HERPESVIRUS-A REVIEW

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Abstract :

Herpes simplex virus (HSV-1andHSV-2) is the virus found all over the world. The sensory nervous system, skin and mucous membranes, are the primary targets of HSV infection. It consists of cold sore or watery blisters on the skin and the mucous membrane of mouth or genitals whichare contagious and ubiquitous. After the infection the virus undergoes the latent phase in the cell bodies of neurons which may reactivate under favorable condition.At present many antiviral drugs like Acyclovir were used for the treatment of disease but problems like drug resistance obstructs to provide an efficient and prolong treatment of the disease. This discussion would aid in understanding the history, morphology, pathogenesis, diagnosis and management of associated HSV related diseases.

Key words:Herpes Simplex Virus, Pathogenesis, Acyclovir.

INTRODUCTION :

The family of herpesvirus contains several human pathogens. Clinically, the herpesvirusexhibits a spectrum of diseases with wide host- cell range or narrow host-cell range. The herpesviruses have ability to establish lifelong persistent infection in their hosts and its periodic reactivation. The recurrent reactivation in immune-suppressed patients may cause serious health complications. The reactivated infection may be clinically different from disease caused by primary infection. Herpesvirus possesses a large number of genes, some of which have proved to be susceptible to antiviral chemotherapy. The herpesvirus that commonly infect humans include herpes simplex virus types 1 and 2, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6 & 7, & Kaposi's sarcoma associated herpesvirus. The Herpes B virus of monkeys can also infect humans. There are nearly 100 viruses of the herpes group that infect many different animal species.[1]

➢ **History:**

Herpesvirus infection has been prevalent from Greek times. Hippocrates described the cutaneous spreading of herpes simplex lesions and scholars of Greek civilization define the Greek word "herpes" to mean "to creep or crawl" in reference the spreading nature of the herpetic skin lesions.[2] Herpes simplex is a viral infection that has been known to mankind for centuries. Genital herpes infection is well known types of

herpes and is therefore usually called "herpes" instead of herpes genitalis. Orofacial herpes is another type of herpes is which affects the face and mouth and leads to cold sores. Other herpes disorder such as ocular or eye herpes, herpetic whitlow(causes lesions on finger or thumb), and herpes simplex encephalitis (herpes infecting the CNS) are less common. Neonatal herpes is passed on by a mother who has been recently exposed to the virus and has passed it onto the baby through infected secretions in the birth canal during childbirth. During this decade new antiviral drugs were developed. These drugspreventsviral multiplication hence called DNA replication inhibitors and were used for the severe and more life threatening infections such as herpes encephalitis, herpes keratitis or to treat those with immune suppression due to HIV, an organ transplant, chemotherapy or radiation therapy. [3]

STRUCTURE AND COMPOSITION

Herpes viruses are large viruses. The outstanding characteristics of Herpes virus as they establish latent infections, persists indefinitely in infected hosts and frequently reactivated in immunosuppressed host.

All herpesviruses have a core of double stranded DNA, in the form of toroid, surrounded by a protein coat that exhibit icosahedral symmetry and has 162 capsomeres. The double-stranded DNA genome (124-235kbp) is linear. A striking feature of herpes virus DNAs is sequential arrangement of base pairs. Herpesvirus genomes possess terminal and internal repeated sequence. Some members such as herpes simplex viruses undergo genome rearrangements, giving rise to different genome "isomers".

The best composition of herpesvirus DNAs varies from 31% to 75% (G+C). There is little DNA homology among different herpesvirus except for herpes simplex virus 1 and 2, which show 50% sequence homology, and human herpesvirus 6 and 7, which display limited (30-50%)sequence homology.[1]

PROPERTIES OF HERPESVIRUSES: [1]

- **Virion:** spherical, 150-200 nm in diameter (icosahedral)
- **Genome:** Double –stranded DNA, linear, 124-235kbp, reiterated sequences
- **Proteins:** More than 35 proteins in virion
- **Envelope:** contains viral glycoproteins, Fc receptors
- **Replication**: Nucleus, bud from nuclear membrane**.**

Table 1: classification of human herpesvirus[4]

Subfamily ("herpesvirinae")	Biologic properties		Genus ("-virus")	Example
	Growth cycle and cytopathology	Latent infections		Common Name
Alpha (α)	Short, cytolytic	Neurons	Simplex	HSV 1

				HSV 2
			Varicello	VZV
Beta (β)	Long, cytomegallic	Glands,kidneys	Cytomegalo	CMV
	Long, lymphoproliferative	Lymphoid tissue	Roseolo	HHV 6 HHV 7
Gamma (√)	Variable, lymphoproliferative	Lymphoid tissue	Lymphocrypto	EBV
			Rhadino	KSHV

HHV: Human Herpes Virus,HSV: Herpes Simplex Virus, VZV: Varicella Zoster Virus, CMV: Cytomegalo Virus, EBV: Epstein- Barr Virus, KSHV: Kaposi's Sarcoma Associated Herpes virus

Infection caused by Human Herpesvirus

- **Herpes Simplex Virus**

There are two types of HSV-type 1(HSV-1) and type 2 (HSV-2). Their genomes are similar in organization and exhibit substantial sequence homology. The two viruses serologically cross-react, but some unique proteins exist for each type. The HSV growth cycle requires 8-16 hours for completion. The HSV genome is large (about 150kbp) and can encode atleast 70 polypeptides.

At least 8 viral glycoproteins are amongst the viral late genes products. One (gD) is the most potent inducer which neutralizes antibodies. Glycoprotein C is the complement (C3b) binding protein, and gE is an Fc receptor, binding to the Fc portion of IgG. Glycoprotein G is type-specific and allows for antigenic discrimination between HSV-1 (gG-1) and HSV-2 (gG-2)[5]

HERPES SIMPLEX VIRUS (HSV-1);

HSV-1 is spread by contact of infected saliva. Primary infections with HSV-1 are common over 6 months oldchildren. On initial contact with HSV-1, more than 90% of persons develop a subclinical form of primary herpes. Clinical infections are self-limiting and include acute gingivostomatitis (vesicular eruption in the mouth), pharyngitis, cold sores, keratoconjunctivitis, or skin lesions (on nongenital areas) and sometimes more severe and even fatal infections occur, such as encephalitis.

During primary infection (clinical or subclinical) neutralizing antibodies were developed. Despite these antibodies, the virus occurs in a latent form. The latent virus may be reactivated by environmental factors such as heat and cold, by hormonal or emotional disturbances, or by other stimuli is known as recurrent herpes which is characterized by superficial vesicles (cold sores, fever blisters.)

Sometimes, HSV-1 (and also HSV-2) can cause neoplastic transformation in tissue cultures of hamster embryo cells and human fibroblasts.

HERPES SIMPLEX VIRUS (HSV-2)

HSV-2 transmitted sexually or from maternal genital infection. In women, infection is associated with small, painful blisters on the cervix, vagina, urethra, and anus. In men the lesions are on the penis, in the urethra, or around the anus. The lesions heal without leaving scars. The disease is most contagious during presence of lesions. After the disappearance of lesions the virus remains latent from a few weeks to a year or longer. Recurrent genital herpes is frequent. The clinical symptoms include fever, painful urination, inflammation of the inguinal lymph glands, and genital soreness. Infection in pregnant women may result in serious neonatal disease with dissemination of the virus to the skin, eyes, central nervous system, and visceral organs of the newborn. [6]

Table 2: comparison of HSV -1 and HSV -2[5]

Characteristics	HSV -1	HSV-2
Biochemical		
ViralDNA base composition(G+C)	67%	69%
Buoyant density of DNA (g/cc)		
Buoyant density of virions (g/cc)	1.726	1.728
Homology between viral DNAs		
Biologic	1.271	1.267
Animal vectors or reservoirs		
Site of latency	~50%	~50%
	None	None
	Trigeminal ganglia	Sacral ganglia

Clinical		
Primary infection:		
Gingivostomatitis	+	–
Pharyngotonsilitis	+	–
Keratoconjunctivitis	+	–
Neonatal infections	±	+
Recurrent infection:		
Cold sores,fever blisters	+	–
Keratitis	+	–
Primary or recurrent infection:		
Cutaneous herpes		
Skin above the waist		
Skin below the waist	+	–
Hands or arms	–	+
Herpetic whitlow	+	+
Eczema herpeticum	+	+
Genital herpes	+	–
Herpes encephalitis	±	+
Herpes meningitis	+	–
	±	+

➢ **Transmission**

HSV-1 infections are usually limited to the oropharynx and keratitis in eyes;virus is either spread by respiratory droplets or by direct contact with infected saliva. HSV-2 is usually transmitted sexually. However both viruses are capable of causing lesions at the site of infection and can cause life threatening diseases in newborns, patients with HIV or patients undergoing immunosuppressive treatment. Transmission among humans involves physical contact.

➢ **Symptoms**

Symptoms of HSV infection included watery blisters in the skin or mucous membranes of the mouth, lips or genitals. Lesions heal with scab characteristics of herpetic disease. Sometimes the viruses cause very mild atypical symptoms. However as neurotropic and neuro invasive viruses, HSV-1 and HSV -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 diseases of viral reactivation or outbreaks, the virus on nerve cell becomes active and is transported via the neuron's axon to the skin, where virus replication and shedding occurs and cause new sores.[7]

➢ CLINICAL FINDINGS

Herpes simplex virus type 1 and 2 may cause many clinical entities and the infections may be primary or recurrent.

Depending upon site of infection HSV divided into following:

A. Oropharyngeal disease: Primary HSV-1 infections are asymptomatic. In small children (1-5 years of age)symptomatic disease occurs most frequentlythat involves the buccal and gingival mucosa of the mouth. The incubation period is short (about 3-5 days, with a range of 2-12 days), and clinical illness lasts 3 weeks. Symptoms include fever, sore throat, vesicular and ulcerative lesions, edema, gingivostomatitis,submandibular lymphadenopathy, anorexia and malaise. Gingivitis (swollen, tender gums) is the most striking and common lesson. Primary infections in adults commonly cause pharyngitis, tonsillitis and localizedlymphadenopathy may occur.Recurrent disease is characterized by a cluster of vesicles localized at the border of the lip. At the outset intense pain occurs which fades over 4-5 days. Lesions progress with pustular and crusting stages and healing without scarring is usually complete in 8-10 days. The lesions may recur, repeatedly and periodicallyat the same location. The frequency of recurrences varies widely among individuals.

B. Keratoconjunctivitis: The initial infection with HSV-1 may be in the eye,producing severe keratoconjuctivities. Recurrent lesions of the eye appear as dendritic keratitis or corneal ulcers or as vesicles on the eyelids. There is progressive involvement of the corneal stroma, with permanent opacification and blindness.

C. Genital Herpes: Genital disease is usually caused by HSV-1 can also cause clinical episodes of genital herpes. Primary genital herpes infection can be severe, with illness lasting about 3 weeks. It consists of vesiculo-ulcerative lesions of the penis of the male or of the cervix, vulva, vagina, and perineum of the female. The lesions are very painful and associated with fever, malaise, dysuria, and inguinal lymphadenopathy. Complications include extragenital lesions (~20% of cases).Viral excretion persists for about 3 weeks. Due to the antigenic cross-reactivity between HSV-1 and HSV-2, preexisting immunity provides protection against heterotypic infection. A limited number of vesicles appear that heal in about 10 days. Virus is shed for only a few days. The persons shedding virus can transmit the infection to sexual partners.

D. Skin Infections: Intact skin is resistant to HSV, so cutaneous HSV infections are not common in healthy persons. Cutaneous infections are often severe and lifethreatning when they occur in individuals

with disorders of the skin, such as eczema or burns,that permit extensive local viral replication and spread. Eczema herpeticum is a primary HSV-1 infection in a person with chronic eczema.

E. Encephalitis: A severe form of encephalitis may be produced by herpesvirus. Polymerase chain reaction amplification of viral DNA from cerebral spinal fluids has replaced viral isolation from brain tissue obtained by biopsy or at postmortem examination as the standard assay for specific diagnosis of encephalitis. The disease carries a high mortality rate and those who survive have residual neurologic defects. About half of patients with HSV encephalitis appear to have primary infectionsand the rest half appear to have recurrent infection.

F. Neonatal Herpes: HSV infection of the newborn may be acquired in uterus during before or after birth. The infant unable to limit the replication and spread of HSV and has apropensity to develop severe disease.The most common route of infection is for HSV to be transmitted to the newborn during birth been used in pregnant women with genital herpes lesions.

G. Infection in Immunocompromised Hosts: Immunocompromised patients are at increased risk of developing severe HSV infections which include patients immunosuppressed by disease or therapy, individual with malnutrition, transplant recipients (renal, cardiac, and bone marrow), hematologic malignancies and patients with AIDS suffer more frequent and more severe HSV infections. Herpes lesions may spread and involve the respiratory tract, esophagus, and intestinal mucosa. [8]

- **Herpes Virus Replication**

➢ **REPLICATION CYCLE INVOLVES FOLLOWING STEPS:**

1.HSV virion attaches to host cell along with the envelope glycoprotein (gC) onto heparan sulfate moieties of cellular proteoglycans. Viral gD is believed to blind to a secondary cellular receptor.

2.The viral envelope fuses to the plasma membrane in a pH-independent fashion such a that the nucleocapsid enters the cytoplasm. gB, gD, and gH are instrumental glycoproteins.

3. Along with the cytoskeleton the capsid travels to a nuclear pore where the viral DNA is released.The linear genome enters the nucleus and circularizes.

4.The viral DNA is transcribed into mRNA by cellular RNA polymerase II. In herpesviruses, viral gene expression is tightly regulated and divided into 3 kinetic classes of expressions.

1. A tegument protein associates with 2 cellular proteins, and the complex transactivates transcription of HSV's five immediate-early (IE or alpha) genes. IE genes generally encode regulatory proteins.

2. An IE protein starts transcription of the early (E or beta) genes. These gene products are enzymes used to increase the pool of nucleotides for replication of virus.

3. Viral structural proteins are produced by activation of late (L or gamma) genes.

5.All mRNA transcripts are translated into protein in the cytoplasmafter transcription in the nucleus. The proteins can go to the nucleus sequentially and either stay in the cytoplasm or become a part of the membrane bilayer.

6. Empty capsids are formed by assembling capsid proteins in the nucleus.

7.Nucleocapsids formed by packing of full-length viral DNA.

8. The nucleocapsids associate with segments of the nuclear membrane where tegument and glycosylated envelope proteins have bound. This association triggers envelopment by budding through the nuclear membrane.

9. Enveloped virions accumulate in the endoplasmic reticulum (ER).

10. Mature virions are released by exocytosis.

11. Virus-specific proteins are also found on the plasma membrane of infected cells.[9]

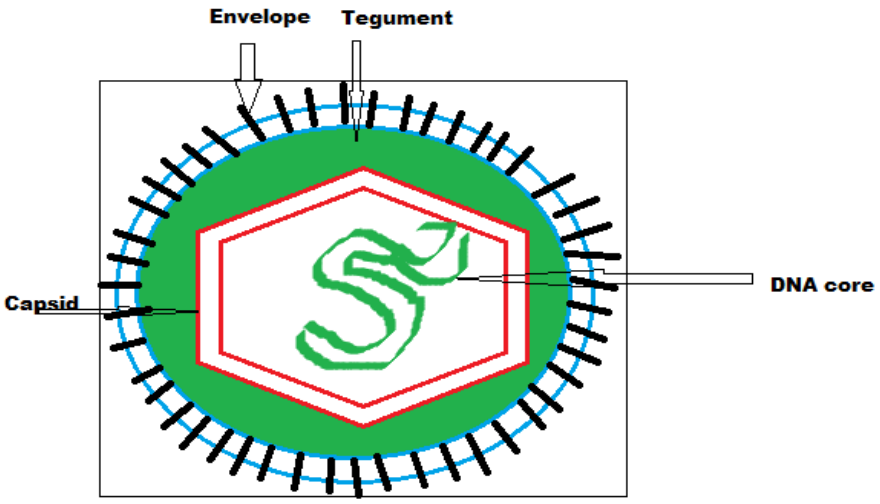

Fig. 1 HSV replication

○ Immunity :

Many newborn acquires passively transferred maternal antibodies. These antibodies are lost during the first 6 months of life, and the period greatest susceptibility to primary herpes infection occurs between ages 6 months and 2 years. Transplacentally acquired antibodies from the mother are incapable to protect against infection of newborns. HSV-1 antibodies begin to appear in early childhood, by adolescence, they are present in most persons. During the age of adolescence and sexual activityantibodies to HSV-2 rises.

During primary infections, IgM antibodies appear transiently and followed by IgG and IgA antibodies that persist for long periods. The more severe the primary infection or the more frequent the recurrences, the greater the level of antibodies response. Cell- mediated immunity and non-specific host factors (NK cells, interferon)are important in controlling both primary and recurrent HSV infections.

After primary infectionrecovery,the virus is carried in a latent state in the presence of antibodies. These antibodies do not prevent reinfection or reactivation of latent virus but may modify subsequent disease. [8]

Pathogenesis and Pathology

A. Pathology: Because HSV causes catalytic infections, pathologic changes are due to necrosis of infected cells together with the inflammatory response. Lesions induced in the skin and mucous membranes by HSV-1 and HSV-2 are the same and resemble lesions of varicella zoster virus. Characteristics histopathologic changes include ballooning of infected cells, production Cowdry type Aintranuclear inclusion bodies, margination of chromatin, and formation of multinucleated giant cells. The early inclusions virtually fill the nucleus but later condense and are separated by a halo form the chromatin at the nuclear margin. Cell fusion provides an efficient method for cell to cell spread of HSV, in the presence of neutralizing antibody.

B. Primary Infection:HSV is transmitted by contact of a susceptible person.The virus must encounter mucosal surface or broken skin in order for an infection to be initiated. First viral replication occurs at the site of infection. Virus then invades local nerve ending and is transported by retrograde axonal flow to dorsal root ganglia, where after further replication, latency is established. Oropharyngeal HSV-1 infections result in latent infections in the trigeminal ganglia, whereas genital HSV-2 infections lead to latently infected sacral ganglia. Primary HSV infections are usually mild and asymptomatic. Widespread organ involvement can result when an immune-compromised host is not able to limit viral replication and viremia ensures.

C. Latent Infection: Virus resides in latently infected ganglia in a non-replicating state and only a very few viral genes are expressed. Viral persistence in a latently infected ganglia last for the lifetime of the host. No virus can be recovered between the recurrences at or near the usual site of recurrent lesions. Provocative stimuli can reactivate virus from the latent state, including axonal injury, fever, and physical or emotional stress and exposure to ultraviolet light. The replication proceeds at the skin or mucous membranes. In spite of HSV-specific humoral and cellular immunity spontaneous reactivations occur in the host. However, this immunity limits local asymptomatic, reflected only by viral shedding in secretions. More than 80% of the human population harbors HSV-1 in a latent form but only a small portion experience recurrences .It is not known why some individual suffer reactivations and others do not.[8]

EPIDEMIOLOGY

Herpes simplex viruses are distributed worldwide. Animal reservoirs or vectors are not involved with the human viruses. Transmission is by contact with infected secretions. HSV-1 is probably more constantly present in humans. Antibodies developed but the virus is not eliminated from the body.A carrier state is established which lasts throughout life and is initiates transient recurrent attacks of herpes. The HSV-1 infection occurs among children 6 months to 3 years of age. By adulthood, majority of persons have type1 antibodies. Middle class individual in developed countries acquire antibodies later in life than those in lower

socioeconomic populations. The source of infection for children is an adult with symptomatic herpetic lesion or with asymptomatic viral shedding in saliva. HSV-2 is a sexually transmitted disease,so antibodies to this virus are rarely found before puberty. It is estimated that there are about 45 million infected individuals in the USA.

Maternal genital HSV infection poses risks to both mother and fetus. Primary infection before 20 weeks of gestation mayassociate with spontaneous abortion.The fetus may acquire infections a result of viral shedding from recurrent lesions in the mother's birth canal at the time of delivery.However the majority of infants who develop neonatal disease are born to women who do not have a history of genital herpes and are asymptomatic at the time of delivery. [8]

Table 3: laboratory diagnostic tests for herpetic infection[10]

Laboratory tests	Method use to diagnose herpetic infection
1.Morphologic	(i)Electron microscopy (ii)Tzanck smear test (iii)Biopsy
2.Immunomorphologic	(i) Immunofluorescence (ii) The peroxidase-antiperoxidase (iii)Avidin-biotin
3.Serologic	(i)Complement fixation test for serum antibody (ii)Neutralization (iii)Direct hemagglutination (iv)Passive hemagglutination (v)ELISA (Enzyme Linked Immunosorbent Assay) (vi) Western blot technique
4.Virologic	(i) Specific fluorescein-tagged monoclonal antibodies (ii) Restriction endonuclease analysis

PREVENTION ANDTREATMENT

- **Prevention of HSV**

1) Take counterintuitive vaccine to prevent the spread of herpes
2) Take antiviral medicines
3) Take care during pregnancy

4) Practice safer sex

5) Wash your hands[11]

HSV Vaccines:

HSV vaccines may be divided broadly into 2 groups: live or inactive. Live vaccines contain oraganisms capable of at least limited replication in vivo, whereas inactive vaccines are incapable of replicating.[12]

Table 4: HSV vaccines and their advantages and disadvantages.

Vaccines type, category	Advantages	Disadvantages
Live		
Attenuated	Induces broad, durable immunity	Stability and safety concerns
Replication-limited	May have advantages of live- attenuated vaccines but with better safety profiles	May not be as immunogenic as live-attenuated vaccine; some safety concern remain
Vectored	May have advantages of live-attenuated vaccines but with better safety profiles	Because limited HSV gene products are expressed, may not be as immunogenic as live-attenuated vaccines
Inactive		
Inactivated virus	Easily prepared; incapable of causing HIV disease	Not as immunogenic as replicating vaccines; must be combined with adjuvants to induce broader immunity
Subunit	Excellent safety profile and recombinant subunits ensure consistent product	Narrow immunity due to limited number of epitopes; must be combined with adjuvants to induce cellular responses

Treatment

Several antiviral drugs have proved effective against HSV infections, including acyclovir and vidarabine. Both are inhibitors of viral DNA synthesis. The drugs inhibit herpesvirus replication and may suppress clinical manifestation. Experimentalvaccines of various types are being developed. One approach is to use purified glycoprotein antigens found in the viral envelope, expressed in some recombinant system, or synthetic peptides to these glycoproteins. Such vaccines might be helpful for prevention of primary

infections. However a recombinant HSV-2 glycoprotein vaccines tested in a recent multicenter trial induced high levels of neutralizing antibody but failed to protect against acquisition of genital infections.[13]

Table 5: current anti HSV drugs and their target[14]

Type	Drug	Target
Guanosine analogs	Acyclovir (ACV, Zovirax 1)	TK,DNA polymerase, competitive dGTP,chain termination
	Valacyclovir(VACV,Valtrex1)	TK,DNA polymerase, competitive dGTP, chain termination
	Famciclovir (FCV, Famvir 1)	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

Pyrophosphate analog	Foscarnet (FoscavirTM)	DNA polymerase, non-competitive HSV DNA polypyrophosphate site
Others	Docosanol Ftibamzone, TDA	Viral envelope DNA polymerase

Table 6: Targets of anti HSV natural product[15]

Source	**Co**mpound	Target	Reference
Myrothamnusflabellifolia	Polyphenol fraction	Glycoprotein gD	15
Rhododendron Ferrugineum	Polyphenol fraction	Glycoprotein gD	16
Rumexacetosa	Polypheno and flavone fraction	Glycoprotein gD	17
Chamaecyparis obtuse	Yatein(phenylpropanoid)	ICP0 and ICP4 genes	18
Nelumbonucifera	Ethanolic Extract	ICP0 and ICP4 mRNA	19
Curcuma longa	Curcumin(polyphenol)	P300/CBP histone acetyltransferase	20
Tripterygiumhypoglaucum	Alkaloid fraction	UL30,UL39 and US6 genes	21
Tethayacrypta	Ara-A(nucleoside)	Viral DNA polymerase	22,23
Scopariadulcis	Scopadulciol(terpene)	TK	24
Psychotriaserpens	Ethanolic extract	TK and ICP27 mRNAs	25

RISK FACTOR:

HSV as a risk factor ofAlzheimer's Disease (AD) and HIV:

Alzheimer's Disease (AD) leads to the occurrence of bilateral hippocampal- inner temporal lesions resulting in profound verbal memory loss. HSV has been detected in the brain of many AD patients, both bydirect detection virus DNA by PCR and by the detection of intrathecal antibodies. Genital herpes is a major risk factor for HIV type 1 transmission.[26]

COMPLICATIONS

Neurological complications:

1. Neonatal herpes simplex encephalitis
2. Acute aseptic meningitis in adults
3. Recurrent aseptic meningitis
4. Cranial neuropathy
5. Sacral rediculopathy
6. Bell's palsy
7. ANS dysfunctions
8. Transverse myelitis

Dermatological Complications:

1. Eczema herpeticum
2. Erythema Multiforme[27]

Table 7: abbreviations used in review article.

HHV	Human Herpes Virus
HSV	Herpes Simplex Virus
VZV	Varicella Zoster Virus
CMV	Cytomegalo Virus
EBV	Epstein- Barr Virus
KSHV	Kaposi's Sarcoma Associated Herpes virus

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