/article/abs/pii/S037887410000266X		
	The study investigated the anti-HSV activity of a sulfated derivative (FR-S) of β-D-glucan from Agaricus brasiliensis. FR-S significantly reduced HSV-1 and HSV-2 attachment (EC50 = 0.32 μg/ml and 0.10 μg/ml, respectively), possibly interacting with glycoprotein gC. It also inhibited viral penetration more effectively than heparin and reduced cell-to-cell spread of both HSV types. Synergy was observed with acyclovir.	https://karger.com/int/article/57/6/375/181960/Antiherpetic-Mechanism-of-a-Sulfated-Derivative-of		
	Sulfated polysaccharides, such as MI-S derived from Agaricus brasiliensis mycelia demonstrated significant inhibitory activity against HSV-1 (KOS and acyclovir-resistant 29R strains) and HSV-2 strain 333, with high selectivity indices. Mechanistic studies revealed that MI-S inhibited viral attachment, penetration, and cell-to-cell spread, as well as reducing the expression of key HSV proteins. It also exhibited synergistic effects with acyclovir.	https://pubmed.ncbi.nlm.nih.gov/21787804/		
	Water and methanol extracts from Lentinus edodes, Boletus edulis, and Pleurotus ostreatus were tested for antiviral properties against herpes simplex virus type 1 (HSV-1). Water extracts showed significant inhibition of virus infection, with pre-treatment inhibiting 60% and addition during adsorption up to 80%. In vitro virus replication was also markedly inhibited, with IC50 values ranging from 26.69 mg·ml-1 to 35.12 mg·ml-1. Antiviral activity correlated with polysaccharide fractions, particularly β-glucans.	https://openurl.ebsco.com/EPDB%3Agcd%3A13%3A21148461/detailv2?sid=ebsco%3Aplink%3Ascholar&id=ebsco%3Agcd%3A84015211&crl=c		
	The study explored the antiviral potential of polysaccharides derived from Agaricus brasiliensis, a traditional medicinal mushroom. Polysaccharide (PLS), carboxymethylated (CPLS), and sulfated (SPLS) derivatives, along with fractions (F1–F3) from PLS, were tested against herpes simplex virus and bovine herpesvirus in HEp-2 cell cultures. PLS, SPLS, and F3 demonstrated dose-dependent inhibition of both virus strains, while F1, F2, and CPLS showed no significant effect even at higher concentrations.	https://www.sciencedirect.com/science/article/pii/S0141813012003832		
	In murine models of ocular, cutaneous, and genital HSV infections, MI-S (A sulfated polysacchride derivative of Agaricus) was administered topically or orally. Oral MI-S reduced disease severity in cutaneously infected mice and decreased vaginal disease scores, viral titers, and mortality in genital HSV-2 infections. MI-S showed potential as an oral agent for reducing HSV lesions and as a microbicide to prevent sexual transmission of HSV-2.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3716167/		

Shiitake	Water and methanol extracts from Lentinus edodes, Boletus edulis, and Pleurotus ostreatus were tested for antiviral properties against herpes simplex virus type 1 (HSV-1). Water extracts showed significant inhibition of virus infection, with pre-treatment inhibiting 60% and addition during adsorption up to 80%. In vitro virus replication was also markedly inhibited, with IC50 values ranging from 26.69 mg·ml-1 to 35.12 mg·ml-1. Antiviral activity correlated with polysaccharide fractions, particularly β-glucans.	https://openurl.ebsco.com/EPDB%3Agcd%3A13%3A21148461/detailv2?sid=ebsco%3Aplink%3Ascholar&id=ebsco%3Agcd%3A84015211&crl=c		
	The study evaluated the toxicity and antiviral effects of aqueous extracts from several higher mushrooms, including Lentinula edodes (shiitake), Pleurotus ostreatus (oyster), Inonotus obliquus (chaga), and Hydnellum compactum (compact tooth). Intraperitoneal administration of the extracts at doses of 0.4-2 mg per mouse prior to contamination by a single LD50 of Herpes simplex type 2 resulted in 100% survival for Lentinula edodes and Pleurotus ostreatus extracts and 90% survival for Inonotus obliquus and Hydnellum compactum extracts.	https://pubmed.ncbi.nlm.nih.gov/24738237/		
	Lentinula edodes showed activity against herpes simplex-II (HSV-2), while the extracts displayed no toxicity towards normal human peripheral blood mononuclear cells (PBMCs) but exhibited moderate toxicity against various cancer cell lines.	https://www.mdpi.com/1420-3049/26/15/4623		
	The extract JLS-S001 from Lentinus edodes mycelia effectively inhibited the release of infectious herpes simplex virus type 1 (HSV-1) from African green monkey kidney cells. This inhibition was not attributed to JLS-S001's impact on HSV-1 adsorption or penetration into the cells, as it did not affect virus-specific nucleocapsid protein expression or nucleocapsid presence within cell nuclei. However, JLS-S001 treatment reduced the expression of various HSV-1 glycoproteins, indicating its interference with late stages of virus replication, possibly during nucleocapsid assembly, budding, and egress from the cells.	https://pubmed.ncbi.nlm.nih.gov/8387258/		
	The study investigated the effects of GFS, a preparation of Tasmanian Undaria pinnatifida, on Herpetic infections and its in vitro activity. Patients with active or latent Herpetic infections were monitored after ingesting GFS. Results showed increased healing rates in active infections and asymptomatic status in latent infections. In vitro, GFS inhibited Herpes viruses and stimulated human T cells.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC139995/		
	Extracts from marine algae were tested against HSV-1 and HSV-2, showing good activity when added early in infection. Plaque reduction assays revealed EC(50) values ranging from 2.5-3.6 µg/ml for HSV-1 and 0.7-6.6 µg/ml for HSV-2. These extracts had potent virucidal activity at low concentrations and showed no significant toxicity.	https://pubmed.ncbi.nlm.nih.gov/19576248/		
	The fucoidan demonstrated strong antiviral effects against both herpes simplex virus type 1 (HSV-1) and HSV-2.	https://pubmed.ncbi.nlm.nih.gov/15340195/		
	The antiviral activity of galactofucan sulfate (GFS), derived from Undaria pinnatifida, was assessed against 32 clinical strains of herpes simplex virus (HSV). GFS demonstrated significant potency against both HSV-1 and HSV-2, with a median IC(50) of 32 micro g/mL for HSV-1 and 0.5 micro g/mL for HSV-2. Particularly, GFS was notably more effective against HSV-2 strains. Mechanistically, GFS inhibited viral binding and entry into host cells. Additionally, GFS showed no cytotoxicity at concentrations exceeding 4.0 mg/mL.	https://pubmed.ncbi.nlm.nih.gov/15305315/		
	In a murine model of intraperitoneal HSV-1 infection, immediate administration of 1C3 (derived from Gigartina skottsbergii) at 30 mg/kg resulted in 87.5% animal survival ($p < 0.005$), with a delayed mean day of death in non-surviving mice. Administering multiple doses within 48 hours post-infection didn't improve survival. However, significant protection (40% survival, $p < 0.05$) was observed when virus and compound were injected via different routes. No toxicity was recorded.	https://pubmed.ncbi.nlm.nih.gov/16491446/		

Seaweed	Lambda-carrageenan 1T1, kappa/iota-carrageenan 1C1, and mu/nu-type 1C3 from Gigartina skottsbergii have potent antiviral activity against HSV-1 and HSV-2, with IC50 values ranging from 0.4 to 3.3 microg/ml and no cytotoxic effects. They mainly inhibit virus adsorption, with 1T1 showing virucidal action, while 1C1 and 1C3 interfere with virus-cell interaction.	https://pubmed.ncbi.nlm.nih.gov/10517311/		
	The study evaluated the protective effect of 1T1, a lambda-carrageenan from Gigartina skottsbergii, in a murine model of HSV-2 genital infection. Pre-infection treatment with 1T1 protected 9 out of 10 mice from HSV-2-induced lesions and mortality, compared to 10% survival in control mice. 1T1 also completely blocked virus shedding in vaginal secretions. Reinforcing pre-treatment with a second dose 2 hours after infection resulted in total protection, even with administration 60 minutes before infection.	https://pubmed.ncbi.nlm.nih.gov/15498610/		
	The study investigated the antiviral potential of extracts from two brown macroalgae, Macrocystis pyrifera and Durvillaea antarctica, against herpes simplex viruses (HSV) types 1 and 2. Both extracts showed activity against acyclovir-sensitive and resistant HSV strains. Protein components in the extracts significantly contributed to their antiviral activity. In an animal model of HSV-1 skin infection, the extracts reduced disease severity and lesion duration more effectively than acyclovir and mock treatments, with D. antarctica extract performing best.	https://www.frontiersin.org/journals/microbiology/articles/10.3389/fmicb.2020.02006/full		
	The study evaluated organic extracts from 36 species of marine algae from the Brazilian coast for their anti-HSV-1 and anti-HSV-2 activity resistant to Acyclovir. Most extracts exhibited 86.1% activity against HSV-1 and 55.5% activity against HSV-2.	https://www.scielo.br/j/rbfar/a/ZjFMzwSKVbtjRLp8PHdDc8L/?lang=en		
	Hot water extracts from six brown seaweed species from Hong Kong were evaluated for their antiviral properties against herpes simplex virus types 1 and 2 (HSV-1 and HSV-2). The extracts showed significant inhibition of HSV-1 and HSV-2 with low cytotoxicity. Particularly, extracts from Hydroclathrus clathratus and Lobophora variegata demonstrated potent anti-HSV activity compared to the others.	https://link.springer.com/article/10.1631/jzus.B0820154		
	This study assessed seven modified polysaccharides from Enteromorpha compressa against herpes simplex virus (HSV). At 100 µg/ml, SU1F1 achieved 100% viral inhibition until 4 hours post-treatment.	https://www.sciencedirect.com/science/article/abs/pii/S0141813016316294		
	Polysaccharides from four seaweed species were evaluated for antiviral activity against Herpes simplex virus type 1 (HSV-1). Polysaccharides from Sargassum fluitans and Solieria filiformis showed antiviral activity with EC50 values of 42.8 µg/ml and 136.0 µg/ml, respectively, at non-cytotoxic concentrations.	https://journals.sagepub.com/doi/abs/10.1177/1934578X1701200602		
	This study investigated the subchronic toxicity and anti-HSV-1 activity of dolabelladienetriol (D1), a diterpene from Dictyota pfaffii, in rats and mice, respectively. Rats received oral D1 (15 mg/kg/day) for 50 days, showing no significant adverse effects on behavior, body weight, or blood parameters. Some liver and kidney alterations were observed, similar to those with ACV treatment, while other tissues remained unaffected. In mice, D1 showed anti-HSV-1 activity comparable to ACV.	https://www.sciencedirect.com/science/article/abs/pii/S027323001730065X		
	a methanol extract of Symphyocladia latiuscula and its fractions demonstrated antiviral activity against various types of herpes simplex virus without cytotoxicity. The major component, 2,3,6-tribromo-4,5-dihydroxybenzyl methyl ether (TDB), exhibited significant activity against HSV-1 strains. Oral administration of the MeOH extract and TDB delayed the onset of skin lesions in mice infected with HSV-1 and limited lesion development without toxicity.	https://www.jstage.jst.go.jp/article/bpb/28/12/28_12_2258/_article/-char/ja/		
	Solieria filiformis, a type of seaweed, was studied for bioactive compounds using enzyme-assisted extraction (EAE). Different protease (PRO) and carbohydrase (AMG) combinations significantly improved extraction yields. The resulting Water Soluble Enzymatic Hydrolysates (WSEHs) showed antiherpetic activity (EC50 4.5 ± 0.4 µg mL−1) and antioxidant capacity, particularly under the 2:1 PRO:AMG combination.	https://www.sciencedirect.com/science/article/abs/pii/S0141813020352223		

	The study investigated the anti-herpetic activity of sulfated polysaccharides (SPs) extracted from seaweeds collected during stranding events in France and Mexico. Semi-refined polysaccharides (sr-SPs) from Halymenia floresii exhibited strong activity against HSV-1 with an EC50 of 0.68 µg/mL and a selectivity index (SI) of 1470, without cytotoxicity. The sr-SPs demonstrated significant antiviral activity during viral adsorption assays, with an EC50 of 0.38 µg/mL.	https://www.mdpi.com/1660-3397/20/2/116		
	Oral fucoidan administration protected mice from HSV-1 infection, increased macrophage and B cell activity, and enhanced NK and CTL responses. These findings suggest that oral fucoidan intake may provide protective effects against HSV-1 by inhibiting viral replication and boosting immune responses.	https://pubmed.ncbi.nlm.nih.gov/18068106/		
Glycyrrhiza	Animal studies mentioned in this review showed reduced mortality and viral activity in herpes simplex virus encephalitis	https://pubmed.ncbi.nlm.nih.gov/17886224/		
	Glycyrrhizic acid ninhibits the growth and cytopathology of various DNA and RNA viruses without affecting cell activity or replication. Furthermore, glycyrrhizic acid irreversibly inactivates herpes simplex virus particles.	https://pubmed.ncbi.nlm.nih.gov/233133/		
	This study investigated glycyrrhizin's potential to disrupt cellular adhesion during herpes simplex virus (HSV) infection. Using rat cerebral capillary vessel endothelial cells (CCECs) and polymorphonuclear leukocytes (PMN), researchers found that glycyrrhizin significantly reduced adhesion force and stress between CCEC and PMN, suggesting a potential role in mitigating inflammatory responses in HSV infection.	https://pubmed.ncbi.nlm.nih.gov/21874590/		
	This study investigated the impact of glycyrrhizin (GR) from licorice root extract on mice with herpetic encephalitis induced by herpes simplex virus 1 (HSV-1). Administering GR intraperitoneally increased survival rates by approximately 2.5 times and reduced HSV-1 replication in the brain to 45.6% of the control level.	https://pubmed.ncbi.nlm.nih.gov/11394578/		
	The antiviral properties of GPS (glycyrrhiza polsacchrides) were examined in vitro using L-929 and FL cell lines infected with seven types of DNA or RNA viruses. Results indicate that GPS can inhibit the growth of VSV, AdVIII, HSV-1, or VV and suppress cytopathic effects, protecting cultured cells from virus infection.	https://pubmed.ncbi.nlm.nih.gov/2550028/		
	Glycyrrhetic acid, the sapogenol of glycyrrhizin, demonstrated 10 times superior activity compared to glycyrrhizin itself, indicating its potential role in the in vivo efficacy against HSV-1 replication.	https://pubmed.ncbi.nlm.nih.gov/16141560/		
	The study investigated the effect of glycyrrhizin (GR) on the resistance of thermally injured mice to herpes simplex virus type 1 (HSV) infection. When thermally injured mice were treated with GR, their resistance to HSV improved to levels observed in normal mice. Additionally, normal mice given GR-treated MNCs had a 95% survival rate when exposed to HSV, compared to an 80% mortality rate in those not treated with GR.	https://pubmed.ncbi.nlm.nih.gov/7721345/		
	The study aimed to assess the effectiveness of a novel combination of Lactobacillus acidophilus and Glycyrrhiza glabra root extract against Herpes simplex virus-1 (HSV-1) and Vesicular Stomatitis Virus (VSV). Results showed a significant increase in Vero cell survival and reduction in HSV-1 and VSV titers compared to untreated cells.	https://pubmed.ncbi.nlm.nih.gov/37391715/		
	The study investigated the effects of Glycyrrhiza glabra on HSV-1. Various concentrations of G. glabra extract were tested on Vero cells infected with HSV-1 at different incubation times. Significant differences were observed in efficacy between different incubation periods and treatment methods. The findings suggest potential antiviral properties of G. glabra, warranting further in vitro experiments to confirm its antiherpetic activities.	https://pubmed.ncbi.nlm.nih.gov/25368801/		
	Glycyrrhiza inhibited plaque formation for HSV-1 and HSV-2 at 0.606 mM concentration.	https://journals.lww.com/iphr/abstract/1994/26030/in_vitro_studies_on_the_effect_of_glycyrrhizin.6.aspx		

	Our study investigated glycyrrhizin's potential to disrupt cellular adhesion in HSV infection. We observed increased adhesion between rat cerebral capillary vessel endothelial cells (CCECs) and polymorphonuclear leukocytes (PMN) during HSV infection, which glycyrrhizin significantly reduced. This suggests glycyrrhizin may mitigate HSV-induced inflammatory responses by inhibiting CCEC-PMN adhesion.	https://link.springer.com/article/10.1007/s12013-011-9271-8		
	Chemically modified glycyrrhizin compounds were tested for their impact on HIV-1 and HSV-1 replication. One compound, featuring a heteroannular diene structure at the C and D rings, matched glycyrrhizin's potency against HIV-1, fully inhibiting cytopathogenicity at 0.16mM. It also exhibited efficacy against HSV-1, with a 50% inhibitory concentration of 0.5μM.	https://www.jstage.jst.go.jp/article/cpb1958/39/1/39_1_112/_article/-char/ja/		
	Non-toxic concentrations of Glycyrrhiza glabra for Vero cells were determined. Then, its antiviral effects were assessed using TCID50 and IF methods. Results revealed that the extract hindered HSV replication primarily during the early replication cycle.	https://jmp.ir/article-1-412-en.html		
	Licorice flavonoids and polyphenols underwent quantitative structure-activity relationship analysis. The alkaline extract showed higher anti-HIV activity, while the water extract, particularly the flavonoid-rich fraction, exhibited stronger anti-HSV activity and tumor-specific cytotoxicity.	https://iv.iiarjournals.org/content/30/6/777.short		
	This review mentions glycyrrhizic acid exhibiting promising antiviral effects against human gammaherpesviruses.	https://pubmed.ncbi.nlm.nih.gov/24173639/		
B12	This study investigates the potential role of folic acid and vitamin B12 in controlling recurrent herpetic keratitis, a result of herpes simplex virus type 1 reactivation. Epigenetic regulation of virus reactivation, particularly through the Latency-Associated Transcript (LAT) region, has been previously demonstrated. The study involved 50 patients with recurrent herpetic eye disease, measuring their levels of vitamin B12 and folic acid during the acute phase of the disease. Over a one-year follow-up period, the recurrence rate of herpetic keratitis was significantly lower in patients with higher blood levels of vitamin B12 and folic acid.	https://doiserbia.nb.rs/Article.aspx?ID=0042-845019000375		
	This study examines the combined effects of Neurotropin® (NTP) and methylcobalamin (MCB) on postherpetic pain (PHP) in mice following herpes simplex virus type-1 (HSV-1) infection. Treatment with NTP and MCB from day 10–29 after infection effectively inhibited PHP, with the combined treatment showing earlier efficacy compared to individual treatments. MCB reduced ATF3 expression and increased GAP-43 and SPRR1A expression in the dorsal root ganglion (DRG), while increasing non-myelinated neurons in the lesional skin. NTP increased NTF3 mRNA levels in keratinocytes, while MCB increased NGF mRNA levels in Schwann cells. These findings suggest that combined NTP and MCB treatment could be beneficial for managing PHP, potentially due to their diverse analgesic mechanisms.	https://www.sciencedirect.com/science/article/abs/pii/S0923181124000185		

SIMPLIX Ingredient Research Summary

Ingredient	Data for Ingredient	Reference
Lysine	The study examined the effects of topical lysine therapy on cutaneous herpes simplex virus (HSV) inoculations and subsequent dorsal root ganglia (DRG) infection in guinea pigs. HSV was recovered from all inoculated sites, but lysine-treated skin remained clinically normal compared to untreated controls.	https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.1890280105
	The study assessed the effectiveness of an ointment combination of L-lysine with botanicals and other nutrients in relieving symptoms of facial and circumoral herpes. Conducted with an outcome model, involving thirty participants. By the third day, it achieved full resolution in 40% of participants, reaching 87% by the end of the sixth day, significantly shortening the normal course of the disease.	https://www.anaturalhealingcenter.com/documents/Thorne/articles/herpes10-2.pdf
Andrographis	In this study, prednisolone-treated BALB/c mice were cutaneously infected with HSV-1 KOS strain and treated with IPAD (analog of andrographolide) cream. IPAD cream significantly delayed skin lesion development, reducing the HSV DNA copy number and gD gene expression by day 5 ($P < 0.01$). No irritation was observed at the application site.	https://journals.sagepub.com/doi/full/10.1177/20402066221089724
Zinc	The study assessed the effectiveness of an ointment combination of zinc, L-lysine with botanicals and other nutrients in relieving symptoms of facial and circumoral herpes. Conducted with an outcome model, involving thirty participants. By the third day, it achieved full resolution in 40% of participants, reaching 87% by the end of the sixth day, significantly shortening the normal course of the disease.	https://www.anaturalhealingcenter.com/documents/Thorne/articles/herpes10-2.pdf
	The study evaluated topical zinc sulfate ($ZnSO_4$) for treating herpes genitalis. Patients received 1%, 2%, or 4% $ZnSO_4$ for three months. Recurrence rates were tracked for six months. Results showed lower recurrence with higher $ZnSO_4$ concentrations, notably 4% $ZnSO_4$ being most effective. Control group patients had higher recurrence rates. Overall, $ZnSO_4$ demonstrated efficacy in treating herpes genitalis, particularly at higher concentrations, with minimal side effects.	https://journals.lww.com/ijst/fulltext/2013/34010/herpes_genitalis___topical_zinc_sulfate__an.7.aspx
	Topical zinc medicated collagen sponges (ZnCS) inserted intravaginally after Herpes simplex Type 2 (HSV-2) infection in mice markedly reduced virulence, suppressing vaginitis, encephalitis, and mortality. Daily replacement of ZnCS was effective. Systemic zinc before infection didn't affect disease progression. Only topical ZnCS increased Zn levels in the genital tract. Systemic zinc reduced inflammatory cells, but topical administration prevented HSV-2 replication and systemic disease.	https://www.sciencedirect.com/science/article/abs/pii/002432057990239X
	Carraguard, despite showing safety, did not prove effective against HIV. However, it exhibited activity against HPV and HSV-2. Zinc acetate combined with Carraguard protected mice against high-dose HSV-2 challenges, resulting in 75 to 85% survival rates. These promising results support further evaluation of these gels for HIV and HSV-2 prevention.	https://journals.asm.org/doi/full/10.1128/aac.05461-11
	In vitro tests evaluated punicalagin and zinc delivery across epithelial membranes susceptible to HSV infection. Both substances permeated all membranes, with greater amounts crossing the epidermal membrane. Recovered punicalagin levels were similar across membranes. The hydrogel effectively delivered both compounds, showing potential for treating HSV infections with virucidal and anti-inflammatory effects.	https://www.sciencedirect.com/science/article/abs/pii/S0928098716303025
	This study investigated the antiviral properties of pomegranate rind extract (PRE) in combination with zinc (II) ions against Herpes simplex virus (HSV). Various zinc salts showed enhanced virucidal activity with PRE against HSV-1. Punicalagin, a compound in PRE, exhibited potent virucidal activity. However, PRE demonstrated stronger antiviral effects than punicalagin, comparable to aciclovir, even against aciclovir-resistant HSV strains. The combination of PRE and zinc (II) presents a promising topical treatment for HSV infections, including cold sores, without cytotoxic effects.	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0179291

	A modified gel containing zinc acetate (ZA) and carrageenan (CG) showed efficacy against simian-human immunodeficiency virus reverse transcriptase (SHIV-RT) and herpes simplex virus 2 (HSV-2) in animals. Macaques treated with ZA/CG had a 66% reduction in vaginal SHIV-RT infection. Moreover, 60% to 80% of mice remained uninfected after high-dose vaginal or rectal HSV-2 challenge.	https://journals.asm.org/doi/full/10.1128/aac.00796-13		
Vitamin C	This is a review of natural alternatives like lysine, vitamin C, zinc, vitamin E, adenosine monophosphate, and lemon balm which can offer safe and effective treatment options for active lesions or recurrence prevention orally or topically.	https://www.biogetica.com/wp-content/uploads/2012/12/www.anaturalhealingcenter.com_documents_Thorne_articles_HerpesSimplex.pdf		
Melissa officinalis	Two significant studies, one involving 115 patients and another placebo-controlled double-blind study with 116 patients, contributed to the evidence supporting the antiviral activity of a specially prepared dried extract from Melissa leaves (Melissa officinalis L.) against herpes simplex infections.	https://www.sciencedirect.com/science/article/abs/pii/S094471131180019X		
	Melissa officinalis essential oil was examined for its antiviral effect on HSV-1 and HSV-2. In vitro tests showed significant inhibition of both viruses, with a 50% inhibitory concentration (IC50) at high dilutions of 0.0004% for HSV-1 and 0.00008% for HSV-2. At noncytotoxic concentrations, plaque formation was markedly reduced, with 98.8% inhibition for HSV-1 and 97.2% for HSV-2. Time-on-addition assays revealed that Melissa oil inhibited viral activity before adsorption but not after penetration into host cells, indicating a direct antiviral effect.	https://www.sciencedirect.com/science/article/abs/pii/S0944711308001128		
	This double-blind randomized study compared the clinical efficacy of Melissa gel and 5% acyclovir cream in treating recurrent herpes labialis (RHL). Sixty healthy participants experiencing RHL were randomly assigned to receive either Melissa gel or acyclovir cream for seven days. Clinical parameters including lesion size, pain severity, erythema presence, and healing time were evaluated on days one, two, four, and seven. Results showed no significant differences between the two groups in lesion size, healing time, or erythema presence, except on the fourth day. However, pain severity differed significantly between the two groups on the second and fourth days. While Melissa gel effectively reduced pain severity on these days.	https://brieflands.com/articles/jjnpp-18429		
Mushroom	A peptide derived from the antiviral protein RC28 of the mushroom Rozites caperata showed strong antiviral activity against herpes simplex virus-1 (HSV-1) both in cell culture and topically in a mouse keratitis model. In Vero cells, the peptide reduced viral yields by at least 1.2 logs, while in the animal model it delayed the onset of stromal keratitis and reduced disease severity.	https://www.dl.begellhouse.com/journals/708ae68d64b17c52,336a63ca4b6b8f52,4de6a6e97d9f0d43.html		
Seaweed	sulfated galactan crude extracts and main fractions from two Brazilian red seaweeds demonstrated antiherpetic activity, with inhibitory concentration 50% (IC50) values ranging from 0.5 to 5.6 µg/ml, without causing cytotoxic effects. The galactans showed broad-spectrum antiviral activity against both HSV-1 and HSV-2, mainly by inhibiting virus adsorption. Topical treatment with sulfated galactans provided significant protection against murine vaginal infection with HSV-2.	https://www.sciencedirect.com/science/article/abs/pii/S014181300400008X		
	The study explores the antiviral effects of aqueous extracts from two brown macroalgae against herpes simplex viruses (HSV) type 1 and type 2. Both extracts show activity against HSV strains, including resistant ones. In an animal model of HSV-1 skin infection, topical application of these extracts reduce disease severity and lesion duration better than acyclovir, with Durvillaea antarctica being particularly effective.	https://www.frontiersin.org/journals/microbiology/articles/10.3389/fmicb.2020.02006/full		
	The study investigates the anti-herpetic efficacy of Canistrocarpus cervicornis extract ointment in mice. Four groups were tested: untreated, extract ointment, Acyclovir cream, and ointment base. Lesion development was monitored for 16 days post-infection. The extract and Acyclovir groups showed significantly less severe lesions than the untreated and ointment base groups. The extract did not affect body weight or biochemical parameters, suggesting low toxicity.	https://link.springer.com/article/10.1007/s10811-016-0865-9		

Glycyrrhiza	The study formulates and evaluates a gel containing extracts of herbs like Melissa, sumac, licorice, rosemary, and geranium, known for antimicrobial and antiviral properties, to shorten the recovery period of recurrent herpes labialis. Formulations incorporating these extracts were assessed for physicochemical properties, viscosity, mucoadhesive strength, and drug release. Among the formulations, F11 (carbopol 940, 1% and Na CMC, 3%), with higher viscosity and mucoadhesion and slower drug release, emerged as the most promising for treating and reducing the recovery time of recurrent labial herpes infections.	https://journals.lww.com/derj/_layouts/15/oaks.journals/downloadpdf.aspx?an=01439444-201815030-00001		