



REVIEW ON HERPES SIMPLEX VIRUS: CAUSES, AVAILABLE DRUGS AND FUTURE PROSPECTS

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ABSTRACT

Herpes simplex virus (HSV-1 and HSV-2) is one of the disease which is found all over the world. It causes cold sore or watery blisters on the skin and the mucous membrane of mouth or genitals, and they are contagious and ubiquitous. It can spread with the contact of the saliva of the infected person. After the primary infection the virus undergoes latent phase in the cell bodies of neurons which may reactivate if favorable condition is provided. At present many antiviral drugs were suggested for the treatment of disease and these have been suggested by many computational and wet lab studies. Drugs like Acyclovir and other are available in the market for the treatment of HSV but problems like drug resistance prevent them to provide an efficient and prolong treatment of the disease. In this study, an analysis of natural and chemical compounds were done which are reported to inhibit various targets (Proteins) to suppress Herpes Simplex Virus disease.

KEYWORDS: *Herpes Simplex Virus, Acyclovir, Neural latency.*



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INTRODUCTION

Herpes Simplex Virus Type 1 belongs to the family *Herpesviridae*¹, subfamily is *Alphaherpesvirinae* and genera *Simplexvirus*². It is a linear double stranded DNA virus that can infect human host naturally¹. The herpesvirus family can be divided into alpha, beta and gamma subgroups which consist of over 100 double stranded DNA viruses among which only eight herpesviruses are known to commonly infect humans³.

Viral structure

There are four components of herpes simplex virion: double stranded DNA genome (152 kb)⁴ enclosed in an icosahedral nucleocapsid surrounded by a proteinaceous tegument and a lipoprotein envelope⁵. The DNA core which is enclosed in icosahedral capsid consist of 162 capsomeres^{4,6}. Out of 11 different glycoproteins (gB, gC, gD, gE, gG, gH, gI, gJ, gK, gL, and gM) at least 8 glycoproteins are involved in envelop synthesis⁴.

Mechanism of viral entry into the host cell

There are three phases of Virus-induced membrane fusion⁷. The functions of viral glycoproteins in the fusion process (close apposition, hemifusion, and complete fusion) are characterized by the three fusion process^{7,8,9}. Four membrane glycoprotein (gC, gD, gB and gHL complex) mediates the fusion process. Mutants lacking any one of the four glycoproteins are not infectious as their replication is blocked at membrane fusion¹⁰. The current model for HSV-1 fusion is that the required glycoproteins form a fusion complex^{11,12}, where gC binds a cell surface receptor (herpesvirus entry mediator, nectin-1, or modified heparan sulfate), inducing a conformational change that leads to fusion mediated by gB and/or gHL^{12,13}. gB and gH are the most likely candidates to be involved in Phases II and III of the fusion process.

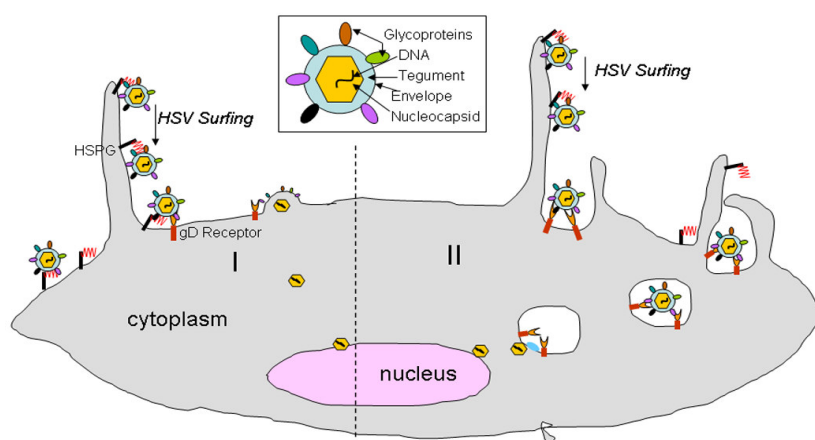


Figure 1
HSV virion and its two major modes of entry into cell¹⁴

Structural components of a typical HSV virion are shown (box) above (fig. 2)¹⁴. HSV particles initially associate with filopodia-like membrane protrusions via heparan sulfate proteoglycan (HSPG). Unidirectional transport of extracellular particles bound to filopodia (HSV surfing) then brings the particles closer to the cell body for

entry via interactions with the cellular receptors including gD receptor and possibly gB receptor. Fusion at the plasma membrane results in the release of the naked viral nucleocapsid in the cytoplasm for transport to the nucleus. Fusion at the plasma membrane is a pH-independent process¹⁰.

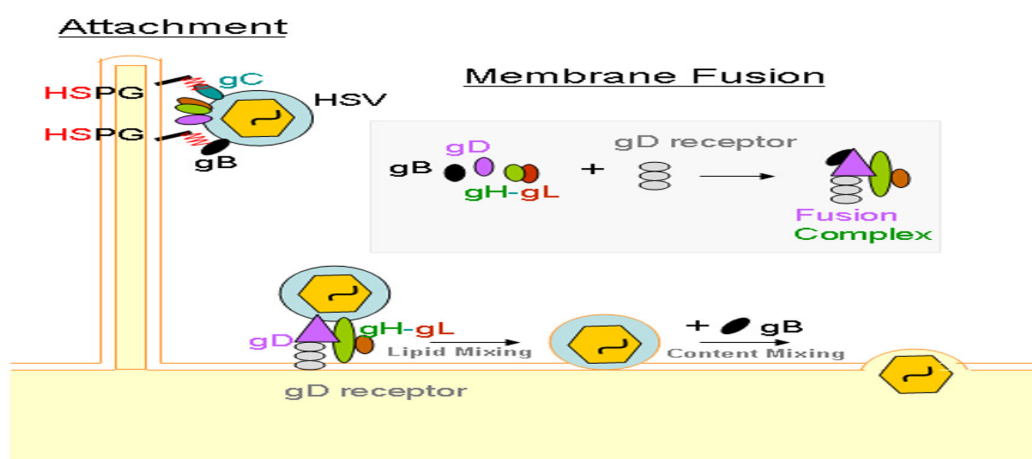


Figure 2
Molecular interactions that facilitate HSV entry¹⁴

Initial attachment to cells is mediated by interaction between heparan sulfate proteoglycans (HSPGs) with HSV glycoproteins gC and/or gB as shown in (fig 3). Membrane fusion is required for the penetration of viral nucleocapsid and the tegument into the cytoplasm. Glycoprotein gB-gH-gL together forms the fusion complex. Interaction between gB, gH-gL and a gD receptor may be sufficient to bring conformational changes within gD to trigger merging of viral and cellular membranes or lipid mixing. However, a fourth glycoprotein, gB, is also required the release of the tegument and the nucleocapsid into the cytoplasm¹⁴.

Transmission

Symptomatic disease caused by HSV-1 is typically limited to cold sores of the mouth and keratitis in the eyes. HSV-2, in contrast, is mostly responsible for genital lesions. However, both viruses are capable of causing lesions on same body sites and both can cause life-threatening diseases in immunocompromised individuals including newborns, patients with human immunodeficiency virus (HIV) or patients undergoing immunosuppressive treatment². Transmission among humans involves physical contact and often occurs during kissing (HSV-1) or sexual intercourse (HSV-2). Herpes simplex viruses can affect areas of skin exposed to contact with an infected person. An example of this is herpetic whitlow which is a herpes infection on the

fingers. This was a common disease of dental surgeons prior to the routine use of gloves when conducting treatment on patients. Both viruses may also be transmitted vertically during childbirth, although the real risk is very low¹⁵. The risk of infection is minimal if the mother has no symptoms or exposed blisters during delivery. The risk is considerable when the mother gets the virus for the first time during late pregnancy¹⁶. It needs to be acknowledged that the genital HSV-1 infection has been common for a long time. For example, a Japanese study of women, published in 1976, documented 43% of genital herpes as caused by HSV-1¹⁷. In 1977, a university health clinic study showed that 37% of women with clinical diagnosis of genital herpes had HSV-1 isolated¹⁸. Among people with newly acquired genital herpes in Seattle in the mid to late 1980s, 32% had genital HSV-1 infection¹⁹. Still, several well done studies have shown that the relative proportion of genital HSV-1 isolates has increased even more strikingly in the past two decades²⁰. Two potential explanations that have been put forth include a decrease in HSV-1 acquisition among children, leaving them susceptible to HSV-1 in adolescence, and increase in oral-genital contact, or initiation of oral sex instead of genital-genital sex, among adolescents. Population based studies, although few have looked at secular trends in HSV-1 infection, do not suggest a prominent decrease in HSV-1

seroprevalence²¹. Genital herpes is the most prevalent sexually transmitted disease (STD) in the United States. The most accurate estimates derived from seroprevalence surveys show that 1 person in 5 in the United States is infected with herpes simplex virus (HSV) type 2²²; these data are widely purported to estimate the impact of genital HSV. However, the estimates ignore the contribution of sexually acquired HSV-1 to the epidemic of genital herpes. Infection with HSV-1 usually causes cold sores²³.

Symptoms

Symptoms of herpes simplex virus infection include watery blisters in the skin or mucous membranes of the mouth, lips or genitals²⁴. Lesions heal with a scab characteristic of herpetic disease. Sometimes, the viruses cause very mild or atypical symptoms during outbreaks. However, as neurotropic and neuroinvasive viruses, HSV-1 and -2 persist in the body by becoming latent and hiding from the immune system in the cell bodies of neurons. After the initial or primary infection, some infected people experience sporadic episodes of viral reactivation or outbreaks. In an outbreak, the virus in a nerve cell becomes active and is transported via the neuron's axon to the skin, where virus

replication and shedding occurs and cause new sores²⁴.

HSV as a risk factor of Alzheimer's disease (AD) and HIV

Although it has a very different course from Alzheimer's disease (AD), it leads to the occurrence of bilateral hippocampal-inner temporal lesions resulting in profound verbal memory loss, characteristic of AD²⁵. HSV has been detected in the brain of many AD patients, both by direct detection of virus DNA by polymerase chain reaction (PCR)²⁶ and by the detection of intrathecal antibodies²⁷. Genital herpes is a major risk factor for human immunodeficiency virus type 1 transmission²⁸.

Therapeutics

A number of therapeutics are available against HSV, of which predominantly include nucleoside analogues such as trifluorothymidine (TFT), and topical/oral acyclovir. Approximately, US \$17.7 million is expended annually to treat 59,000 new, and 29,000 recurrent, cases of herpetic eye diseases in the United States. Oral acyclovir alone costs \$8,532 US dollars per ocular episode averted. If antiviral prophylaxis were more effective, the cost per infection would decrease by 51%²⁹. Some drugs available for treatment of herpes simplex virus are:

A. Acyclovir (Zovirax®)

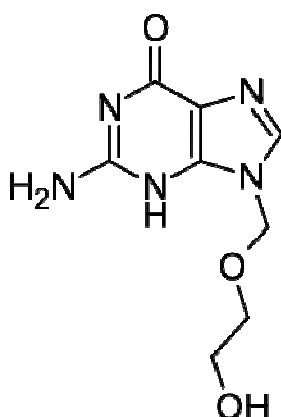


Figure 3
Showing the structure of Acyclovir (2-Amino-1,9-dihydro-9-((2-hydroxyethoxy)methyl)-6H-purin-6-one)

This was the first of a potent new class of antiviral agents, licensed in the 1982. It quickly replaced vidaribine for use in HSV infection. Available in oral, intravenous and topical (latter form generally not recommended because of minimal effectiveness) formulations. DrugBank id-DB00787 have chemical formula $C_8H_{11}N_5O_3$ whose molecular mass is 225.21 g/mol. It has half-life of 2-4 hours and have bioavailability of 15-20% available. Aciclovir is converted to aciclovir monophosphate by viral thymidine kinase, which is then converted by host cell kinases to aciclovir triphosphate (ACV-TP)³⁰. ACV-TP, competitively inhibits &

inactivates HSV-specified DNA polymerases preventing further viral DNA synthesis without affecting the normal cellular processes^{30, 31, 32}. General side effects of drug include ($\geq 1\%$ of patients) nausea, vomiting, diarrhea, encephalopathy and headache. If administered in high doses can cause hallucinations. Very rarely it can cause effects ($< 0.1\%$ of patients) like coma, seizures, neutropenia, leukopenia, crystalluria, anorexia, fatigue, hepatitis etc³³. It is available under various brand names like Cyclovir, Herpex, Acivir, Acivirax, Zovirax, Zoral, Xovir and Imavir.

B. Valacyclovir (Valtrex®)

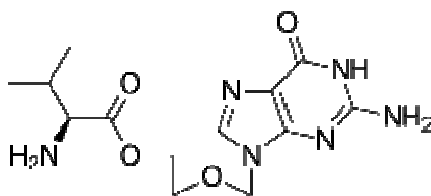


Figure 4

Showing the structure of Valacyclovir((S)-2-[(2-amino-6-oxo-6,9-dihydro-3H-purin-9-yl)methoxy]ethyl-2-amino-3-methylbutanoate)

Parent compound (prodrug) of Acyclovir that is well absorbed and rapidly metabolized to the active form. It has the advantage of a 3-5x higher bioavailability, thus delivering higher levels of active drug with less frequent dosing. Its DrugBank id-DB00577 have chemical formula $C_{13}H_{20}N_6O_4$ whose molecular mass is 324.336 g/mol. It has a half-life of < 30 minutes and have bioavailability of 55%. Valacyclovir is an esterified version of aciclovir which shows greater oral bioavailability (about 55%) than aciclovir (10–20%). It is converted by esterases to the active drug acyclovir and amino acid valine, via hepatic first-pass metabolism. Aciclovir is selectively converted into a monophosphate form by viral thymidine kinase, which is much more effective (3000 times)

in phosphorylation of aciclovir than cellular thymidine kinase. Subsequently, cellular kinases convert the monophosphate form into active triphosphate form, aciclo-GTP. Aciclo-GTP is a very potent inhibitor of viral DNA polymerase and have approximately 100 times higher affinity to viral than cellular polymerase. Its monophosphate form also incorporates into the viral DNA, resulting in chain termination. It has also been shown that the viral enzymes cannot remove aciclo-GMP from the chain resulting in inhibition of further activity of DNA polymerase. Aciclo-GTP is rapidly metabolized within the cell, possibly by cellular phosphatases³⁴. General side effects of drug are same as that of Acyclovir³³. It is available under brand name Valtrex.

C. Famciclovir (Famvir®)

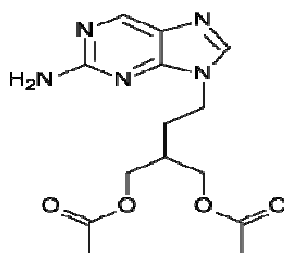


Figure 5
Showing the structure of Famciclovir (2-[(acetyloxy)methyl]-4-(2-amino-9H-purin-9-yl)butyl acetate)

Parent compound (prodrug) of penciclovir, a newer nucleoside analog which requires phosphorylation with viral thymidine kinase to become active (like acyclovir), so cross resistance occurs. Famciclovir inhibits the viral thymidine kinase less effectively than acyclovir, but has higher intracellular levels (good oral bioavailability) and a longer half-life (18-20h) than acyclovir, so its efficacy is similar despite less frequent dosing intervals. Its DrugBank id-DB00426 have chemical formula $C_{14}H_{19}N_5O_4$

whose molecular mass is 321.332 g/mol. It has a half-life of 2–2.3 hours and has a bioavailability of 75-77%. During the clinical trials carried out in 1997 it was found that valaciclovir was more effective than famciclovir at suppressing latent viral shedding of Herpes for long-term treatment^{35,36,37}. Side effects include mild to extreme stomach upset, headaches, mild fever. It is available under the brand name Famvir.

D. Foscarnet

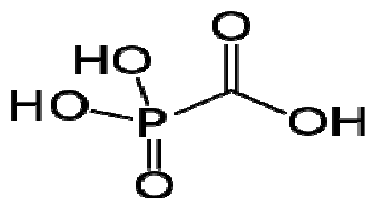


Figure 6
Showing the structure of Foscarnet (Phosphonoformic acid)

A phosphate analogue, it inhibits viral DNA polymerase at the pyrophosphate binding site and has little effect on cellular polymerases. Foscarnet does not require phosphorylation to become active, so it is effective against the TK-negative strains that are resistant to acyclovir, valaciclovir and famciclovir. It is currently licensed for the treatment of CMV infections, but is also used for therapy of acyclovir-resistant HSV and VZV as well. Its DrugBank id-DB00529 have chemical formula

CH_3O_5P whose molecular mass is 126.005 g/mol. It has a half-life of 3.3-6.8 hours and is administered intravenously. Foscarnet is a structural mimic of the anion pyrophosphate³⁸ that selectively inhibits the pyrophosphate binding site on viral DNA polymerases at concentrations that do not affect human DNA polymerases. General side effects include nephrotoxicity, electrolyte disturbances and genital ulceration etc.

Table 1
Current anti HSV drugs and their targets⁴⁰

Type	Drug	Target
Guanosine analogs	Acyclovir (ACV, Zovirax1)	TK, DNA-polymerase, competitive dGTP, chain termination
	Valacyclovir (VACV, Valtrex1)	TK, DNA-polymerase, competitive dGTP, chain termination
	Famciclovir (FCV, Famvir1)	TK, DNA-polymerase, competitive dGTP, chain termination
	Penciclovir (PCV, Vectavir1/Denavir1)	TK, DNA-polymerase, competitive dGTP, no chain termination
	Vidarabine (Ara-A, Arasena A/Vira-A1)	TK, DNA-polymerase, competitive dGTP, chain termination
Pyrimidine analogs	Brivudine (BVDU, Zostex1/Helpin1)	DNA polymerase, competitive dTTP, no chain termination
	Trifluridine (Viroptic1)	DNA polymerase, inhibitor incorporated in both cellular and viral DNA
	Idoxuridine (IDU, Virungent1/Stoxil1)	DNA polymerase, competitive dTTP
Pyrophosphate analog	Foscarnet (FoscavirTM)	DNA polymerase, non-competitive HSV DNA Pol pyrophosphate site
Others	Docosanol	Viral envelope
	Ftibamzone, TDA	DNA polymerase

Although acyclovir (a class C medication) is not FDA-approved for use in pregnancy, numerous studies have demonstrated its safety during pregnancy, and the CDC maintained acyclovir pregnancy registry has failed to show any increase in fetal anomalies in women who received acyclovir during the first trimester of pregnancy³⁹. The newer medications, valacyclovir and famciclovir, are both class B medications, but like acyclovir, neither is FDA-approved for use in pregnancy. Women should be carefully inspected for lesions immediately prior to delivery and Cesarean section should be performed for any woman with typical prodromal symptoms or lesions consistent with HSV. Cesarean section, if performed within 4 - 6 hours of membrane rupture, has been shown to reduce the risk of infection in neonates of mothers with primary HSV infection³⁹. Infants surviving neonatal HSV disease with CNS involvement had improved neurodevelopmental outcomes when they received suppressive therapy with oral acyclovir for 6 months¹⁶.

Current strategies to treat HSV infection

A) Computational approach for HSV treatment

Bioinformatics approach help us to identify several compounds that can potentially block the interaction between active residues of gB and gH-gL complex, suggesting their capability

to inhibit the viral fusion and entry into the host cell. Compounds like (3-Chloro Phenyl) Methyl-3,4,5Trihydroxybenzoate(CPMTHB), ZINC01972391 and ZINC04799874 are found to be common strong inhibitors for both gB and gH-gL glycoproteins⁴¹. Molecular docking study also shows that the natural antiviral plant metabolite Geraniin has more affinity for the thymidine kinase enzyme of HSV-1 as compared to existing anti-herpes drug Acyclovir⁴² and compoundoxoquinoline-acylhydrazone also shows the anti-herpes activity⁴³.

B) Natural compounds based study

Natural products generally hold a wide spectrum of actions against different targets. This may contribute to low selectivity, but it can likewise result in comprehensive therapy: namely, one compound targets several proteins, several compounds in a plant target one protein, and/or several herbs target several proteins. This concept, particularly in traditional Chinese medicine, is called integrity⁴⁰. Various anti-herpes compounds are there which are categorized into the following classes

1) Terpenoids

Terpenoids with anti-HSV activity includes monoterpenoids, sesquiterpenoids,

diterpenoids, iridoids, triterpenoids and saponins⁴⁴.

2) Flavonoids

Flavonoids, such as flavones, flavonols, flavanones, isoflavones, anthocyanidins, chalcones and flavanonols, have broad antiviral activity. They are abundant in many plant seeds, citrus fruits, olive oil, tea and red wine⁴⁰.

3) Phenols and polyphenols

The phenols were found to have virucidal activity against HSV and delayed the herpes virus infections. Caffeic acid, obtained from *Plantago major*, exhibited the strongest activity against HSV-1⁴⁵.

Table 2
Table showing the targets of the anti-hsv natural products

Source	Compound	Target	Reference
<i>Myrothamnus flabellifolia</i>	Polyphenol fraction	Glycoprotein gD	46
<i>Rhododendron ferrugineum</i>	Polyphenol fraction	Glycoprotein gD	47
<i>Rumex acetosa</i>	Polyphenol and flavone fraction	Glycoprotein gD	48
<i>Chamaecyparis obtuse</i>	Yatein (phenylpropanoid)	ICP0 and ICP4 genes	49
<i>Nelumbonucifera</i>	Ethanol extract	ICP0 and ICP4 mRNA	50
<i>Curcuma longa</i>	Curcumin (polyphenol)	P300/CBP histone acetyltransferase	51
<i>Tripterygium hypoglucum</i>	Alkaloid fraction	UL30, UL39 and US6 genes	52
<i>Tethyacrypta</i>	Ara-A (nucleoside)	Viral DNA polymerase	53,54
<i>Scopariadulcis</i>	Scopadulciol (terpene)	TK	55
<i>Psychotriaserpens</i>	Ethanol extract	TK and ICP27 mRNAs	56

CONCLUSION

There are a variety of natural options available for the prevention and treatment of *Herpes simplex* infections. Although traditional cell-based screening systems provide ample opportunities for detecting anti-HSV-1 compounds, its probability is low and the antiherpetic targets are not named. High throughput screenings (HTS), especially which target specific viral proteins are essential for virus replication, such as helicase-primase complex that represent more efficient means for discovery of novel drugs with clarified action mechanisms. The most promising extracts and

fractions of natural materials should undergo further isolation and refinement steps so as to distinguish the dynamic ingredients and clarify the chemical nature and mechanisms of natural process of these powerful anti-HSV molecules. Additionally, integrative approaches in chemical biology have potential to provide important insight into the mechanism of anti-HSV activity of the discourses and treat the infection.

Conflict of Interest

Conflict of interest declared none.

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