Ethnomedicines and ethnomedicinal phytophores against herpesviruses

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Abstract. Herpesviruses are important human pathogens that can cause mild to severe lifelong infections with high morbidity in susceptible adults. Moreover, Herpes simplex virus (HSV) type 2, for example, has been reported to be responsible for increased transmission and disease progression of human immunodeficiency virus (HIV). Therefore, the discovery of novel anti-HSV drugs deserves great efforts. Herbal medicinal products have been used as source of putative candidate drugs in many diseases. However, in case of viral diseases the development of antivirals from natural source is less explored probably because within the virus there are few specific targets where the small molecules can interact to inhibit or kill the virus. The currently available antiherpes drugs are nucleoside analogs that did not cure the lifelong or recurrent infections and the use of these drugs often lead to the development of viral resistance coupled with the problem of side effects, recurrence and viral latency. However a wide array of herbal products, used by diverse medicinal systems throughout the world, showed high level of antiherpesvirus activities and many of them have complementary and overlapping mechanism of action, either by inhibiting viral replication, or viral genome synthesis. This chapter will summarize some of the promising herbal extracts and purified compounds isolated from the herbal sources by several laboratories. Cases with proven *in vitro* and documented *in vivo* activities, along with their structure-activity relationship against herpesviruses are discussed.

Keywords: herbal medicine, herpesvirus, latency-associated transcripts, structure-activity relationship.

Introduction

Over the centuries herbal medicinal products formed the basis of medicaments in Africa, China [1], India [2] and in many other civilizations [3]. The traditional healers have long used herbal products to prevent or cure infectious conditions but today the clinical virologists are interested in herbal products as (i) the effective life span of any antiviral drug is limited, (ii) many of the viral diseases are intractable to most of the orthodox antivirals and (iii) the problems of viral drug resistance, latency and recurrence in immunocompromised hosts. Moreover, the rapid spread of emerging and reemerging viral diseases has spurred intensive investigation into the herbal products. Additionally the rapid

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rate of species extinction [4] leads to irretrievable loss of structurally diverse and potentially useful phytochemicals. Most of the herbal medicinal products are the secondary metabolites of plants and are species/strain-specific with diverse structures and bioactivities, synthesized mainly for defense against predators, as the natural version of chemical warfare. This chapter will summarize some of the promising extracts and compounds, isolated from herbal medicinal source, having antiherpesvirus activity, reported from several laboratories with proven *in vitro* and some documented *in vivo* activities, along with their structure-activity relationship (SAR).

The Herpesvirus

The herpesviruses belong to *Herpesviridae*, a family of DNA viruses that cause diseases in humans and animals [5,6]. In Greek, the word *herpein* means ''to creep'', referring to the latent, reoccurring and lytic infections typical of these viruses. There are eight distinct viruses (Table 1) in this family that are known to cause disease in humans [7,8].

All human herpesviruses (HHV) contain a large double-stranded, linear DNA with 100–200 genes encased within an icosahedral protein capsid wrapped in a lipid bilayer envelope, called virion. Following binding of viral envelope glycoproteins to host cell membrane receptors, the virion is

Table 1. Members of human *Herpesviridae*.

Type	Synonym	Subfamily	Pathophysiology
HHV-1	Herpes simplex virus-1 (HSV-1)	*Alphaherpesvirinae*	Oral and/or genital herpes (orofacial)
HHV-2	Herpes simplex virus-2 (HSV-2)	α (alpha)	Oral and/or genital herpes (genital)
HHV-3	Varicella zoster virus (VZV)	α (alpha)	Chickenpox and Shingles
HHV-4	Epstein–Barr virus (EBV) Lymphocryptovirus	*Gammaherpesvirinae* γ (gamma)	Infectious mononucleosis, Burkitt's lymphoma, CNS lymphoma (in AIDS patients), post-transplant lymphoproliferative syndrome (PTLD), nasopharyngeal carcinoma
HHV-5	Cytomegalovirus (CMV)	*Betaherpesvirinae*	Infectious mononucleosis-like syndrome, retinitis, etc.
HHV-6, 7	Roseolovirus	β (beta)	Roseola infantum or *exanthem subitum*
HHV-8	Kaposi's sarcoma-associated herpesvirus (KSHV), a rhadinovirus	γ (gamma)	Kaposi's sarcoma, primary effusion lymphoma, some multicentric Castleman's disease

internalized and dismantled, allowing viral DNA to migrate to the host cell nucleus, where viral DNA replication and transcription occurs. One successful replication cycle of Herpes simplex virus (HSV) depend upon a number of steps: virion entry, ''expression''discuss transcription as well as translation of the viral genome? Of viral immediate-early (α) genes such as infected cell protein (ICP) 0 and 4, early (β_1, β_2) genes including DNA polymerase and thymidine kinase and late (γ_1, γ_2) genes containing glycoprotein B (gB), ICP5 and gC, and unpaired DNA replication [9]. During symptomatic infection, infected cells transcribe *lytic* viral genes, but sometimes a small number of viral genes (*latency-associated transcripts*, LAT) accumulate, and the virus can persist in the host cell indefinitely. The primary infection is a self-limited period of illness, but long-term latency is symptom-free. Following reactivation, transcription of viral genes switches from LAT to multiple *lytic* genes and consequently leading to enhanced replication and virion production. Herpesviruses are common pathogens that cause localized skin infections of the mucosal epithelia of the oral cavity, the pharynx, the esophagus and the eye, or genitals, depending upon the type involved [10]. Moreover, herpesvirus infections may also cause severe problems to infected individuals due to the properties such as (i) the virus establish latent infections that can be periodically reactivated. (ii) Under certain circum-stances, the virus can produce serious infections of the central nervous system including acute necrotizing encephalitis and meningitis; the viruses may also produce fatal infections in patients with immune deficiencies [11]. (iii) The immediate-early genes of HSV-1 can stimulate the activation of genes belonging to different viruses such as human immunodeficiency virus (HIV) [12], Varicella zoster virus (VZV) [13] or human papillomavirus type 18 [14]. Additionally, HSV infections were reported to be a significant risk factor for transmission of HIV/AIDS [15,16]. HSV-2 is also known as oncogenic virus which has the ability to convert cells into tumor cells [17]. Infection with herpesvirus can also lead to scarification, a major cause of blindness in developing nations [18]. Acute and recurrent HSV infections remain a most important health problem. The search for selective antiviral agents has been vigorous in recent years, but the need for new antiviral therapies still exists since many of the problems relating to the treatment of HSV infections remain unresolved, such as generation of viral resistance and conflicting efficacy in recurrent infection and in immunocompromised patients [19].

Control of Herpesvirus infection

The herpesvirus causes a lifelong infection with high morbidity. Although no cure is available nucleoside analogs have been extensively investigated in the search for effective antiherpesvirus agents [20], of which acyclovir [9-(2-hydroxyethoxymethyl) guanosine], a highly selective antiherpetic agent

widely used for the systemic treatment of herpesvirus infections, because acyclovir is specifically phosphorylated by viral thymidine kinase in infected cells [21,22]. However, acyclovir-resistant herpesvirus has been isolated in immunocompromised patients [23,24]. Moreover, there are no effective agents that can control neonatal infections as well as infections caused by other viruses of *Herpesviridae*. Therefore, it is desirable to develop new antiherpesvirus agents that substitute for or complement acyclovir group of drugs. But the development of antiherpetic agents from herbal medicinal products is less explored, probably because there are a very few specific viral targets for small molecules to interact with [25,26].

Several herbal medicinal products are potential sources of functional foods due to their various biological activities such as immunomodulatory and antitumor functions [27,28]. Even today nearly 80% of the world population utilize herbal medicinal products for primary health care [29,30]. However, ethnopharmacology provides an alternative approach for the discovery of antiherpesvirus agents by utilizing the generation old wisdom of ethnic community. Numerous studies showed that phloroglucinol [31], anthraquinones [32], polysaccharides [33], triterpenes [34], polyphenols and flavonoids [35,36] isolated from herbal sources have inhibitory activities against the replication of herpesviruses. Owing to the amazing structural diversity and broad range of bioactivities herbal medicinal products can be explored as a source of complementary antiherpetic agents, as many of them are reported to inhibit several steps of replication cycle and certain cellular factors of herpesviruses. It has been reported that a thiazolylsulfonamide BAY 57-1293 inhibits herpesvirus helicase-primase with potent *in vitro* and *in vivo* antiherpetic activity [37,38]. Another promising natural antiherpetic agent, *n*-docosanol, completed clinical evaluation and approved by the U.S. Food and Drug Administration as a topical treatment for *herpes labialis* [39–41]. These findings indicated that the natural products are still potential sources in the search for new antiherpetic agents [42,43]. A list of some potential herbal medicinal extracts having antiherpes activities are presented in Table 2.

In vitro *and* in vivo *antiherpetic activity with crude herbal products*

During the last 50 years numerous broad-based screening programme conducted throughout the world to evaluate the *in vitro* and *in vivo* antiviral activity of hundreds of herbal products, showed that many such products had strong antiherpesvirus activity and some can be used in the treatment of diseases caused by the members of *Herpesviridae* [44–49]. Canadian researchers reported the *in vitro* antiherpesvirus activities of grape, apple and strawberry juices while the leaf extract of *Melia azadirachta* (*Azadirachta indica*) inhibits DNA viruses like smallpox, chicken pox, poxvirus and HSV [50]. The water-soluble extract from narcissus bulb [51], the infusion of

Table 2. In vitro and *in vivo* antiherpesvirus activities of some important medicinal plants of diverse culture.

Virus	Name of plants	Compound (class)	References
Herpesvirus	*Mallotus japonicus*	Phloroglucinol (terpene)	[31]
	Rheum officinale	–	[58]
	Geum japonicum, *Syzygium aromaticum*	Eugeniin	[164]
	Annona sp., *Beta vulgaris*	–	[62]
	Geranium sanguineum L.	–	[19]
	Polygonium punctatum, *Sebastiana braselliensis*, *Lithraea molleiodes*	–	[63]
	Solanum sp.	Spirostanol (steroid) glycoside	[166]
HSV	*Sapium seiferum*	Methyl gallate	[114]
	Flos verbasci	–	[52]
	Pongamia pinnata	–	[54]
	Many plants	Propolis	[117]
	Eupatorium articulum	–	[64]
	Brysonima verbascifolia	–	[75]
	Holoptelia integrifolia, *Nerium indicum*	–	[76]
	Bistrychia montagnei	Sulfated galactan	[181]
	Boussiangaultia gracilis, *Serissa japonica*	–	[79]
	Geum japonicum, *Syzygium aromaticum Terminalia chebula*, *Rhus javanica*	Flavonoids, terpenoids, essential oil	[61] [60]
HSV-1	*Scoparia dulcis*	Scopadulcic acid B	[141]
	Geranium sanguineum L.	Polyphenol complex	[91]
	Rheum officinale, *Aloe barbadensis*, *Cassia angustifolia*	Anthroquinone, flavones	[32]
	Aloe emodin	Rosmarinic acids (phenolics)	[32]
	Houttuynia cordata	–	[57]
	Helichrysum aureonitens	–	[59]
	Melaleuca leucadendron, *Nephelium lappaccum*		[65]
	Stephania cepharantha	*N*-methylcrotasparine (alkaloid)	[65,173]
	Melia azedarach	28-Deacetylsendanin	[146]
		Meliacine (peptide)	[179]
	Rhizoma polygonia Cuspidati, *Radix Astragali*		[67]
	Morus alba	Mulberocide (flavonoid)	[181]

Table 2. (*Continued*)

Virus	Name of plants	Compound (class)	References
	Maesa lanceolata	Maesasaponin (saponin)	[120]
	Minthostachys verticillata	Pulegone (essential oil)	[156]
	Scrophularia scorodonia, *Bupleurum nigidum*	Iridoids (saponins)	[168]
	Solanum torvum	Torvanol, torvoside (flavonoid)	[124]
	Santalum album, Lemon grass	Essential oil	[46]
	Artemisia douglasiana, *Eupatorium patents Tessaria absinthioides*	Essential oil	[159]
	Moringa oleifera, *Aglaia odorata*, *Ventilago enticulata*	Polyphenol	[82]
	Agrimonia pilosa, *Punica granatum*	Polyphenol	[95]
	Cretastigma willmattianum		[83]
HSV-2	*Barteria lupulina*, *Clinacanthus nutans*		[68]
	Glyptopetalum scerocarpum	Sclerocarpic acid (terpene)	[143]
	Cedrela tubiflora	Acidic polysaccharide	[182]
	Terminalia arjuna	Casuarinin (tannin)	[167]
	Melissa officinalis	Essential oil	[160]
	Rhus javanica	Morin (triterpene)	[87]
HSV-1 and HSV-2	*Maesa lanceolata*	Maesasaponin (saponin)	[147]
	Prunella vulgaris	Anionic polysaccharide	[184]
	Trixis praestans, *Cunilla spicata*	–	[66]
	Centell asiatica, *Mangifera indica*	Asiaticoside, mangiferin	[119]
	Phyllanthus orbicularis	Polyphenol	[72]
	Eucalyptus, Australian Tree Tea	Essential oil	[157]
	Eupatorium patens	Essential oil	[159]
	Homalium cochinchinensis	Salicin, cochinolide, tremulacin	[96]
	Geum japonicum	Eugeniin (tannin)	[87]
	Alstonia macrophylla	Ursolic acid (triterpene)	[174]
VZV	Aloe emodin, *Aloe barbadensis*	Rosmarinic, chlorogenic, caffeic acids (phenolics)	[32]

Table 2. (*Continued*)

Virus	Name of plants	Compound (class)	References
CMV	*Listeria ovata*, *Urtica dioca*	Lectins	[177]
	Allium sativum		[56]
	Nigella sativa	Essential oil	[71]
	Geum japonicum, *Syzygium aromaticum Terminalia chebula*, *Rhus javanica*	Flavonoids, terpenoids, esstential oil	[61] [60]
EBV	*Phyllanthus myrtifolius*, *Phyllanthus urinaria*	Ellagotannin	[165]
	Syzygium aromaticum	Ellagitannin (tannin)	[46]

Notes: HSV, Herpes simplex virus; VZV, Varicella zoster virus; CMV, cytomégalovirus and EBV, Epstein–Barr virus.

Flos verbasci [52] as well as the British Columbian plants *Cardamine angulata*, *Conocephalum conicum*, *Polypodium glycyrrhiza* [53] showed antiherpesvirus activity. The seed extract of an Indian medicament *Pongamia pinnata* inn showed *in vitro* anti-HSV activity [54], while the hot water extracts of 32 traditional medicaments used in China, Indonesia and Japan showed antiherpesvirus activity, of which 12 extracts were found to reduce the development of skin lesions caused by HSV-1 significantly and prolonging the mean survival time of HSV-1-infected mice [55]. Interestingly, the garlic extracts showed inhibitory activity against human cytomegalovirus (CMV) *in vitro* [56], while the steam distillate of *Houttuynia cordata* showed inhibitory activity against HSV-1 [57]. Wang *et al*. [58] reported the antiherpesvirus activity of ethanol extract of *Rheum officinale* Baill root and rhizome, while the aqueous extracts of *Helichrysum aureonitens* (Asteraceae) shoots inhibit HSV-1 [59]. The therapeutic activity of *Terminalia chebula* was demonstrated against HSV *in vivo* [60], while Japanese researchers found that *Terminalia chebula* significantly suppressed MCMV (murine CMV) yields in lungs of treated mice and also inhibit the replication of human CMV *in vitro* and in immunosuppressed mice. Hence, *Terminalia* may be beneficial for the prevention of CMV diseases in immunocompromised patients [61], but *Geranium sanguineum* L. showed antiherpesvirus activity [19]. Prescreening of Colombian plants used for the treatment of a variety of diseases revealed the antiherpetic activity by the aqueous extract of *Beta vulgaris*, ethanol extract of *Callisia grasilis* and the methanol extract of *Annona* sp. (CC_{50} 49.6×10^3 mg/ml) with acceptable therapeutic indexes (TIs) [62]. Similarly, the aqueous extracts of Argentinean medicament *Polygonium punctatum*, *Lithraea molleiodes*, *Sebastiana braselliensis* and *Sebastiania klotzschiana* used in infectious diseases showed *in vitro* antiherpetic activity (ED_{50} 39-169 μg/ml) with no cytotoxicity [63]. Interestingly, the aqueous extract of the most potent antiherpetic plant of South America *Eupatorium*

articulum inhibits HSV-1 at 125–250 μg/ml [64]. The extracts of seven traditional remedies of Indonesia demonstrated good anti-HSV-1 activity at 199 μg/ml, of which the methanol extracts of *Melaleuca leucadendron* (Myrtaceae) fruits and *Nephelium lappaceum* (Sapindaceae) pericarp significantly prolonged the development of skin lesions and reduced the mouse mortality [65]; while the hydromethanolic extracts of 23 Brazilian folk remedies including *Trixis praestans* (Vell) Cabr and *Cunila spicata* Benth showed strong inhibitory activity against HSV-1 and HSV-2 [66]. The combination of two Chinese herbs *Rhizoma Polygoni* Cuspidati and *Radix Astragali* at 1:1 is reported to annihilate HSV-1 F strain synergistically, with 20–80% plaque reduction. The combination can inhibit multiplication with combination index of <1.0 and is virucidal for HSV-1 F strain [67]. The Thai folk medicinal plant *Barleria lupulina* Lind and *Clinacanthus nutans* (Burm.f) Lindua (Acanthaceae) inhibit five clinical isolates and control strain (G strain) of HSV-2 [68], while aqueous extracts of *Nepeta nepetella*, *Nepeta coerulea*, *Nepeta tuberosa* (150–500 μg/ml), *Dittrichia viscosa* and *Sanguisorba minor magnolii* (50–125 μg/ml) of Iberian Peninsula showed strong anti-HSV-1 activity [69]. The oral administration of Japanese oriental medicineTJ-41 (200 mg/kg/day) is beneficial for the treatment of HSV-1 infection in immunocompromised cancer patients receiving chemotherapy [70], while the i.p. administration of black seed oil of *Nigella sativa* to BALB/c mice against a susceptible strain of MCMV strikingly inhibits the virus titers in spleen and liver. This striking antiviral effect against MCMV infection is probably mediated by increasing of M&phi number and gamma interferon (IFN-γ) production [71]. The aqueous extract of leaves and stems of *Phyllanthus orbicularis* (Euphorbiaceae) exhibited selective antiviral indexes of 12.3 and 26 against bovine HSV-1 and HSV-2, respectively; and impaired the replication of both viruses in a concentration-dependent manner, partially due to a direct interaction with virus particles or their entry into the cell [72]. Strong anti-HSV activity was also reported with *Byrsonima verbascifolia* extract, a remedy of skin infections in Colombia [73]. The anti-HSV-1 effect of essential oil-containing mouthwash (LA & TLA) on Vero cell monolayer showed that the undiluted LA and TLA completely inhibited HSV-1 McIntyre strain up to 1:2 dilutions, suggesting its preprocedural use in reducing viral contamination of bioaerosols during dental care [74]. Strong anti-HSV activities were noticed in methanolic extracts of 13 plants used in the treatment of skin infections in four regions of Colombia, where the most potent extract was *Byrsonima verbascifolia* L. HBK (2.5 μg/ml), indicating that these plants represent an untapped source of potentially useful antivirals [75]. Rajbhandari *et al*. [76] noticed that the Nepalese medicine *Holoptelia integrifolia* and *Nerium indicum* exhibited considerable anti-HSV activity without cytotoxicity. As the increasing use of acyclovir, ganciclovir and foscarnet against HSV, VZV and CMV leads to the emergence of drug-resistant strains, so when 31 herbs of Chinese medicine used as antipyretic

and anti-inflammatory remedy were screened, the ethanol extract of *Rheum officinale* and methanolic extract of *Paeonia suffruticosa* prevented the attachment and penetration of HSV; while the aqueous extract of *Paeonia suffruticosa* and ethanolic extract of *Melia toosendan* inhibited HSV attachment, indicating that these herbs have a potential for new anti-HSV compounds [77]; while *Senecio ambavilla* of La Reunion Island had anti-HSV-1 activity [78]. The hot water extracts of two medicinal plants of Taiwan exhibited anti-HSV activity with different degrees of potency, suggesting that these extracts merit further investigation [79]. Similarly, the extract of *Boussingaultia gracilis* var. *pseudobaselloides* (Basellaceae) and *Serissa japonica* (Rubiaceae) of Taiwan inhibits HSV-1 [80]. When BCC-1/KMC cells were infected with HSV and then cultured with hot water extract of *Bidens pilosa* L. var. minor (Blume) Sherff or *Houttuynia cordata* Thunb, the *Bidens pilosa* significantly inhibited the replication of HSV at 100 μg/ml (11.9% for HSV-1; 19.2% for HSV-2), whereas *Houttuynia cordata* had the same effect at 250 μg/ml (10.2% for HSV-1; 32.9% for HSV-2). The ED_{50} of HSV-1 and HSV-2 for *Bidens pilosa* was 655.4 and 960 μg/ml, respectively, but for *Houttuynia cordata* it was 822.4 and 362.5 μg/ml, with selective indexes above 1.04, but *Houttuynia cordata* had better effect against HSV-2 with low ED_{50}, indicating its usefulness against HSV-2 infection [81]. In a plaque reduction assay, 11 Thai medicinal plants exhibited anti-HSV activity at 100 μg/ml. Among them *Aglaia odorata*, *Moringa oleifera* and *Ventilago denticulata* were effective against thymidine kinase-deficient HSV-1 and phosphonoacetate-resistant HSV-1 strains. Significantly the extract of *Moringa oleifera* at 750 mg/kg per day delayed the development of skin lesions, prolonged the mean survival times and reduced the mortality of HSV-1 infected mice; while *Aoringa odorata* and *Ventilago denticulata* significantly reduce the development of skin lesions ($P<0.05$), similar to acyclovir. There was no significant difference between acyclovir and *Moringa oleifera* in prolonging the mean survival times. As these extracts were nontoxic in effective doses, hence may be possible candidates for new anti-HSV agent [82]. Chen *et al.* [83] reported that the extract of *Ceratostigma willmattianum* had anti-HSV-1 activity at 50% toxic concentration with an IC_{50} of 29.46 mg/l and TI of 36.56. While the same extract at 50% inhibiting concentration had IC_{50} of 9.12 mg/l and TI of 36.18, similar to acyclovir. Further study reveals that the extract interfere HSV-1 absorption, inhibit gD DNA replication and gD mRNA expression. Recently Tshikalange *et al.* [84] found that the extracts of *Senna petersiana*, a folk remedy of sexually transmitted diseases, have strong anti-HSV activity. On the contrary, Cheng *et al.* [85] reviewed the anti-HSV activity of *Terminalia arjuna*, *Myrica rubra*, *Thea* (*Camellia*) *sinensis* and *Pterocarya stenoptera* extracts, as well as their active phytochemicals alkaloids, flavonoids, saponins and quinines having anti-HSV activity with their mechanisms of action. A recent study by Ramzi *et al.* [86] with the methanol and hot aqueous extracts of 25

different plant species, used in Yemeni traditional medicine growing on the island Soqotra showed that 17 plants including *Boswellia ameero*, *Boswellia elongata*, *Buxus hildebrandtii*, *Cissus hamaderohensis*, *Cleome socotrana*, *Dracaena cinnabari*, *Exacum affine*, *Jatropha unicostata* and *Kalanchoe farinacea* have anti-HSV and anti-influenza A (IC_{50} 0.7–12.5 μg/ml).

A large number of isolated compounds from diverse chemical group(s) like phenolics, flavonoids, terpenoids, anthraquinones, phloroglucinol, lectins and sugars have promising antiherpetic activities [87]. The antiherpesvirus activities of several isolated compounds from herbal sources, with their probable mode of action, as reported from different laboratories, are presented in Table 3.

Phenolics and polyphenols

Phenolics are one of the largest groups of nonessential dietary components with diverse structure and activity, including 8,000 different compounds widely distributed in the plant kingdom. Phenolics are consisting of a hydroxyl group (–OH) attached to an aromatic hydrocarbon group, the simplest of the class is phenol (C_6H_5OH). Although similar to alcohols, phenols are unique since the –OH group is not bonded to a *saturated* carbon atom. They have relatively higher acidities due to the aromatic ring tightly coupling with the oxygen and a relatively loose bond between the oxygen and hydrogen. Loss of a hydrogen ion (H^+) from the hydroxyl group of a phenol forms a negative phenolate ion. The three most important groups of dietary phenolics are *flavonoids*, *phenolic acids* and *polyphenols*. Flavonoids are the largest and most studied group. Phenolic acids form a diverse group that includes the hydroxybenzoic and hydroxycinnamic acids. Phenolic polymers (known as tannins) are compounds of high molecular weight having two classes: hydrolyzable and condensed tannins. Phenols have traditionally been considered as antinutritive due to the adverse effect of tannins on protein digestibility. However, recent research showed that these compounds are biologically active and may possess some disease-preventive properties [88], as some polyphenolic complex can inhibit the reproduction of HSV [89]. Many phenolics are consumed in the diet that have health-promoting activities like inhibition of atherosclerosis, cancer, certain infections and can act as antioxidant (chelate metals, inhibit lipoxygenase and scavenge free radicals). A review on the organoleptic effects, metabolism and bioavailability of phenolics in humans, by Martinez-Valverde *et al*. [90], will be of great interest.

The simplest bioactive phytochemicals with a single substituted phenolic ring belongs to a wide group of phenylpropane that are in the highest oxidation state and have wide range of antiviral activities. It has been reported that the polyphenolic complex of *Geranium sanguineum* L. (Geraniaceae) inhibits HSV-1 multiplication [91], while the water extract of *Geranium sanguineum* L. aerial roots containing flavonoids, catechins and condensed tannins inhibit

Table 3. Antiherpetic antivirals from diverse chemical groups.

Natural product	Source	Antiviral activity ($\mu g\,ml^{-1}$)	Reference
Alkaloids			
Cepharanthine (Fig. 65)	*Stephania cepharantha*	HSV[a]	[65,173]
FK-3000 (Fig. 63)	*Stephania cepharantha*	HSV-1 (7.8)[b,c]	[65,173]
Harmine (Fig. 64)	*Ophiorrhiza nicobarica*	HSV-2 (300)[c,d]	[174]
Bis-benzylisoquinoline (Fig. 61),			
Protoberberine, morphine (Fig. 62),	*Stephania cepharantha* HAYATA	HSV-1 (18)[b]	
N-methylcrotsparine		ACV^R HSV-1, HSV-2 (7.8–9.9)[b]	
		(90, 71, 81)[e]	[65,173]
Phenolics			
Caffeic acid (Fig. 1)	*Plantago major*	HSV-1(15.3)[f], VZV[a]	[93]
Caffeic acid (Fig. 1)	*Plantago major*	HSV-2 (87.3)[f,d]	[93]
Chlorogenic acid (Fig. 1)	*Aloe barbadensis*	HSV-1 (47.6)[b]	
		HSV-2 (86.5)[b]	[32]
Procyanidin A1 (Fig. 7)	*Vaccinium vitis-idaea*	HSV-2[a,g]	[85,98]
Procyanidin C1 (Fig. 7)	*Crataegus sinaica*	HSV-1[a,d]	[99]
Prodelphinidine-*O*-gallate	*Myrica rubra*	HSV-2 (5.3)[b,d,g]	[94]
Rosmarinic acid (Fig. 2)	*Plantago major*	VZV[a]	[93]
Xanthohumol (Fig. 8)	*Humulus lupulus*	HSV[a,c]	[101]
Polyphenolic complex	*Geranium sanguineum* L.	HSV-1	[91]
Polyphenolic compounds	*Agrimonia pilosa*		
	Pithecellobium clypearia		
	Punica granatum	HSV-1	[95]
Polyphenols	*Geranium sanguineum* L.	HSV-1, HSV-2 (3.6–6.2)[f]	[19]
	Artocarpus lakoocha		
	Millettia erythrocalyx	HSV[a]	[140]
	Cretastigma willmaltianum	HSV-1 (9.12[b], 36.5)[e,d,h]	[83]
	Barleria lupulina	HSV-2[a]	[68]
Cochinolide B, tremulacin	*Homalium cochinchinensis*	HSV-1, HSV-2	[96]
Asiaticoside (Fig. 20)	*Centella asiatica*	HSV[a]	[119]
Mangiferin (Fig. 21)	*Mangifera indica*	HSV-1[a], HSV-2[a]	[119]
Propolis	Many plants	HSV	[117]
Flavonoids			
Amentoflavone (Fig. 23)	*Rhus succedanea*	HSV[i]	[186]
Catechin (Fig. 4)	Orange, grape	HSV-1[a]	[110]
Galangin (Fig. 15)	Helichrysum aureonitens	HSV[a]	[118]

Table 3. (*Continued*)

Natural product	Source	Antiviral activity ($\mu g\,ml^{-1}$)	Reference
Glycyrrhizin (Fig. 26)	Glycyrrhiza glabra	HSV-1	[46]
Hesperidin (Fig. 14)	Orange, grape	HSV[a]	[110]
Mulberroside C	Morus alba	HSV-1[a]	[125]
Resveratrol (Fig. 35)		HSV[a]	[136]
		HSV[a,h]	[139]
Oxyresveratrol (Fig. 36)	*Millettia erythrocalyx*	HSV[a]	[140]
Robustaflavone (Fig. 24)	*Garcinia multiflora*	VZV[a]	[123]
Torvanol A (sulfated isoflavone)	*Solanum torvum*	HSV-1 (9.6)[b]	[124]
Torvoside H (steroidal glycoside)	*Solanum torvum*	HSV-1 (23.2)[b]	[124]
Acetal Torvanol	*Solanum torvum*	HSV-1 (17.4)[b]	[124]
Quercetin (Fig. 13)	*Caesalpinia pulcherrima*	HSV-1 (24.3)[e], (20)[j,d]	[79,80]
Leachianone G	*Morus alba* L.	HSV-1 (1.6)[b]	[125]
Mulberroside C	*Morus alba* L.	HSV-1 (75.4)[b]	[125]
Phloroglucinol (Fig. 19)	*Mallotus japonicus*	HSV[a]	[31]
Methyl gallate (Fig. 18), methyl-trihydroxybenzoate	*Sapium sebiferum*	HSV[a]	[114]
Flavone glycoside	*Butea monosperma*	HSV[a]	[126]
Terpenes/sterols			
Apigenin (Fig. 29)	*Ocimum basilicum*	HSV-1[a]	[127]
Betulinic acid (Fig. 41)	Ocimum basilicum	HSV (2.6)[f]	[152]
	Syzygium claviflorum	HSV[a]	[151]
Epiafzelechin (Fig. 47)	*Cassia javanica*	HSV-2[a]	[153]
Isoborneol (Fig. 48)	*Melaleuca alternifolia*	HSV-1, 2 (0.06)[b,d]	[154,158]
Lupenone (Fig. 43)	*Euphorbia segetalis*	HSV-1, HSV-2[a]	[149]
Moronic acid (Fig. 42)	*Myrceugenia euosma*	HSV (3.9)[f]	[145]
	Rhus javanica	HSV-2[a]	[145]
Pulegone (Fig. 49)	Minthostachys verticillata	HSV-1 (10)[k]	[156]
Putranjivain A (Fig. 44)	*Euphorbia jolkini*	HSV-2 ($6.3\,\mu M$)[b,d,g]	[150]
Ursolic acid (Fig. 46)	*Geum japonicum*		
Sclerocarpic acid (sesquiterpene)	*Glyptopetalum sclerocarpum*	HSV-1, HSV-2	[143]
Scopadulcic acid B (diterpenoid)	*Scoparia dulcis* L.	HSV-1 (16.7)[e,d]	[141]
Triterpenes	*Cochlospermum tinctorium*	EBV[a,d]	[144]
	Crataegus pinatifida	HSV[a]	[144]
Quassinoids (Fig. 39)	–	EBV[a,d]	[142]
Limonoid, 28-deacetylsendanin	*Melia azedarach*	HSV-1 (1.46)[b,d,l]	[146]
Asiaticoside (Fig. 20)	*Centella asiatica* L.	HSV-1[a], HSV-2[a]	[119]
Mangiferin (Fig. 21)	Mangifera indica L.	HSV-1[a], HSV-2[a]	[119]

Table 3. (*Continued*)

Natural product	Source	Antiviral activity ($\mu g\,ml^{-1}$)	Reference
Steroidal glycoside	*Solanum* sp.	HSV[a]	[166]
Schizarin	*Kadsura matsudai*	HSV[a]	[170]
Salicin	*Homalium cochinchinensis*	HSV-1[a], HSV-2[a]	[96]
Volatile oil	*Melissa officinalis* L.	HSV-2[a]	[160]
Essential oil	*Minthostachys verticillata*	HSV[a]	[156]
	Melaleuca alternifolia	HSV[a]	[157]
	Eucalyptus	HSV[a]	[157]
	Santolina insularis	HSV[a]	[155]
Black seed oil	*Nigella sativa*	MCMV[a]	[71]
	Nelumbo nucifera	HSV-1[a]	[176]
Thiazolylsulfonamide	–	HSV[a,m]	[37,38]
Saponins			
8-Acetylharpagide, scorodioside	Bupleurum nigidum	HSV-1 (500)[b]	[168]
Saikosaponin (Fig. 58)	*Scrophularia scorodonia*	VSV[a]	[168]
Maesasaponin A	*Maesa lanceolate*	HSV-1[a], HSV-2[a]	[147,120]
Saponin glycosides (spirostane, tomatidane)	*Solanum* sp.	HSV-1[a]	[166]
Tannin			
Casuarinin (Fig. 57)	*Terminalia arjuna*	HSV-2 ($1.5\,\mu M$)[b,g]	[167]
Casuarinin (Fig. 57)	*Terminalia arjuna* L.	HSV-2[a]	[167]
Eugeniin (Fig. 55)	*Geum japonicum*	HSV-1[a], HSV-2[a], EBV[a]	[164]
	Syzygium aromaticum	Herpes virus	[164]
Samaragenin B	*Limonium sinensi*	HSV-1[a]	[36]
Isomeranzin	*Clausena heptaphylla*	HSV[a]	[133]
Ellagitannins	*Phyllanthus myrtifolius*, *Phyllanthus urinaria*	EBV[a,h]	[165]
Euglobal-G1–G3	*Eucalyptus grandis*	EBV[a]	[162]
n-Docosanol	–	HSV-1[a]	[41,39]
Lignans			
Yatein (Fig. 60)	*Chamaecyparis obtusa*	HSV-1[a,d,h]	[172]
Carbohydrate			
Polysaccharide	*Selerotium glucanicum*	HSV-1[a]	[33]
Acidic polysaccharide	*Cedrela tubiflora*	HSV-2[a,d]	[182]
Anionic polysaccharide	*Prunella vulgaris*	HSV-1 (100)[c], HSV-2 (10)[c]	[184]
Sulfated galactans	*Bostrychia montagnei*	HSV[a,d]	[181]
	Many plants	HSV[a,d]	[180]
Galactofucan	*Undaria pinnatida*	HSV-1, HSV-2[a]	[183]
Proteins and peptides			
Meliacine	*Melia azedarach*	HSV-1[a,d]	[179]
		HSV-1[a]	[179]

Table 3. (*Continued*)

Natural product	Source	Antiviral activity ($\mu g\,ml^{-1}$)	Reference
Mannose-specific lectins	*Listera ovata*	CMV (0.08)[f]	[178]
(GlcNAc)*n*-specific lectin	*Urtica dioica*	CMV (0.3–9)[f]	[177]

Notes: HSV, Herpes simplex virus; VZV, Varicella zoster virus; CMV, cytomegalovirus; MCMV, murine cytomegalovirus and EBV, Epstein–Barr virus.
[a]$IC_{50}/EC_{50}/ED_{50}$ not available.
[b]IC_{50}.
[c]Virus-induced cytopathic effects.
[d]Virus replication/multiplication.
[e]TI.
[f]EC_{50}.
[g]Attachment and penetration.
[h]Infected cell polypeptide/DNA polymerase inhibitor.
[i]DNA replication/gene expression inhibitor.
[j]SI, Inhibit:
[k]ED_{50}.
[l]Thymidine kinase.
[m]Helicase-primase.

HSV-1 and HSV-2 (EC_{50} 3.6–6.2 μg/ml) in a dose-dependent strain-specific manner with least toxicity. But at MIC_{90} (120 μg/ml) the extract exhibits strong extracellular inactivation in HSV-1 Kupka strain-infected albino guinea pigs and delayed the development of herpetic vesicles [19]. Hence, they pointed out that polyphenolics like caffeic acid, chlorogenic acid (Fig. 1) and rosmarinic acid (Fig. 2) derivatives can inactivate HSV-1 and VZV. *Sydiskis et al.* [32] found that the hot glycerin extracts containing anthraquinones isolated from *Rheum officinale*, *Aloe barbadensis*, *Rhamnus frangula*, *Rhamnus purshianus* and *Cassia angustifolia* can inactivate HSV-1; while the purified aloe emodin is virucidal to HSV-1, HSV-2 and VZV by partial disruption of envelopes of these viruses. Interestingly caffeic acid phenethyl ester (CAPE), an active component of propolis from honeybee hives (Fig. 3), showed anticancer, anti-inflammatory, immunomodulatory and anti-HSV activities [92]. The aqueous extract of *Plantago major* L., a popular ethnomedicine used in Ayurveda, traditional Chinese medicine (TCM) and Chakma Talika Chikitsa of "Chakma" tribes of Chittagong Hill, Bangladesh, for treating several ailments from cold to viral hepatitis, was reported to posses antiherpesvirus activity; while its isolated phenolics caffeic acid (Fig. 1) exhibited the strongest activity against HSV-1 (EC_{50} 15.3 μg/ml, SI 671) and HSV-2 (EC_{50} 87.3 μg/ml, SI 118), by inhibiting viral multiplication suggesting its potential use for treatment of HSV infection [93]. The SAR studies revealed that chlorogenic acid and caffeic acid can be developed as an improved antiherpes agent [87]. The SAR studies revealed that the

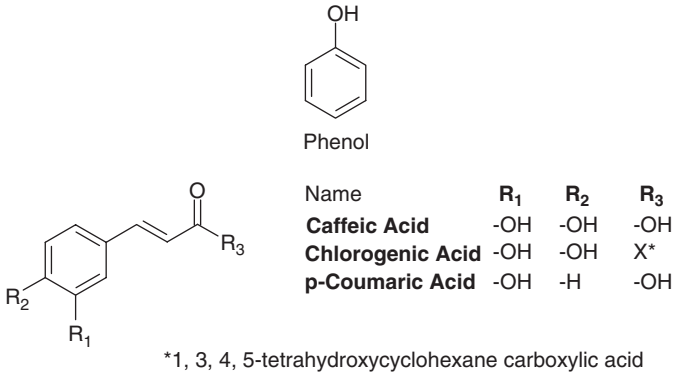


Fig. 1. Structure of caffeic acid and its derivatives.

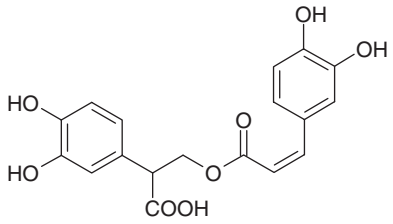


Fig. 2. Rosmarinic acid.

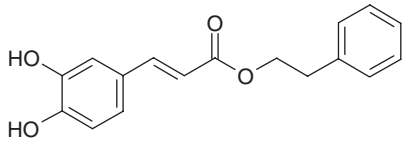
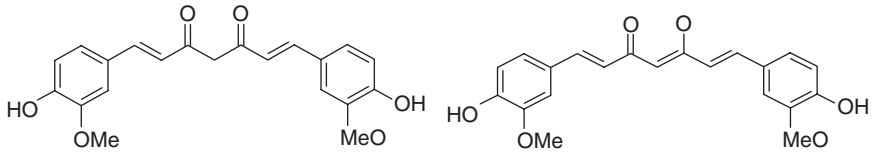


Fig. 3. Caffeic acid phenyl ester.

site(s) and number of hydroxyl groups on phenols are responsible for their antiviral activity as found with the catechin (Fig. 4), catechol (Fig. 5) and pyrogallol (Fig. 6). The prodelphinidin-di-*O*-gallate isolated from *Myrica rubra* bark demonstrated *in vitro* anti-HSV-2 activity by inhibiting viral attachment and penetration, reducing viral infectivity and affecting the late stage of infection [94]; while the polyphenolics of *Agrimonia pilosa*, *Pithecellobium clypearia* and *Punica granatum* showed anti-HSV-1 activity [95]. Cochinolide B, tremulacin and tremuloidin isolated from *Homalium cochinchinensis* root bark showed activity against HSV-1 and HSV-2 [96]. Polyphenols and proanthocyanidins isolated from *Hamamelis virginiana* bark had remarkable anti-HSV-1 activity [97] while proanthocyanidins A1 (Fig. 7) isolated from *Vaccinium vitis-idaea* block HSV-2 attachment and



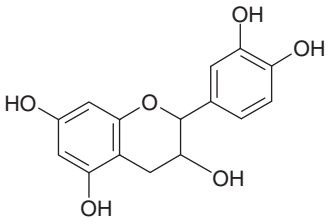


Fig. 4. Catechin ($C_{15}H_{14}O_6$).

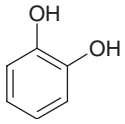


Fig. 5. Catechol ($C_6H_6O_2$).

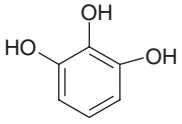


Fig. 6. Pyrogallol.

penetration [98], but oligomeric procyanidins of *Crataegus sinaica* significantly inhibit HSV-1 [99], as proanthocyanidins nonspecifically bind proteins, but selectively inhibit nuclear factor kappa B (NFkB)-dependent gene expression, as reported with proanthocyanidin C1 (Fig. 7) that modulate apoptosis and inhibit NFkB activities [100]. A xanthohumol (Fig. 8)-enriched *Humulus lupulus* (hop) extract showed moderate activity against HSV-1 ($TI > 1.9$) and HSV-2 ($TI > 5.3$) and CMV with low IC_{50}, while its isomer iso-alpha acids revealed better activity against CMV, suggesting that it might serve as a lead for synthesizing more active antiherpetic agent [101]. An interesting SAR is noted with dimeric procyanidins (Fig. 7) and related polyphenols, where epicatechin-containing dimers (Figs. 9 and 10) showed pronounced anti-HSV activities, as the *o*-trihydroxyl groups in the B-ring and the double interflavan linkages lead to

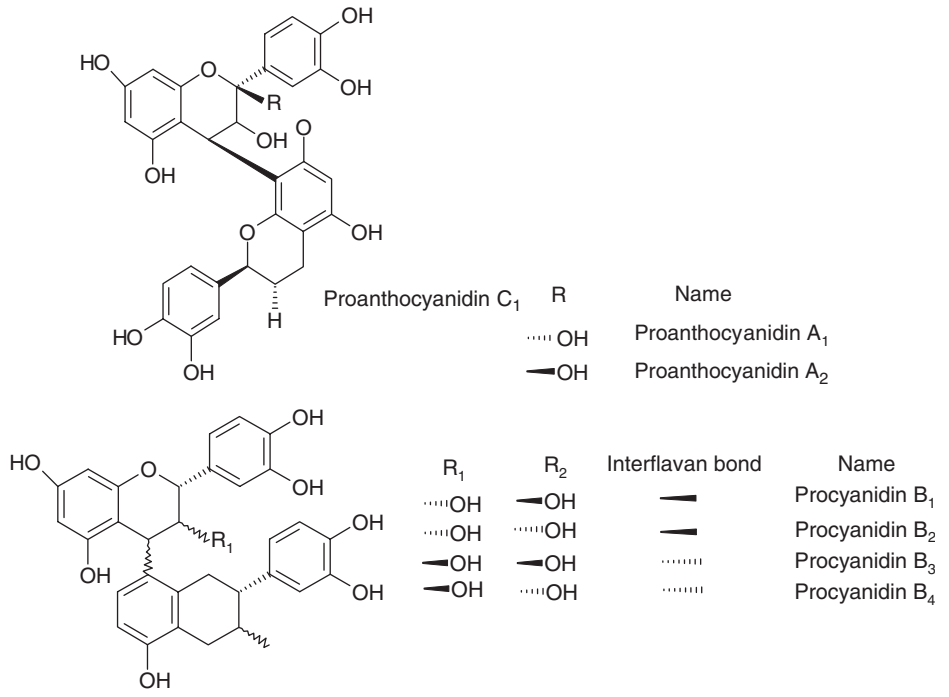


Fig. 7. Proanthocyanidins.

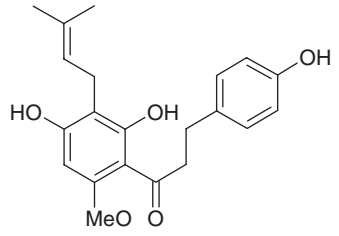


Fig. 8. Xanthohumol.

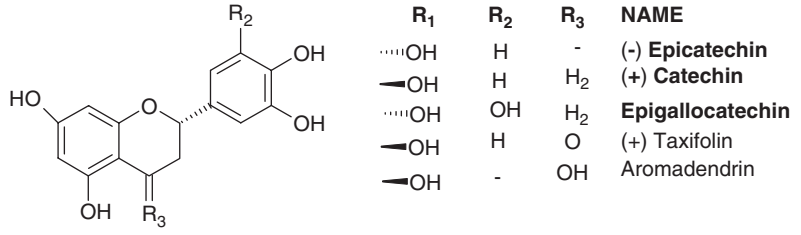


Fig. 9. Epicatechin and its dimmers.

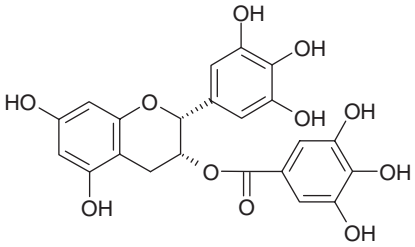
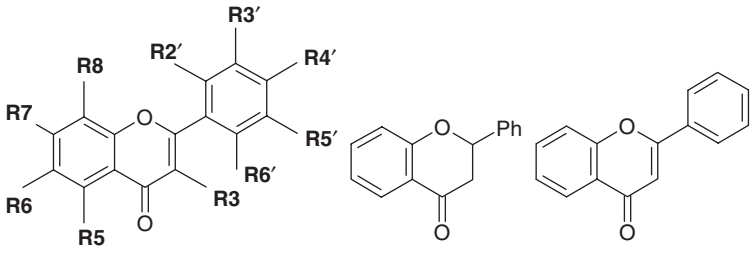


Fig. 10. (−) Epigallocatechin-3-*O*-gallate.

a significant increase of the anti-HSV effects. The phenolics like flavonoids and dimeric stilbenes from *Artocarpus gomezianus* Wall. ex tréc., phloroglucinol derivatives from *Mallotus pallidus* Airy Shaw and coumarins from *Triphasia trifolia* (Burm.f.) P. Wilson when tested against HSV-1 and HSV-2 showed that the bis-hydroxyphenyl structure as a potential target for anti-HSV drugs development [102]. The polyphenols often showed virucidal activity, which may be due to their association with proteins and/or host cell surfaces, resulting in reduction or prevention of viral adsorption [103].

Flavones, flavonoids and flavonols

Flavonoids are a group of natural polyphenolics occurring in fruits, vegetables and beverages, and can exert potent antioxidant and several other effects [104,105]. Bioflavonoids, the basis of many herbal remedies are considered as health-promoting, disease-preventing dietary compounds, and some have therapeutic application or used as prototypes for drug development. Increased intake of flavonoids was found to be associated with reduced risk of cardiovascular and inflammatory diseases, cancer and infections may be due to their inherent capacity to counteracting oxidative stress by scavenging reactive oxygen and nitrogen-free radical species [105,106]. Flavones are hydroxylated phenolics containing one carbonyl group (Fig. 11) instead of two in quinines, while the addition of a third hydroxyl group yields a flavonol (Fig. 11). The flavonoids (Figs. 11 and 12) occur as a C_6–C_3 unit linked to an aromatic ring and are synthesized in response to microbial infections, hence had broad spectrum of antimicrobial activity. Several reviews [44,107,108] have emphasized the great variety of viruses tested and also the diversity of methods used which demonstrated antiviral activities of flavonoids by direct inactivation or antireplicative effects. Several flavonoids like quercetin (Fig. 13), procyanidin and pelargonidin are virucidal to HSV [109] and the direct inactivation of HSV by catechin (Fig. 4) and hesperidins (Fig. 14) has also been verified [110]. Till date, only a few studies have been reported on the anti-HSV activity of flavonoids (Figs. 11 and 12). The flavonoids quercetin (Fig. 13), and galangin (Fig. 15), naringenin (Fig. 11), kaempferol (Fig. 16) and 3-methyl kaempferol



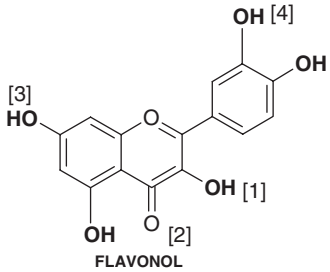
FLAVONOID **FLAVONE** **FLAVONOL**

Compound	R3	R5	R6	R7	R8	R2′	R3′	R4′	R5′
Flavanol									
(+/-) Catechin hydrate	OH	OH	H	OH	H	H	OH	OH	OH
Epicatechin	OH	OH	H	OH	H	H	OH	OH	H
Epicatechin gallate	OH	OH	H	OH	H	OH	OH	H	H
Epigallocatechin	OH	OH	H	OH	H	H	OH	OH	H
Epigallocatechin gallate	OH	OH	H	OH	H	H	OH	OH	OH
Flavanone									
Naringenin	H	OH	H	OH	H	H	H	OH	H
Naringin	H	OH	H	Rg	H	H	H	OH	H
Flavone									
Apigenin	H	OH	H	OH	H	H	H	OH	H
Chrysin	H	OH	H	OH	H	H	H	H	H
Luteolin	H	OH	H	OH	H	H	OH	OH	H
Rutin	M/g-py	OH	H	OH	H	H	H	OH	OH
Flavonol									
Baicalin	H	OH	OH	OH	H	H	H	H	H
Fisetin	OH	H	H	H	H	H	OH	OH	H
Galangin	OH	OH	H	OH	H	H	H	H	H
Kaempferol	OH	OH	H	OH	H	H	H	OH	H
Myricetin	OH	OH	H	OH	H	H	OH	OH	OH
Quercetin	OH	OH	H	OH	H	H	OH	OH	H
Isoflavone									
Genistein	H	OH	H	OH	H	H	H	OH	H

Rg, Rahmno glucoside; M/g-py, Rutin manno/gluco-pyranosyl

Fig. 11. Structure of different flavonoids.

(Fig. 17) showed potent antiherpetic activity in Vero cells [111], and the antiviral activity of flavonoids (Fig. 12) is due to the inhibition of viral attachment and penetration or inhibition of reverse transcriptase (RT) enzyme [112] and augmentation of the degree of sulfation [113]. Kane *et al.* [114] reported that the methyl gallate (Fig. 18) and methyl-3,4,5-trihydroxy-benzoate (Fig. 18) from *Sapium sebiferum* are the potent and highly specific



FLAVONOL

Remove OH at [1]: Flavone
Replace OH at [1] with 3rd ring: Isoflovone
Replace O at [2] with H: Anthocyanin
Replace OH at [3] with Glucose;
Remove OH at [4]; Remove OH at [1]:Glucoside

Flavonoids	Toxicity CC_{50} (μM)	Antiviral activity EC_{50} (μM)		Selectivity index (SI)	
		HSV-1	HSV-2	HSV-1	HSV-2
Acyclovir	500	50.0	50.0	10.0	10.0
(+/-) Catechin	>1,000	4.0	6.2	250.0	60.0
EC	100	2.5	35.0	40.0	2.9
ECG	500	4.0	63.0	125.0	7.9
EGC	250	2.5	NA	100.0	NA
EGCG	100	2.5	NA	40.0	NA
Naringenin	750	4.0	22.5	187.5	33.3
Naringin	1,000	2.5	NA	400.0	NA
Apigenin	250	5.0	NA	50.0	NA
Chrysin	10	2.5	NA	4.0	NA
Luteolin	100	5.0	NA	20.0	NA
Rutin	10,000	5.0	NA	2,000.0	NA
Baicalin	1,000	5.0	NA	200.0	NA
Fisetin	100	2.5	NA	40.0	NA
Galangin	1,000	2.5	NA	400.0	NA
Kaempferol	50	15.0	NA	3.3	NA
Myricetin	100	5.0	NA	20.0	NA
Quercetin	100	5.0	35.0	20.0	2.9
Genistein	250	5.0	50.0	50.0	5.0

CC_{50} is the 50% cytotoxic effect concentration; EC_{50} is the 50% effective concentration; Selectivity index (SI) = CC_{50}/EC_{50}. NA, Not available
HSV-1: herpes simplex virus type 1 (KOS strain); HSV-2: herpes simplex virus type 2 (G strain).
EC, Epicatechin; ECG, Epicatechin gallate; EGC, Epigallocatechin; EGCG, Epigallocatechin gallate.

Fig. 12. SAR of some flavonoids against HSV-1 and HSV-2.

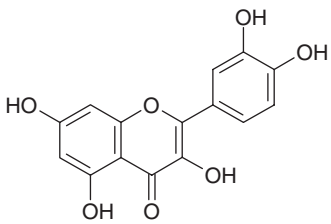


Fig. 13. Quercetin (3,3′,4′,5,7-pentahydroxy flavone).

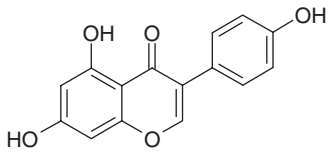


Fig. 14. Hesperidin.

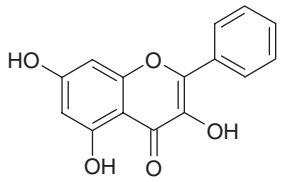


Fig. 15. Galangin.

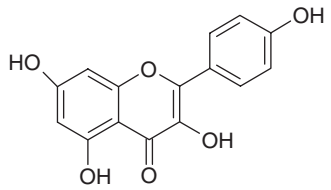


Fig. 16. Kaempferol (3,4′,5,7-tetrahydroxy flavone).

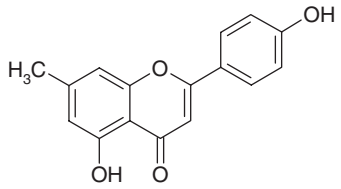


Fig. 17. 3-Methyl kaempferol.

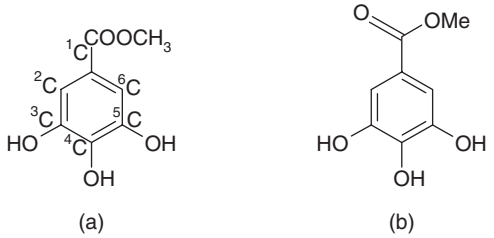


Fig. 18. (a) Methyl gallate and (b) methyl benzoate.

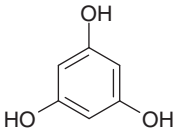


Fig. 19. Phloroglucinol.

inhibitor of HSV, but the phloroglucinol (Fig. 19) derivatives of *Mallotus japonicus* (Euphorbiaceae) had antiherpetic activity [31]; while the combination of flavonoids and acyclovir inhibit herpesviruses in cell culture [115]. Traditionally, herbal medicinal products rely on both ''pure'' single-plant preparations and mixed formulations with many plants. Propolis, a crude extract of the balsam of various trees inhibits acyclovir-resistant HSV-1 and VZV due to the synergistic action of a mixture of terpenoids, flavonoids, benzoic acids esters and phenolic acid esters; while flavone and flavonol were active in isolation against HSV-1 [116]. In another study propolis and 3-methyl-but-2-enyl caffeate showed to inhibit HSV activities [117], while 0.5% aqueous extract of propolis showed 50% inhibition of HSV-1 infection and prevention of animal infection by blocking virus absorption and/or inhibition of early steps of viral replication [92]. The hesperidin (Fig. 14) of orange and grape inhibits replication of HSV, catechin (Fig. 4) inhibits infectivity of HSV-1, but quercetin (Fig. 13) inhibits all, as the small structural differences of these compounds are critical to their activity [110]; while antibacterial galangin or 3,5,7-trihydroxyflavone (Fig. 15) isolated from *Helichrysum aureonitens* had significant activity against HSV-1 [118]. The *Centella asiatica* L., *Maclura cochinchinensis* Cornor, and *Mangifera indica* L. used as herpesvirus remedies in Thailand are found to inhibit HSV-1 and HSV-2 in plaque inhibition assay, as well as inhibition of infectious HSV-2 virion production in infected Vero cells. Combinations of each of these extracts with acyclovir resulted either in synergistic, subadditive or additive interaction in a dose-dependent manner, due to the active constituent asiaticoside (Fig. 20) of *Centella asiatica* and mangiferin (Fig. 21) of *Mangifera indica* with good therapeutic potential [119]. The virucidal activities of iridoid maesasaponin of *Maesa lanceolata* against HSV-1 are found to be due to diacylation [120]. The morin (Fig. 22), a flavonoid group, isolated from ethyl acetate extract of *Maclura cochinchinensis* have powerful anti-HSV-2 activity (EC_{50} 38.5–53.5 μg/ml), due to free hydroxyl groups [121]. The amentoflavone (Fig. 23) and robustaflavone (Fig. 24) isolated from *Rhus succedanea* and *Garcinia multiflora* inhibits HSV *in vitro* while VZV were inhibited by rhusflavanone and succedaneflavanone [122,123]. The C-4 sulfated isoflavone torvanol A and the steroidal glycoside torvoside H, isolated from *Solanum torvum* fruits had strong anti-HSV-1 activity [124]. It was found that the quercetin (Fig. 13) of *Caesalpinia pulcherrima* Swartz possessed a broad-spectrum antiviral activity against HSV-1 and ADV-8

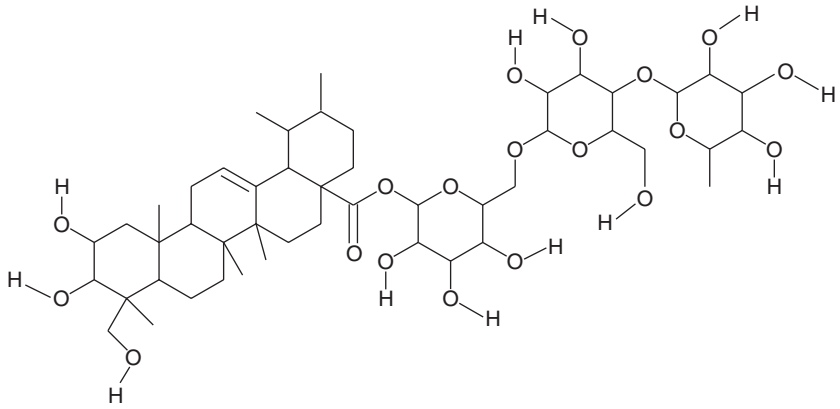


Fig. 20. Asiaticoside.

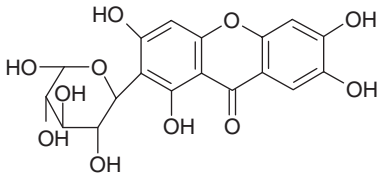


Fig. 21. Mangiferin ($C_9H_{18}O_{11}$).

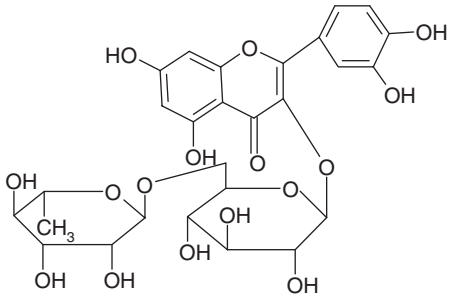


Fig. 22. Morin (2′,3,4′,5,7-pentahydroxy flavone).

(EC_{50} 24.3–50 mg/l, SI 20.4–60), by inhibiting early stage of multiplication with SI values greater than 20, suggesting the potential use of this compound for treatment of HSV infection [80]. The prenylated flavonoid flavescenones derivative leachianone G (Fig. 25) isolated from the root bark of *Morus alba* L. showed potent antiviral activity (IC_{50} 1.6 μg/ml), whereas mulberroside C showed weak activity (IC_{50} 75.4 μg/ml) against HSV-1 [125]. Similarly the isoquercitrin of *Waldsteinia fragarioides* has anti-HSV activity, while glycyrrhizin (Fig. 26) and chrysin (Fig. 27) of many plants showed

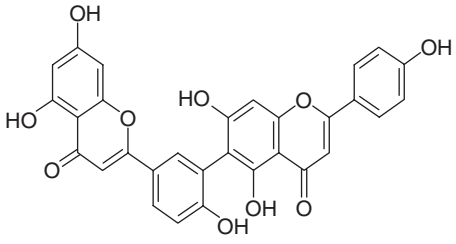


Fig. 23. Amentoflavone.

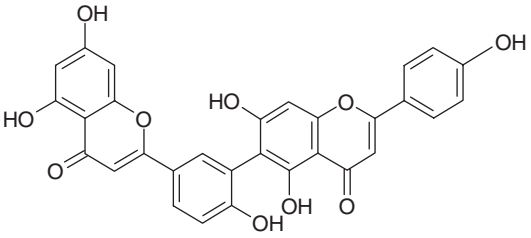


Fig. 24. Robustaflavone.

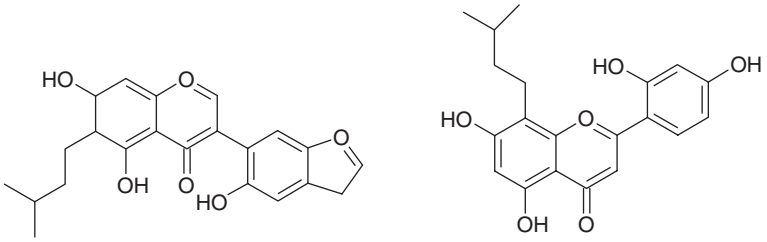


Fig. 25. (a) Flavescenones and (b) leachianone G.

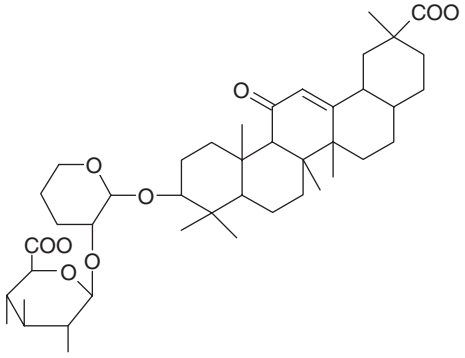


Fig. 26. Glycyrrhizin.

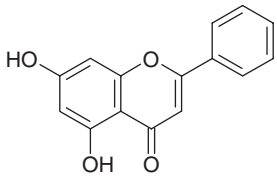


Fig. 27. Chrysin.

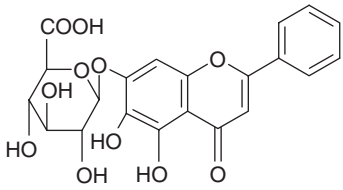


Fig. 28. Genistein.

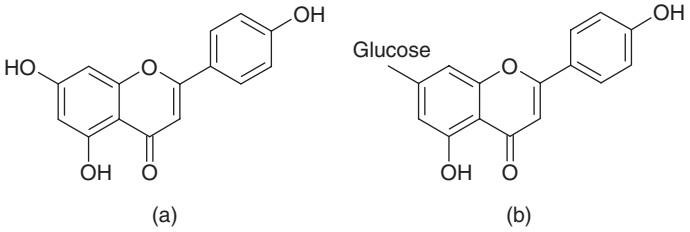


Fig. 29. (a) Apigenin (4′,5,7-trihydroxy flavone). (b) Apigenin-7 monoglucoside.

antiherpetic activities [46]. A flavone glycoside dihydroxy-trimethoxyflavone-β-d-xylopyranosyl-β-d-glucopyranoside of *Butea monosperma* seed showed broad antiviral spectrum [126]. When 18 flavonoids of five classes were tested at various concentrations to Vero cells infected with HSV-1 and HSV-2, most of them showed inhibitory effects on virus-induced cytopathic effect (CPE). Among them, flavanols epicatechin and epicatechin gallate (Fig. 11), isoflavone genistein (Fig. 28), flavanone naringenin and flavonol quercetin (Fig. 13) showed a high level of CPE inhibitory activity. Epicatechin, epicatechin gallate, galangin and kaempferol showed a strong antiviral activity, while catechin, epigallocatechin, epigallocatechin gallate, naringenin, apigenin (Fig. 29), chrysin (Fig. 27), baicalin (Fig. 30), fisetin, myricetin (Fig. 31), quercetin and genistein (Fig. 28) showed moderate inhibitory effects against HSV-1 in plaque reduction assay. Hence, flavanols and flavonols appeared to be more active than flavones, which is due to their structural differences (Figs. 11 and 12). Furthermore, treatment of Vero cells with epicatechin gallate (Fig. 10) and galangin (Fig. 15) before virus adsorption led to a slight enhancement of inhibition by yield reduction assay, indicating that

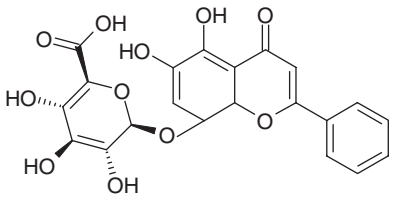


Fig. 30. Baicalin.

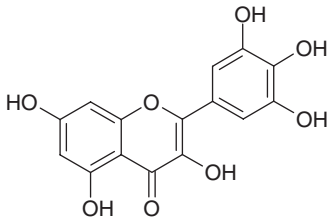


Fig. 31. Myricetin (3,3′,4′,5,5′,7-hexahydroxy flavone).

an intracellular effect may also be involved [127]. Hence, the flavonoids like quercetin, chrysin, epicatechin and (−)-epigallocatechin gallate showed antiherpesvirus activity and it was observed that most of the potent antiviral flavonoids block viral DNA/RNA polymerase, where the degree of inhibition depends on the structure and side chain (Figs. 11 and 12). The evidence of oxidative stress in virus-infected individuals indicates that antioxidants like flavonoids and proanthocyanidins with low oral bioavailability may have some role in controlling viral disease progression [128,129]. The evaluation of *in vivo* effect of antioxidants on viral diseases need monitoring of oxidative stress as excessive antioxidant protection could lean over the balance from oxidative stress to "oxidative deficit". The reactive oxygen species, antioxidants, transcription factors and cytokines are essential for life and a part of human defense network that behaves like a black box. Hence, controlled clinical trials with antioxidants, along with oxidative stress measurement will help to determine the clinical significance of oxidative stress on viral diseases; and dietary intervention with antioxidants could be an inexpensive alternative to the existing antiviral treatment strategies.

Coumarins

The double-ring phenolic compounds made up of fused benzene and α-pyrone rings called coumarin (Fig. 32). The coumarins (Figs. 32 and 33) impart the distinctive sweet smell to newly mown hay. Till date at least 1,300 coumarins have been identified. Though coumarins are highly toxic in rodents, they have a "pronounced species-dependent metabolism" and their derivatives are safely excreted in human urine [130]. Coumarins comprise a

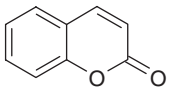


Fig. 32. Coumarins.

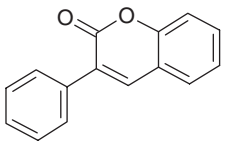


Fig. 33. 3-Phenylcoumarin.

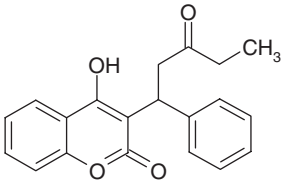


Fig. 34. Warfarin.

vast array of biologically active compounds ubiquitous in herbal medicinal products used in traditional medicine for thousands of years. Coumarins have antithrombotic, anti-inflammatory, antioxidant, vasodilatory, antiallergic, hepatoprotective, anticarcinogenic, enzyme inhibitor, precursors of toxic substances, plant growth hormones, respiration, photosynthesis, as well as in defense against infection. Owing to its phenolic nature with fused benzene and α-pyrone rings coumarins can stimulate macrophages and thereby exert an indirect effect on viral infections like inhibition of recurrences of cold sores caused by HSV-1 [131]; while several structurally novel coumarin derivatives like warfarin (Fig. 34) showed substantial anti-HIV activity that can be used to develop important lead compounds for antiretroviral drugs [132]. The hydroxycoumarins can act as potent metal chelators, free radical scavenger and powerful chain-breaking antioxidants. The topical tree *Clausena heptaphylla* (Roxb.) W. & Arn. (Rutaceae) leaves, widely used in China, India and Vietnam to treat fever, showed anti-HSV activity against HSV-1 and HSV-2 in Vero cells at 0.5 mg/ml (provided 40% protection) with little to no cytotoxicity; while the ethyl acetate extract provided 70% protection against both HSV-1 and HSV-2 with minor cytotoxicity; hence, coumarins of *Clausena heptaphylla* can be developed as an anti-HSV agent [133]. The 1,4-dihydropyridine-5-carboxylic acid and pyridine-5-carboxylic acid derivatives comprising a coumarin group is reported to have broad spectrum of antiviral activities, especially against CMV (AD-169 and Davis strain), HSV-1 (KOS, F, Mclntyre, Thymidine Kinase (TK)-B2006,

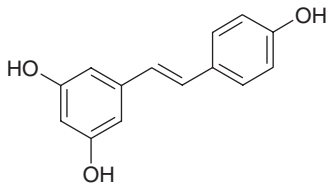


Fig. 35. Resveratrol.

TK-VMW1837, TK-Cheng C158/77, TK-Field C137/101), HSV-2 (G, 196, Lyons) and VZV (TK + OKA, TK + YS, TK − 07/1, TK − YS/R) strains (International patent WO 01/14370, Rephartox B.V.). A recent review on *in vitro* and *in vivo* antiviral, antitumor, anti-inflammatory activities of prenyloxy- and furano-coumarins by Curini *et al*. [134] can be consulted for further studies.

Phytoalexins are hydroxylated derivatives of coumarins, produced in response to microbial infection by many plants, and have anti-infective activity. A polyphenolic phytoalexin resveratrol (http://en.wikipedia.org/wiki/Image:Resveratrol.png; 3,5,4′-trihydroxystilbene; Fig. 35) produced by several plants as defense, is reported to have antimicrobial activities [45] and is used as a nutritional supplement having antiviral, anticancer, neuroprotective, antiaging and anti-inflammatory effects. Resveratrol (http://en.wikipedia.org/wiki/Image:Resveratrol.png; stilbenoid; Fig. 35), a derivate of stilbene is produced by the enzyme stilbene synthase, in two isomeric forms: *cis*- (*Z*) and *trans*- (*E*). The *trans*- form can undergo isomerization to the *cis*- form when heated or exposed to ultraviolet irradiation [135] and is found in varying amounts in grapes, berries, plums, peanuts, *Vaccinium* species, some pines and knotweed. Resveratrol was first isolated from the Peruvian legume *Cassia quinquangulata* in 1974, and its anti-inflammatory activity was recognized in 1997 [25]. It was reported that resveratrol inhibits HSV replication by suppressing NFkB activation [136], as HSV activates NFkB during productive infection as an essential step of its replication cycle [137,138]. Electromobility shift assays demonstrated that resveratrol suppressed NFkB activation in HSV-1, HSV-2 and acyclovir-resistant HSV-1 in a dose-dependent and reversible manner; while reduces mRNA for ICP0, ICP4, ICP8 and DNA polymerase and mRNA for glycoprotein C (a late gene), thus significantly blocked DNA synthesis. These data collectively indicate that resveratrol suppresses HSV-induced activation of NFkB within the nucleus, impairs expression of essential immediate-early, early and late HSV genes and synthesis of HSV DNA [139]. Similarly another phytoalexin oxyresveratrol (Fig. 36) of *Millettia erythrocalyx* and *Artocarpus lakoocha* inhibit both HSV and HIV-1 [140].

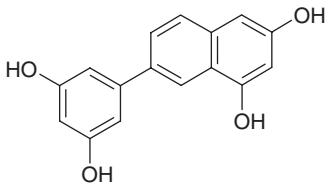


Fig. 36. Isostere of oxyresveratrol.

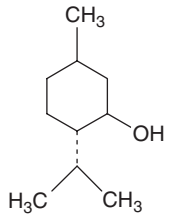


Fig. 37. Terpenoid (menthol).

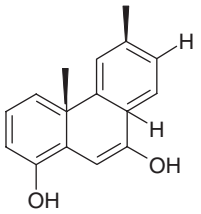


Fig. 38. Scopadulic acid analogs.

Terpenoids and essential oils

Essential oils (*Quinta essentia*), the fragrance of plants, are the phenolic compounds with a C_3 side chain and at a lower level of oxidation without oxygen. The oils that are highly enriched in isoprene structure are called terpenes, and when contain additional elements like oxygen, they are termed as terpenoids (Fig. 37) that are active against many viruses [46,87,128]. Scopadulcic acid B (Fig. 38), a diterpenoid isolated from *Scoparia dulcis* L. was found to inhibit HSV-1 replication *in vitro* (TI 16.7) by interfering with early events of viral growth, effectively prolonged the appearance of herpetic lesions and the survival time in hamster at 100–200 mg/kg/day [141]; while the triterpene quassinoids (Fig. 39) inhibit Epstein–Barr virus (EBV) [142]. Sclerocarpic acid (Fig. 40), a sesquiterpene isolated from the stem bark of *Glyptopetalum sclerocarpum* (Celeastraceae) showed antiviral activity against HSV-1 and HSV-2 [143]. Triterpenes from *Cochlospermum tinctorium* can inhibit EBV [144]. The triterpene betulinic acid (Fig. 41) and moronic acid (Fig. 42) of *Rhus javanica* showed inhibitory activity against

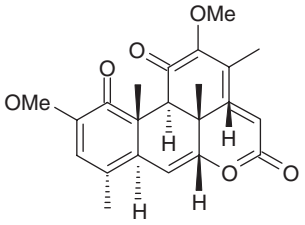


Fig. 39. Quassinoids (quassin).

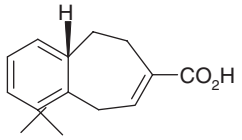


Fig. 40. Sclerocarpic acid.

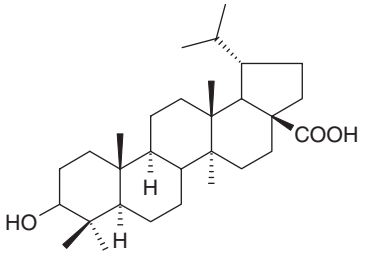


Fig. 41. Betulinic acid.

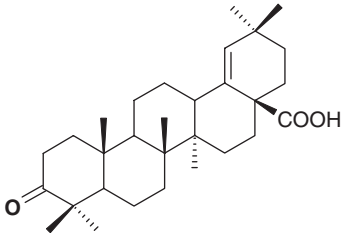


Fig. 42. Moronic acid.

acyclovir-resistant, thymidine kinase-deficient and wild-type HSV-1 strains with an EC_{50} of 2.6–3.9 μg/ml, respectively [145]. Oral administration of moronic acid (Fig. 42) to cutaneously infected mice with HSV-1 significantly retarded skin lesions and/or prolonged the mean survival times of infected mice without toxicity by suppressing virus yields to the brain [145] and therefore, can be a good anti-HSV agent with a different mechanism of

action than that of acyclovir. The limonoid terpene 28-deacetylsendanin (DAS) from *Melia azedarach* fruit showed anti-HSV-1 activity (IC_{50} 1.46 μg/ml) without cytotoxicity (400 μg/ml). Electron microscopy revealed low electron-dense cores of newly synthesized nucleocapsid in nuclei without any extracellular virus particles and the plaque assay confirmed that 77% of progeny viruses killed in DAS-treated virus-infected cells. The virus replication was inhibited along with reduced synthesis of TK at early stage, leading to the formation of defective nucleocapsid [146]. Aqueous EtOH (80%) extracts of two plants used by Rwandan traditional healers to treat infections showed anti-HSV activity, of which MeOH extract of *Maesa lanceolate* containing maesasaponin A exhibited virucidal activity against HSV-1 and HSV-2 [147]. It has been found that the seeds of *Pachyrrhizus erosus* (Leguminosae) contain rotenoids 12a-hydroxydolineone, 12a-hydroxypachyrrhizone with moderate anti-HSV activity [148]. The tetracyclic triterpenes lupenone (Fig. 43) of *Euphorbia segetalis* exhibited strong viral plaque inhibitory effect against HSV-1 and HSV-2 [149]; while the diterpene putranjivain A (Fig. 44), isolated from *Euphorbia jolkini* significantly reduced infectivity (IC_{50} 6.3 μM), inhibit viral attachment and cell penetration as well as late stage of HSV-2 replication [150]. The oleanolic acid (Fig. 45), a triterpenoid saponin of oleanane group inhibits DNA synthesis, while the member of ursane group inhibits capsid protein synthesis of HSV-1 [151]. The extract of *Ocimum basilicum*, sweet basil of Indian and Chinese medicine, showed antiviral activity against diverse virus families. The aqueous and ethanolic extract along with purified apigenin (Fig. 29), linalool and ursolic acid (Fig. 46) from basil showed strong activity against HSV-1. Of these ursolic acid (Fig. 46) showed the strongest activity against HSV-1 (EC_{50} 6.6 mg/l), while apigenin (Fig. 29) showed the highest activity against HSV-2. The antiviral activity of ursolic acid (Fig. 46) is evident during the infection process and the replication phase, indicating its potential against some viruses [152]. A recent study reported that *ent*-epiafzelechin-(4α->8)-epiafzelechin (EEE; Fig. 47) isolated from fresh leaves of *Cassia javanica* L. *agnes* de Wit inhibits HSV-2 replication in a dose-dependent manner

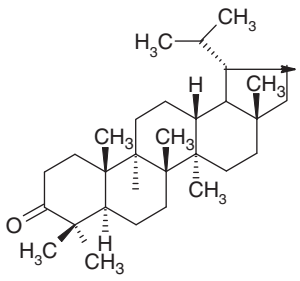


Fig. 43. Lupenone.

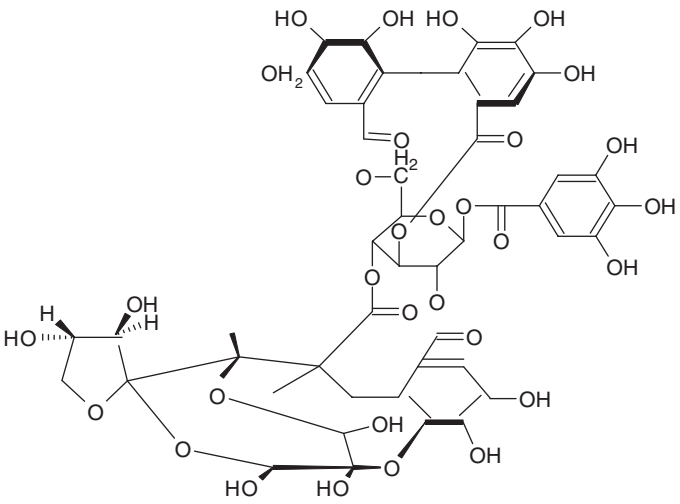


Fig. 44. Putranjivain A.

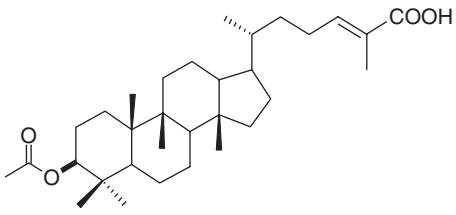


Fig. 45. Oleanolic acid.

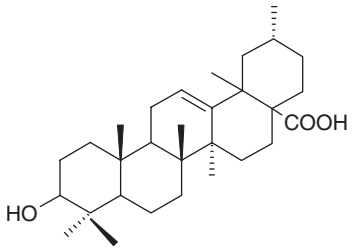


Fig. 46. Ursolic acid.

(IC_{50} $83 \cdot 8 \pm 10 \cdot 9$ and $166 \cdot 8 \pm 12 \cdot 9\,\mu M$) at noncytotoxic concentration by inhibiting penetration and replication at the late stage of viral life cycle [153].

Isoborneol (Fig. 48), a monoterpene essential oils isolated from *Melaleuca alternifolia* exhibited anti-HSV-1 activity by inactivating HSV replication within 30 min of exposure, by inhibiting glycosylation of viral polypeptides without changes in the glycosylation pattern of cellular polypeptides and

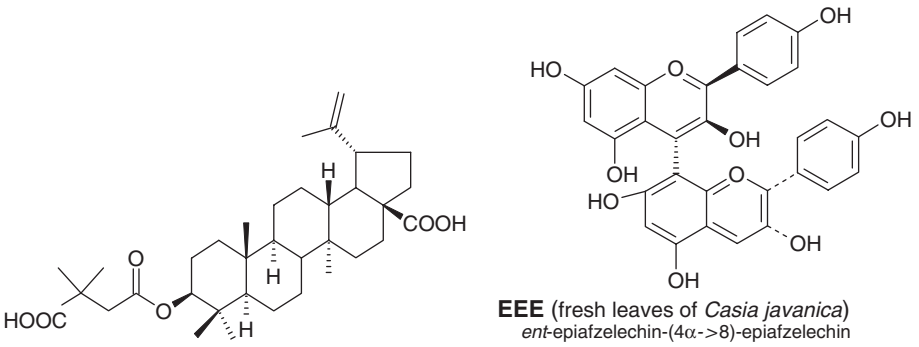


Fig. 47. (a) Epiafzelechin and (b) EEE (fresh leaves of *Casia javanica*) ent-epiafzelechin-4α->8)-epiafzelechin.

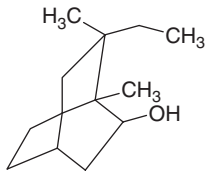


Fig. 48. Isoborneol.

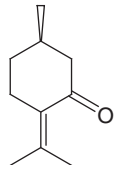


Fig. 49. Pulegone.

affecting the glycosylation of gB at noncytotoxic dose [154], indicating isoborneol (Fig. 48) as an interesting anti-HSV agent. The sandalwood oil from *Santalum album* had a dose-dependent anti-HSV-1 activity, but essential oil of Italian food plant *Santolina insularis* inhibit cell-to-cell transmission of herpesviruses [155]; while pulegone (Fig. 49) of *Minthostachys verticillata* inhibits HSV-1 replication [156]. The terpinen-4-ol (Fig. 50) of Australian Tree Tea *Melaleuca alternifolia* oil used as antimicrobial preservative in cosmetics, exhibited strong virucidal activity against HSV-1 and HSV-2, and at noncytotoxic concentrations plaque formation was reduced by 98.2% (HSV-1) and 93.0% (HSV-2); while with EUO the titers was reduced by 57.9% (HSV-1) and 75.4% (HSV-2), affecting the viruses before or during adsorption by both the oils [157]. Although the active antiherpes components of tea tree and eucalyptus oil are not very clear,

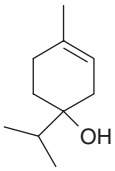


Fig. 50. Terpinen 4-ol.

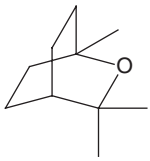


Fig. 51. 1,8-Cineole.

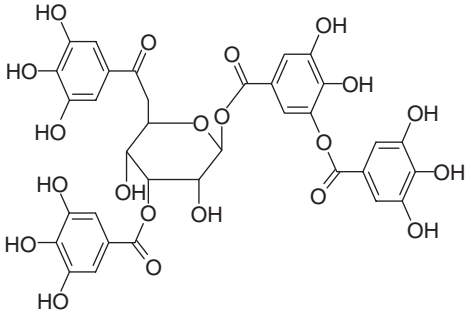


Fig. 52. Tannic acid.

but their application in recurrent herpes infection is promising. The volatile oils 1,8-cineole (Fig. 51) and terpinen-4-ol (Fig. 50) of Egyptian plants *Melaleuca armillaris* were reported to be more effective virucidals than the oils of other *Melaleuca* species [158]. The essential oil of *Artemisia douglasiana* and *Eupatorium patens* inhibit HSV-1 (65–125 ppm) [159], but *Melissa officinalis* oil inhibits HSV-2 replication [160].

Tannins and saponins

Tannins (Figs. 52 and 53) are a group of polymeric plant phenolics (MW 500–3,000) that combine with the collagen protein of animal skins forming leather, or precipitating gelatin from solution (astringency), and are grouped as hydrolyzable and condensed tannins. Hydrolyzable tannins are based on gallic acid (Fig. 54), while the condensed tannins proanthocyanidins are derived from flavonoid monomers. The consumption of tannin-containing beverages, like green teas and red wines, can cure or prevent a variety of illness as tannins can stimulate phagocytic cells, inhibit tumor and wide range

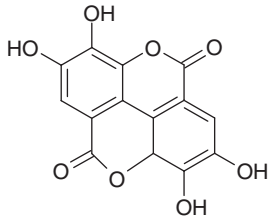


Fig. 53. Ellagic acid.

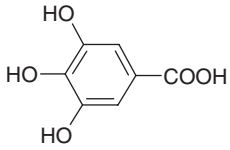


Fig. 54. Gallic acid.

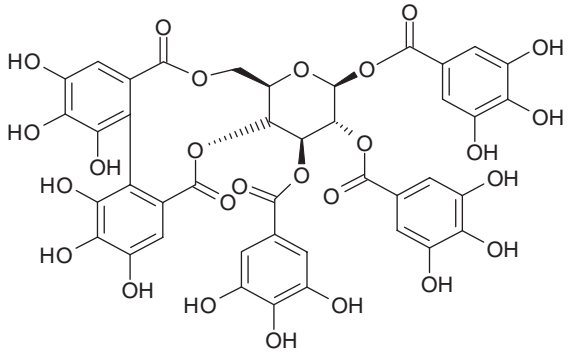


Fig. 55. Eugeniin.

of microbes by forming complex with microbial proteins through hydrophobicity, hydrogen and covalent bonding [161]. Thus, the mode of antiviral action of tannin is to inactivate virus adsorption, transport proteins, polysaccharides and viral enzymes [46,110]. Euglobal-G1–G3 from *Eucalyptus grandis* is reported to inhibit EBV [162], similarly some quassinoids including ailantinol B, ailantinol C and ailanthone can inhibit EBV early antigen activation [163]; while the eugeniin (Fig. 55) and eugenol (Fig. 56) isolated from *Geum japonicum* and *Syzygium aromaticum* block viral DNA polymerase and thereby inhibit acyclovir-resistant thymidine kinase-deficient HSV-1, wild HSV-2 and EBV multiplication [164]. A detailed study on seven ellagitannins isolated from *Phyllanthus myrtifolius* and *Phyllanthus urinaria* (Euphorbiaceae) was found to block EBV DNA polymerase, and the SAR analyses reveal that the corilagin moiety of these tannins is responsible for

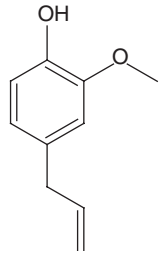


Fig. 56. Eugenol.

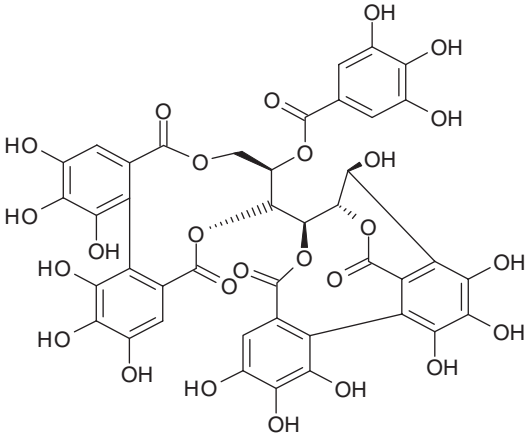


Fig. 57. Casuarinin.

its antiviral activity [165]. The spirostanol saponin glycosides (spirostane, tomatidane, solasodane, nuatigenin, ergostane and furostane dimers) of some *Solanum* species were reported to be inhibitory against HSV-1, and the SAR analysis suggests the importance of oligosaccharide moiety in antiherpes activity [166]. Hydrolyzable tannin casuarinin (Fig. 57) from *Terminalia arjuna* Linn bark is found to be virucidal that inhibits HSV-2 attachment and penetration [167]. In a bioassay-guided fractionation study, samarangenin B isolated from *Limonium sinensi* found to be significantly suppressed HSV-1 multiplication in Vero cells without apparent cytotoxicity. Results indicated that the glycoproteins B, C, D, G (gB, gC, gD, gG), ICP5 and gB mRNA expression in Vero cells were impeded by this compound; while PCR data showed that samarangenin B arrest the DNA replication and decreased DNA polymerase, ICP0 and ICP4 gene expression of HSV-1; and the electrophoretic mobility shift assay demonstrated the interrupted alpha-trans-induction factor/C1/Oct-1/GARAT multiprotein complex formation. Hence, the anti-HSV activity of samarangenin B is mediated partly by inhibiting expression of alpha gene, ICP0 and ICP4, blocking beta transcripts

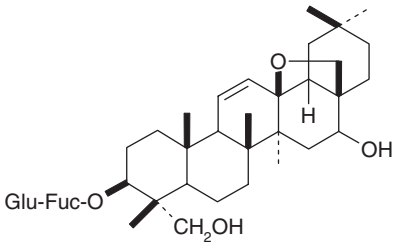


Fig. 58. Saikosaponins.

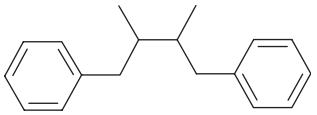


Fig. 59. Lignan.

(DNA polymerase mRNA) and by arresting DNA synthesis and structural protein expression of HSV-1. Hence, samarangenin B can be a potential candidate for a new antiherpetic agent to block HSV replication [36]. The saikosaponins (Fig. 58), iridoids and phenylpropanoid glycoside isolated from *Bupleurum rigidum* and *Scrophularia scorodonia* showed *in vitro* anti-HSV-1 activity where the cellular viability (%) at the nontoxic limit concentrations of the active compounds (500 μg/ml) were verbascoside 53.6%, 8-acetylharpagide 32.1%, harpagoside 43.3%, scorodioside 47.8% and buddlejasaponin IV 56.9% (25 μg/ml); while for the iridoid scorodioside the cellular viability was 30.6% with moderate anti-HSV-1 activity [168].

Lignans

Lignans are cinnamic acid derivatives with two C-6, C-3 units linked with β, β′ (Fig. 59), widely distributed in plants and reported to have antiviral activities [169]. Lignin is a valuable phenolic polymer that gives wood its characteristic brown color, density and mass, which contain about 40% of the weight of the world's forests! The nordehydroguanoferate isolated from the extracts of *Larrea tridentates*, *Rhinacanthus nasutus* and *Kadsura matsudai* had antiherpes activities [170]; while lignans of *Rhus javanica* exhibit anti-HSV-2 activity similar to acyclovir [171]. Lignin–carbohydrate complexes, isolated from the cones of various pine trees (*Pinus parviflora* Sieb. et Zucc., *Pinus densiflora* Sieb. et Zucc., *Pinus thunbergii* Parl., *Pinus elliottii* var. Elliottii, *Pinus taeda* L., *Pinus caribaea* var. Hondurenses, *Pinus sylvestris* L.) or from the seed shell of pine trees *Pinus parviflora* and *Pinus armadii* Franch inhibited the proliferation of HSV. The anti-HSV activity of lignin–carbohydrate complexes was maximum when lignin was added at the time of virus adsorption to the cells and the tannin-related

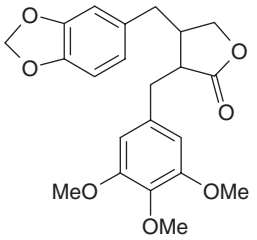


Fig. 60. Yetin.

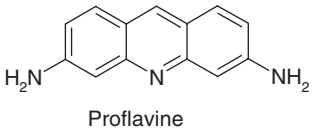


Fig. 61. Isoquinoline derivative.

compounds also showed comparable anti-HSV activity [103]. In a bioassay-guided study, yatein (Fig. 60; C22H23O7; MW 399), a lignan isolated from methanol extracts of Chinese herb *Chamaecyparis obtusa*, significantly inhibits HSV-1 multiplication in HeLa cells without apparent cytotoxicity. When a set of key regulatory events leading to the HSV-1 multiplication was examined, it was found that levels of glycoprotein gB and gC mRNA expression in HeLa cells were impeded by yatein (Fig. 60). Further study revealed that yatein can arrest the replication of HSV-1 DNA, decreased ICP0 and ICP4 gene expression and blocking of alpha-trans-induction factorC1/Oct-1/GARAT multiprotein complex. Hence, the anti-HSV action of yatein (Fig. 60) seems to be mediated by inhibiting alpha gene expression, expression of ICP0 and ICP4 genes, arresting viral DNA synthesis and expression of structural protein, and thereby inhibits HSV-1 replication [172].

Alkaloids

Alkaloids, the heterocyclic nitrogen compounds, have been found to possess antiviral activities against many viruses. MeOH extract of *Stephania cepharantha* HAYATA root tubers, a Chinese medicinal plant, has potent anti-HSV-1 activity (IC_{50} 18 μg/ml), contains bis-benzylisoquinoline (Fig. 61), protoberberine (Fig. 62), morphine and proaporphine alkaloids. Although *N*-methylcrotsparine was active against HSV-1, HSV-1 TK-deficient (acyclovir-resistant) and HSV-2 (IC_{50} 7.8, 9.9 and 8.7 μg/ml) with *in vitro* therapeutic indices of 90, 71 and 81, respectively, the alkaloid FK-3000 (Fig. 63) was found to be a promising anti-HSV drug candidate [173]. The harman (Fig. 64) isolated from *Ophirrhoza nicobarica*, a folklore of Little Andaman, inhibits plaque formation and delayed the eclipse phase of HSV

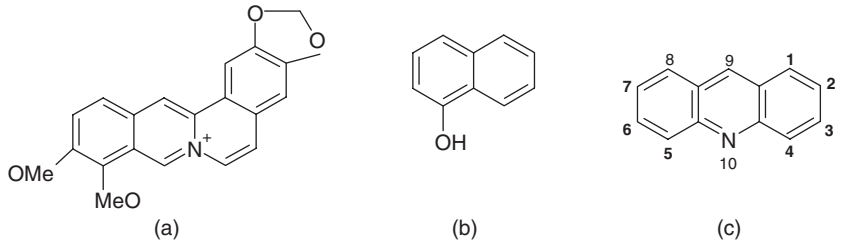


Fig. 62. (a) Berberine, (b) 8-hydroxyquinoline and (c) acridine.

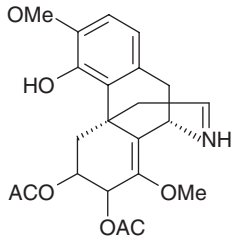


Fig. 63. FK-3000.

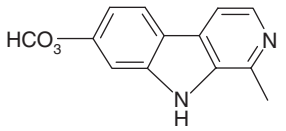


Fig. 64. Harmine.

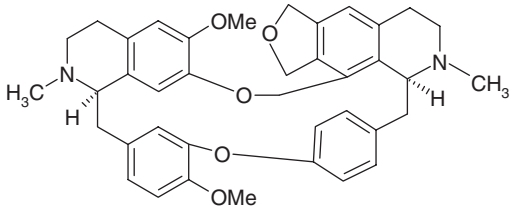


Fig. 65. Cepharanthine.

replication at 300 μg/ml [174]; while the biscoclaurine alkaloid cepharanthine (Fig. 65) isolated from Chinese and Mongolian folklore *Stephania cepharantha* root tuber inhibits HSV-1, along with *in vivo* antitumor, anti-inflammatory, antiallergic and immuno-modulating activity [175]. As cepharanthine (Fig. 65) had strong antiviral activity against both RNA and DNA viruses, hence be a source of potential lead for new antivirals. The *Nelumbo nucifera* (Lotus) Gaertn (Nelumbonaceae) is used throughout

China, Egypt, the Middle East and India for over 1,000 years in gastrointestinal and bleeding disorders. It was reported that the ethanol extracts (100 μg/ml) of both dry and fresh seeds can significantly suppressed HSV-1 replication (IC_{50} 50.0 μg/ml and IC_{50} 62.0 ± 8.9 μg/ml, respectively); while its subfractions NN-B-5 from bioactive (butanol) part showed the highest activity. At 50 μg/ml NN-B-5 inhibits TK-deficient HSV-1 replication in HeLa cells up to 85.9%, suggesting that NN-B-5 attenuates the acyclovir-resistant HSV-1 propagation [176]. Further study revealed that mRNA production and transcription of ICP0 and ICP4 were decreased in treated cells; while the electrophoretic mobility shift assay showed that NN-B-5 interrupted the formation of alpha-trans-induction factor/C1/Oct-1/GARAT multiprotein/DNA complexes. Hence, the anti-HSV action of NN-B-5 seems to be mediated partly through inhibition of immediate-early transcripts, such as ICP0 and ICP4 mRNA and then blocking of all downstream viral products accumulation and progeny HSV-1 production [176].

Lectins, polypeptides and sugar-containing compounds

The antimicrobial peptides are often positively charged and contain disulfide bonds. The mannose-specific lectins of orchid species *Cymbidium hybrid*, *Epipactis helleborine* and *Listera ovata* showed a marked antihuman CMV activity, while the (GlcNAc)*n*-specific lectin from *Urtica dioica* was inhibitory to CMV-induced cytopathicity at an EC_{50} of 0.3–9 μg/ml [177,178]. Meliacine (7α-acetoxymeliaca-14,20,22-trien-3-one), isolated from leaves of *Melia azedarach* L., inhibits HSV-1 replication *in vitro* when examined on experimental corneal HSV-1 (KOS strain) inoculation in Balb/c mice treated with meliacine topically 3 times a day for 4 days (as herpetic stromal keratitis, a leading cause of human blindness is caused by ocular HSV-1 infection). It was found that meliacine significantly reduced the development of keratitis and the histological damage in corneas. The viral titers in eyes of infected and treated mice were 2-fold lower than those corresponding infected control, but mock-infected and treated mice did not reveal any corneal alteration due to the compound. Hence, meliacine exert a strong antiviral action on HSV-1-induced ocular disease in mice with no toxic effects [179]. Meliacine also have potent *in vitro* and *in vivo* anti-HSV-1 activity as it can inhibit infected cell polypeptides, DNA synthesis, nucleocapsids assembly and affect late event in virus life cycle. Ultrastructural analysis of infected cells revealed that meliacine treatment results accumulation of unenveloped nucleocapsids instead of mature virion in cytoplasmic vesicles, suggesting that meliacine block the syntheses of viral DNA and its maturation [46,179].

It has been reported that the sulfated galactans can inhibit herpesvirus multiplication in cell culture [180] and a sulfated galactans from the marine alga *Bostrychia montagnei* is found to inhibit HSV replication *in vitro* [181]. An acidic polysaccharides fraction obtained from *Cedrela tubiflora* leaves inhibits the replication of HSV-2 without cytotoxicity [182], indicating

that the antiviral activity of polysaccharides correlates with molecular weight and sulfate content. Recently Thompson and Dragar [183] reported that galactofucan, a sulfated polysaccharide from aqueous extract of seaweed *Undaria pinnatida* exhibits anti-HSV activity at noncytotoxic dose by inhibiting viral binding and entry into the host cell against clinical strains of HSV-1 (IC_{50} 32 μg/ml), but inhibition was highly significantly against HSV-2 (IC_{50} 0.5 μg/ml; $P<0.001$). A water-soluble anionic polysaccharide isolated from *Prunella vulgaris* L. (Labiatae), a perennial folk medicinal herb of China and Europe, inhibits HSV-1 at 100 μg/ml and HSV-2 at 10 μg/ml [184]; while the anionic polysaccharide of the same herb collected from Japan *showed* specific anti-HSV activity (IC_{50} 10 μg/ml) by competing for cell surface receptor, unlike other anionic carbohydrates [184,185]. The polysaccharide fraction prepared from *Prunella vulgaris* L. (Labiatae) showed that the HSV antigen increased time-dependently in the infected HSV-1 and HSV-2 cells, and polysaccharide fraction (25–100 μg/ml) reduced such antigen expression (EC_{50} 20.6 and 20.1 μg/ml), along with the antigen expression of acyclovir-resistant strain of HSV-1 (24.8–92.6%), showing that polysaccharide fraction has a different mode of anti-HSV action from acyclovir [185].

Conclusions

The diseases caused by the HSV, VZV, CMV, EBV and Kaposi's sarcoma-associated viruses are the global concern for their (i) contiguous nature, (ii) ability to persist lifelong within the host, (iii) development of resistant mutants and (iv) their silent epidemic potential to cause high morbidity. These diseases are not yet curable, though treatable, but sometimes be fatal, especially in neonates and immunocompromised patients; as the complete cure or development of effective vaccine is not yet possible. Moreover, the antivirals used against herpesviruses are expensive and have toxicity. Therefore, development of safe, effective and inexpensive antivirals is among the top global priorities of drug development. Furthermore, the long-term combination therapies for herpesviruses may yield drug-resistant mutants. Therefore, scientists from divergent fields are investigating herbal medicinal products, with an eye to their antiherpesvirus usefulness. In a decade of extensive research, great progress has been achieved in the discovery of antiherpesvirus agents from natural sources. A number of purified molecules have been used as lead compounds because of their specific activity and low toxicity and significant SAR. Some natural phytophores have potential to interfere with particular viral enzymes, cellular fusion and target cell binding, resulting complementary mechanisms of action to the existing antiviral drugs. Although no plant-derived drug is currently in clinical use to treat herpesvirus diseases, promising activities have been shown by some herbal product/natural product-derived candidates of diverse class, particularly the

phenolics, coumarins, flavonoids and alkaloids, in preclinical and clinical trials. Interestingly a number of plant extracts can block virus entry into host cells and/or specific cellular enzymes, which is a very important aspect in the context of viral drug resistance and limited life span of many antiviral drugs. The compounds having alternative mechanism of action, unlike synthetic antivirals, can be the potential candidates to tackle the threats posed by drug-resistant herpesviruses, as it is quite difficult to eliminate herpesvirus diseases by the available antivirals till date.

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