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REVIEW ARTICLE

NATURAL PRODUCTS WITH ANTI-HERPES ACTIVITIES: IN VIVO STUDIES

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Abstract

Herpes are a group of similar viruses that are responsible for a number of infecting diseases, the most important of which are herpes simplex, herpes zoster and pseudopox. Resistance to traditional antiviral medications is becoming increasingly common, making treatment of such infections even more difficult. For example, the usage of nucleoside analogues like acyclovir to target the DNA-polymerase of the virus on a regular and long-term basis promotes the generation of resistant viruses. As a result, a different treatment is required. Natural products, such as herbal remedies, have been shown to have in vitro and in vivo activity against herpes viruses, and have shown to be a valuable source for new antivirals development and separation. The goal of this review is to highlight the most promising extracts and pure chemicals obtained from plants and marine species that have in vivo anti-herpes simplex virus (HSV-1 and HSV-2) action. Natural products as new anti-HSV medications offer a number of benefits, including fewer side effects, minimal toxicity, and lowered resistance, and a variety of ways of deed.

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Introduction:-

Herpes is a developing disease that is caused by herpesviruses infection and replication. There have been more than 80 herpesviruses identified, with eight of them being known human diseases. Herpes simplex viruses are members of the Herpesviridae virus family, that embraces herpes simplex virus-1 HSV-1, HSV-2, varicella zoster virus, Epstein-Barr virus, CMV, herpesviruses types 6,7 and type 8 which is Kaposi's sarcoma-linked in[1,2]. HSV1 is predominantly linked to infections of the mouth, pharynx, face, ophthalmic, and central nervous system, and is spread mostly by oral excretions and non-genital touching. HSV2 is commonly associated with anal and genital infections and is transmitted mostly through genital excretions. Each, however, has the potential to cause This virus is part of a large family of enveloped-DNA viruses that can induce a variety of clinically severe disorders in adults and newborns [5,6]. Illnesses might range from undetectable to life-threatening infections like encephalitis. This Illnesses is marked by the formation of erythematous lesions that degrade swiftly, resulting in harmful ulcers, as well as a variety of clinical manifestations such as fever, malaise, generalized muscle soreness, headaches, itching, and other symptoms that vary depending on the affected part. HSV is a frequent infectious illness, particularly among immunocompromised people. Recurrences are caused by a range of environmental circumstances and are nothing more than clinical indications of a new phase of viral replication and propagation of virus through nerve fibers to appear on the skin again. These environmental circumstances involve emotional stress, fever, UV light exposure, and hormonal changes, among others[1,4,7].infections in all places [2-4].

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Idoxuridine (IDU), the first licensed antiviral drug, was originally used in clinical trials for herpes keratitis in 1960. However, a big advance in antiviral efficacy and safety is on the discovery of nucleoside analogue inhibitors, such as acyclovir (which has high selectivity and low toxicity and is approved as a specific inhibitor of (HSV-1) and (HSV-2) replication), valacyclovir (an acyclovir prodrug), famciclovir (a prodrug of penciclovir), and the second line of antiviral drugs, foscarnet. All of these medications are viral DNA polymerase inhibitors. Drug resistance strains developed easily through changes in the thymidine kinase and/or polymerase viral genes, which is a therapeutic restriction of those nucleoside analogues. As a result, many viruses remain unimmunized, and only a few antiviral medicines have been approved for clinical use [8-10].

When vaccinations and standard medicines are unavailable, it is still appropriate to search for new types of antiviral medications that have extremely efficacious and cost-effective without causing major side effects.

Plants are unquestionably a successful source of medications. As a result, a huge number of remedial plants are now used to cure many disorders; nearly one-third of the world's top-selling pharmaceuticals are natural products or natural product derivatives, demonstrating that natural products have a greater hit rate than synthetic drugs. Many traditional medicinal herbs have been shown to have potent antiviral properties, and some of them have already been utilized to treat viral infections in animals and humans. A variety of metabolites can be found in the natural products of some plants. Some of these metabolites obstruct the replication cycle of many types of DNA or RNA viruses without disrupting the host's metabolism, making them good sources for the progressing of active antiviral medications with minimum few side effects. Additionally to interfering with viral reproduction, these natural plant chemicals may contribute to the amendment or strengthening of the human immune response to viruses, easing symptoms and lowering viral infection death. [11-13].

Flavonoids, alkaloids, saponins, terpenes, quinones, lignans, polysaccharides, tannins, thiosulfinates, steroidal glycoside, and proanthocyanidin are active constituents that have activity against herpes viruses types [14]. This review gives an overview of certain medicinal plants and their metabolites as potential therapy for herpes infections.

Plants with promising anti-HSV activities

Rhus Javanica:

Rhus javanica is a small tree belong to *Anacardiaceae* family and is mainly produced in Korea, China and Japan. The *R. javanica* plant's fruit has traditionally been used as an antidiarrheal, antiperspirant, antitussive, and anticoagulant, among other things. The plant's leaves utilized as a de-toxicant and antivenom for serpent bites, and they're known for other properties such as antioxidant and protecting of liver [15]. Other biological effects of this plant have been described, including anti-inflammatory, antioxidant, anti-herpes, anti-HIV, and anticytomegalus properties. *Rhus javanica* contains several biological components that responsible to these activities, such as gallotannins, phenolics, glycosides, flavonoids, terpenoids, and organic acids [16-20]. Gallic acid, scopoletin, 5-methylresorcinol, phlorizin, methylgallate, 3,4,5-trihydroxyacetophenone 4-O-D-glucopyranoside, and 3-hydroxy-5-methylphenol 1-O-D-(6'-galloyl) glucopyranoside were among the active chemicals identified from *Rhus javanica* nutgall stem bark [21].

Methyl gallate (MG), a key component of *Rhus javanica*, has substantial antioxidant capabilities in addition to antiviral, anticancer, and anti-inflammatory characteristics [22]. Also, two triterpenes with antiherpetic action were discovered, moronic acid (fig.1) and betulonic acid. The two compounds inhibited HSV-1 in vitro with EC50 values of 3.9 and 2.6 g/ml respectively, while moronic acid displayed oral healing effectiveness in infected mice in vivo.

Moronic acid is a pentacyclic triterpenoid made up of olean-18-ene with a carboxy group at position 28. An oleanane hydride is used to make it. [23,24]. Moronic acid sensitivity was found in HSV-1 resistant to acyclovir phosphonoacetic acid, thymidine kinase-deficient HSV-1, and wild type HSV type 2. This compound significantly slowed the development of skin lesions and/or lengthened mean life spans in mice infected cutaneously with HSV-1 when given orally three times daily. Moronic acid inhibits viral generation in the brain more effectively than in the skin. This corresponded to longer average survival times. This derivative has emerged as a viable new candidate for clinical trials[24].

Cloves:

Cloves, another name is *Eugenia aromatica*, are desiccated buds that are picked after the calyces become yellow pink. They come from the evergreen tree *Syzygium aromaticum* (*Myrtaceae*). They are derived from the *Syzygium aromaticum* tree (*Myrtaceae*). Cloves have been utilized for many medical purposes in Ayurveda, Chinese medicine, and Western herbalism from earliest times [25]. The primary *clove* phytochemicals have been identified by several research studies. Essential oil which account about ~20% of dried clove buds, high in eugenol, accounts for 70–90 percent of cloves and is responsible for clove aroma[26,27]. Clove oil is used to treat a variety of ailments including acne, asthma, rheumatoid arthritis, scars, verrucae and allergies; it's also utilized as an anesthetic, antispasmodic, and general antiseptic in medical dentistry [28].

Eugenol (4-Allyl-2-methoxyphenol) (fig.1) is a phenylpropanoids-type chemical compound with high health-promoting properties, making it a multipurpose natural component. Eugenol has many pharmacological qualities such as anesthetic, antiallergic, anti-swelling, antioxidant capacity, anti-inflammatory, anti-carcinogenic, antiviral, neuroprotective ability, hypolipidemic efficiency and anti-diabetic. Additionally, eugenol can protect against hepatotoxicity caused by carbon tetrachloride (CCl₄) [29-31].

Tragoopua and Jatisatienr[32] investigated the antiviral activity of whole cloves, and found that a clove ethanol extract of flower buds had a direct deactivating effect on the particles of standard HSV strains. Furthermore, after treatment with the extract, the overall HSV virus production decreased at 30 h [32]. Eugenol exhibits viral infection constrictions towards herpes simplex viruses, with IC₅₀ values ranging from 16.2 mg mL⁻¹ to 25.6 mg mL⁻¹, according to a study by Benencia and Courreges [33]. Eugenol has been shown to be effective against clinical isolates of the herpes simplex virus-1 (HSV-1). In an *in vivo* model of HSV-1 infection, eugenol was found to be efficacious and the treatment of HSV-1 infected mice with eugenol considerably delayed the onset of herpetic keratitis in the cornea, suggesting that this substance could be effective in the treatment of ocular herpetic infections. Eugenol may not be useful for internal use because the antiviral effect is at least in part due to virucidal activity. However, based on the results of *in vivo* investigations and its stability at room temperature, it could be utilized for topical therapies, especially in conjunction with other medications, because its antiviral activity is minor in comparison to other pharmaceuticals like acyclovir.

Rice:

Rice (*Oryza sativa L.*), a member of the Gramineae family, is one of the world's most important and nutritious cereal crops. Rice is a high-carbohydrate food that also contains a small amount of protein and fat, as well as vitamin B complexes including niacin, riboflavin, and thiamine. In addition to nutritional components, many phytochemicals, such as phenolic acids, flavonoids, terpenoids, steroids, and alkaloids, have been identified as bioactive compounds with a diverse variety of biological functions, that is antioxidant, antimicrobial, anticancer, antidiabetic, and anti-inflammation properties that have been linked to a variety of health-promoting and disease-prevention actions [34,35].

Rice proteinase inhibitors oryzacystatin I (OC-I) and oryzacystatin II (OC-II) belonging to the phytocystatin family. phytocystatins are proteins with low-molecular-weight that identified at a variety of plants, including corn, soybean, and cowpea seeds. The two compounds have different inhibitory effects and share just 55% amino acid identity [36] and both inhibits a different thiol proteinases, papain and cathepsin H, respectively. By inhibiting the proteinase enzyme of herpesviruses, (Aoki et al., 1995) [37] established the *in vitro* and *in vivo* antiviral action of OCs on HSV-1. The findings show that the rice grain derivative OC-I, a novel thiol proteinase inhibitor has anti-herpes action *in vitro* and in a mouse model of HSV-1 keratitis in doses within the therapeutic range with no discernible toxicity. Thus, topical OC-I therapy for HSV-1 infections in humans appears to be possible [37]. OCI molecules are thought to infiltrate infected cells via internalization in order to prevent the polyprotein from being converted

into functional products. These findings show that using cystatin as a proteinaceous material is critical for antiviral activity [38].

Rheum Tanguticum:

Rheum tanguticum (*Polygonaceae*) is a traditional Chinese herbal medicine with a wide range of uses. *R. tanguticum* roots and rhizomes have been utilized in China from ancient years as a purgative, antimicrobial, antipyretic, hemostatic, antineoplastic, antispasmodic, and as a blood-lipid, fatness, blood pressure, and blood urea nitrogen reducer. The plant is also used to treat gastrointestinal and renal issues, as well as to improve blood circulation. Anthraquinone derivatives, anthranone derivatives, distyrene derivatives, tannins, and acyl glycosides have all been identified from *R. tanguticum*, and the anthraquinone and anthrones derivatives being the most prominent bioactive components. Various chromatographic techniques were used to isolate and purify about twenty substances. Seven of these chemicals are anthraquinone and anthraquinone glycosides which are (emodin, rhein, chrysophanol, aloe-emodin, physcion, aloe-emodin-8-O-D-glucopyranoside and chrysophanol-8-O-D-glucopyranoside) [39-41].

The *Rheum tanguticum* roots extract, emodin(fig.1), possesses in vitro and in vivo anti-HSV action according to study by Xionga et al. [42], he discovered that at a dose of 50 g/ml, emodin inhibits HSV-1 and HSV-2 replica in cell culture, by antiviral indexes of 2.07 and 3.53, respectively. In comparison to the viral controls, emodin remedy enhanced the persistence rate of infected mice, elongated survival duration, and exhibited higher effectiveness of HSV deletion from the brain, heart, liver and ganglion. Moreover, emodin's activity towards the virus was found to be equivalent to standard drug acyclovir [42]. Emodin's antiviral mechanism is the subject of numerous theories. Previous research has suggested that emodin may have effect towards the virus by suppressing casein kinase2 (CK2), which phosphorylates many viral proteins required for the virus's life cycle. Another mechanism for emodin activity was to break the lipid bilayer and virus's inactivation. HSV-1 protein UL12, which is involved in DNA processing and capsid egression, was shown to be selectively inhibited by emodin in another work [43].

Houttuynia Cordata Thunb:

The perennial herb *Houttuynia cordata Thunb.* (*H. cordata*) belongs to the Saururaceae family, which is found primarily in Eastern Asia. Antiviral, anticancer, antimicrobial, anti-inflammatory, adjuvanticity, anti-obesity, hepatoprotective, free radical scavenging, antiallergic, antileukemic, chronic sinusitis, and nasal polyps activities are among the pharmacological properties of this plant. Injectable *H. cordata* is currently being employed in the treatment of infectious illness and anaphylaxis [44-46]. Over than 160 isolated compounds belong to flavonoids, phenylpropanoids, alkaloids, steroids, terpenoids, volatile oils, and fatty acids among other phyto-constituents found in plant and which responsible to above activities. Houttuynoids are a new form of flavonoid found in *H. cordata*. Houttuynoids contain anti-herpes virus activity and are made up of a flavonoid core and a houttuynin chain. *H. cordata* extract lowers the infectivity (by >4 log) of various viruses, including the HSV-1 virus, according to study by Hayashi et al. [48].

The first example of a houttuynoid with a bis-houttuynin chain linked to a flavonoid core was identified by Gao et al. [49] which is Houttuynoid M, have a good inhibitory impact on HSV-1, according to pharmacodynamics investigations. Another research on *H. cordata* was shown that houttuynoid A (fig.1) has potent anti-HSV-1 action both in vitro and in vivo. In an HSV-1-infected animal model, this substance deactivated HSV-1 through limiting the fusing of the viral envelope with the plasma membrane, impeding HSV-1 replication and inhibiting the formation of lesions [50]. NF κ B activation has been shown to play a key role in HSV-1 and HSV-2 reproduction according to some investigations, so that constrain of NF κ B activation effectively defeats the virus infection[51].

Gigartina Skottsbergii:

Gigartina skottsbergii is a red seaweed that is found in the far south of South America. Lipids, proteins, carbohydrates, fibers, -glucans, polyphenols, and flavonoids are among the active components identified in this algae. Because it is utilized as a raw material for extracting carrageenans, *Gigartina skottsbergii* has a high commercial value [52-54]. Carrageenans are polysaccharides and according to their physicochemical qualities, such as food grade additives, gelling, thickening, emulsifying, and stabilizing properties, carrageenans are widely employed in the food and pharmaceutical industries. Carrageenans also have biological effects that include antioxidant, antiviral, anticoagulant, immunomodulatory, anticancer, and anti-thrombotic capabilities. Carrageenan also used to make a variety of controlled-release medication delivery systems [55,56].

These polysaccharides are made up of linear chains of consecutive 3-linked β -D-galactopyranosyl and 4-linked α -D-galactopyranosyl units, and the 4-linked unit commonly taking the form of a 3,6-anhydropyranosyl moiety. Sulfate groups may also be replaced for OH groups in these repeating units. The existence/deficiency of anhydrogalactose in the 4-linked unit, as well as the sulfation pattern of the 3-linked unit, define distinct features of these polysaccharides, which have historically been divided into six main forms: ι -, κ -, λ -, μ -, ν -, and θ -Carrageenans [57].

Carrageenans derived from *Gigartina skottsbergii* have recently been shown to be strong and specific inhibitors of herpes in vero cells and the cells of brain such murine astrocytes [58]. μ/ν -, κ/ι -, and λ carrageenans from *Gigartina skottsbergii* have outstanding antiviral activity, according to study by Pujol et al. [59]. The in vivo efficacy of μ/ν -carrageenan, through suppression of viral adsorption and has no anticoagulant activity, was demonstrated in this investigation. Carrageenan has antiviral properties, mostly through preventing the viral attachment stage, viral reproduction, and/or a protective influence on vulnerable cells. Carrageenans' efficacy in the treatment of viral infections has yet to be proven in humans, but due to their anti-herpetic action as inhibitors of virions' initial attachment to the host cell, researchers see it as attractive contestants for infection treatment and prevention [56,58].

Prunella Vulgaris:

Prunella vulgaris (*Lamiaceae*), often known as selfheal, is a perennial plant and used in traditional medicine from ancient times. It is widely distributed in China, Europe, northwestern Africa, and North America. Many research displayed the medicinal applications of this herb that include: Anti-inflammatory, antiviral, antibacterial, anticancer, immunomodulatory, thyroid gland dysfunction therapy, antioxidant and hypoglycemic properties. Organic acids, phenolic acids, sterols, flavonoids, coumarins, phenylpropanoids, polysaccharides, volatile oils, and triterpenoids are the main active components that contribute to these medicinal uses [60-64].

A water-soluble component from *Prunella vulgaris* has previously been demonstrated to have considerable antiviral activity against HIV, HSV, and Ebola virus [65]. Zhang et al.[66] extracted a lignin-carbohydrate complex from *P. vulgaris*'s spike and the complex's in vivo anti-HSV-1 activity investigated in guinea pigs. In guinea pig and mouse models, the complex has a high level of activity against HSV-1 cutaneous infection and HSV-2 vaginal infection. The periodate oxidation test indicated that the carbohydrate part is necessary for anti-HSV action. At this time, it's uncertain if the lignin portion is required for activity; however, the lignin-carbohydrate combination inhibits viral binding and penetration into host cells. The complex's anti-HSV efficacy in vivo has been proven, implying that it could be turned into an effective anti-herpes medication.

Carissa Edulis:

Carissa edulis (*Apocynaceae*) is native to many regions like Australia, Saudi Arabia, Eritrea, Nigeria, Japan and South Africa. Many microbiological illnesses, including venereal, respiratory, and gastrointestinal infections, are treated with this plant. toothache, Sick cell anemia, gastric ulcer, oedema, lung problems, cough, and worm expulsion are all treated with the leaves, stem, and root barks of *Carissa edulis*. *Carissa edulis* stem phytochemical tests revealed the presence of terpenes, steroids, flavonoids, cardiac glycosides, tannins, coumarins, and sesquiterpenes, while the roots revealed the alkaloids incidence, tannins, Carbohydrates, flavonoids, saponins, cardiac glycosides, terpenes, and steroids have been found in the leaves and fruits [67,68].

The anti-herpes simplex virus (HSV) activity of a dried aqueous extract from the root bark of *C. edulis* was tested in *vitro* and in *vivo*. Both resistant and wild strains of HSV were shown to be sensitive to the extract. The extract was even more sensitive to the resistant strains than the wild types and the extract seemed to have synergistic effects on the resistant types. The mortality rate for mice treated with extract was 70-90 percent lower than that of infected untreated mice, which had a 100 percent mortality rate [69].

Terminalia Chebula Retz:

The medicinal plant *terminalia chebula Retz* is abundantly grown in tropical locations throughout southern Asia[70,71]. This plant have many biological activities such as antioxidant, anti-carcinogenic, anti-mutagenic, anti-bacterial, anti-fungal, anti-viral, anti-diabetic, renoprotective, cardioprotective, anti-inflammatory, and anti-arthritis actions. Polyphenols, terpenes, anthocyanins, flavonoids, alkaloids glycosides, coumarin, and tannins are among the phytochemicals that responsible to above health benefits[72-74]. It has shown therapeutic effectiveness against Herpes simplex virus (HSV) in *vitro* and in *vivo* by suppression of retroviral reverse transcriptase activity in virus[73,75].

Kurokawa *et al.* [76] discovered that combining acyclovir with the herbal extract *terminalia chebula Retz* had tough combined beneficial anti-HSV-1 activity in mice, with no toxicity and reduced the development of skin lesions in infected mice and/or extended their average survival periods when compared to using both acyclovir and the herbal extract separately. In contrast to acyclovir treatment alone, the combination reduced viral yields in the skin and brain more effectively than acyclovir alone, and the anti-HSV-1 activity in the brain was better than in the skin.

Moringa Oleifera:

Moringa oleifera (Moringaceae) is found in Africa, Arabia, South Asia, South America, the Himalayan region, India, the Pacific Islands and the Caribbean. This plant is well-known for its active components such as tannins, saponin, flavanoids, steroids, terpenoids, glycosides, anthraquinones, alkaloids, and vitamins. Antimicrobial, anti-inflammatory, antioxidant, antihyperglycemic, anticancer, antiviral, and antifungal properties are all attributed to the presence of these components [77-80].

Lipipun *et al.* [81] found that the plant extract was effective in treating HSV-1 infection both *in vivo* and *in vitro*. At a dose of 750 mg/kg per day, the aqueous extract of *M. oleifera* significantly delayed the formation of skin damages, lengthened survival periods, and there was a reduction in mortality in mice infected with HSV-1. These findings further revealed that antiviral constituents in plant extracts were absorbed preferentially from the gastrointestinal system and produced an HSV-1 suppression action that was not linked to toxicity.

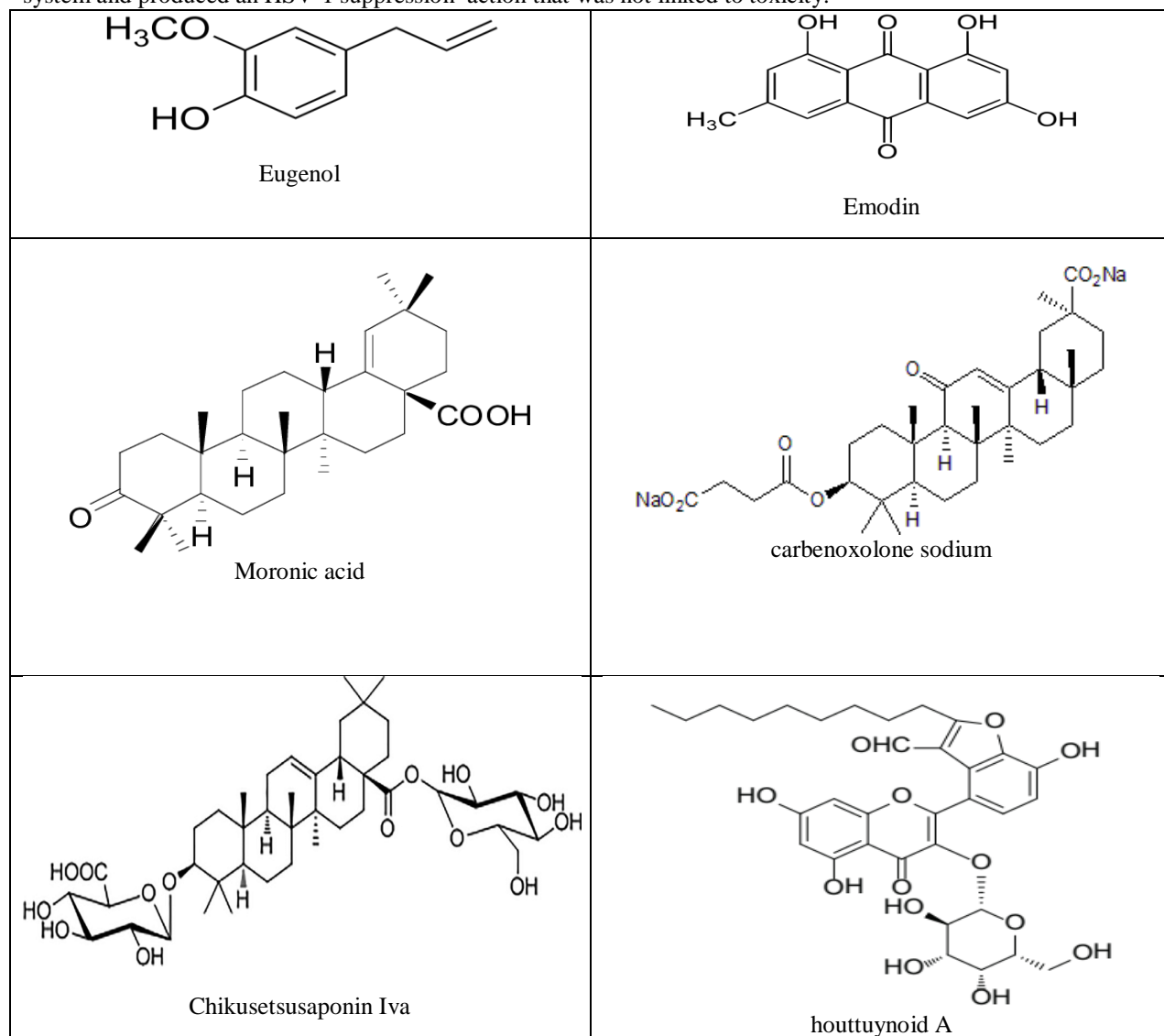


Figure1:- Chemical Structures of Plants Bioactive Constituents as Remedial for Herpesviruses.

Licorice (*Glycyrrhiza Glabra*):

Glycyrrhiza glabra (*Leguminosae*) is a medicinal plant found in Asia as well as portions of Europe and thought to have originated in Iraq. This herb is frequently used in Ayurvedic medicine [82]. Triterpene saponins (e.g., glycyrrhizin), tannins, phytosterols, flavonoids (e.g., liquiritin), sugars, choline, amino acids, coumarins, ascorbic acid, and other bioactive components are found in licorice. *Glycyrrhiza glabra* has been demonstrated to have anti-inflammatory, antibacterial, antioxidant, antimalarial, antispasmodic, and anti-hyperglycemic activities according to many studies. Antiulcer, antiviral, antihepatotoxic, antifungal, and antiherpes simplex properties have also been investigated. This herb's roots comprise 1 to 9% glycyrrhizin, a pharmacological compound with anti-infective, antiviral, antioxidant, and anti-inflammatory activities. Elevated blood pressure is one of the most regularly reported negative effects of licorice supplementation[83,84].

Several viruses, including the herpes simplex virus, have been demonstrated to be inhibited by glycyrrhizic acid. Glycyrrhetic acid, the aglycone of glycyrrhizin found in *Glycyrrhiza glabra*, is used to make carbenoxolone(fig.1). In vitro and in vivo, carbenoxolone was found to have relatively substantial action against the herpes virus [85]. The roots of *Glycyrrhiza glabra* were utilized to make a 2% topical acid cream containing carbenoxolone sodium (Fig.1) in a study directed by Partridge and Poswillo[85]. This cream was used to remedy 12 patients with acute oral herpetic (HSV) infections. After applying the cream six times a day for 24–48 hours, illness symptoms such as discomfort and dysphagia were eliminated. Ulceration and lymphadenopathy, on the other hand, were observed to heal in 24–72 hours.

***Bidens Pilosa*:**

Bidens pilosa, a member of the Asteraceae family, is an annual weed originate in tropical and subtropical climates. It is a valuable source of food and medication for both people and animals. *B. pilosa* extracts and/or compounds have antitumor, antiinflammatory, antidiabetic and antihyperglycemic, antioxidant, immunomodulatory, antimalarial, antimicrobial, antihypertensive, vasodilatory, and antiulcerative activities, according to many scientific studies. They are also effective in treating many illnesses such as headache, wounds, angina, metabolic syndrome, digestive and infectious diseases[86-88]. Phenylpropanoids, polyacetylenes, polyphenols, triterpenes, saponins, and alkaloids were found in phytochemical screening investigations of *B.pilosa*. The bioactive phytochemical substances, including sesquiterpene lactones, polyacetylenes, and flavonoids, appear to be linked to the plant's medicinal properties. *B. pilosa* phytochemicals and essential oil were shown to contain an exploitable amount of phenolic compounds the most powerful radical scavenging [88].

B. pilosa's anti-HSV-1 activity was tested in the skin of HSV-1-infected mice. At 1 g/kg per dosage, the *B. pilosa* extract was given orally every 12 hours for 18 days following infection. *B.pilosa* proved efficient against thymidine kinase-deficient and phosphonoacetate-resistant HSV-1 strains. In comparison to the control, treatment with *B. pilosa* extract enhanced the survival rate of HSV-1-infected mice and delayed the onset and progression of skin lesions. The findings suggest that *B. pilosa* has anti-HSV action, making it a potentially helpful medical plant for treating HSV infection and acyclovir -resistant forms observed after acyclovir therapy[89].

***Ventilago Denticulate*:**

Ventilago denticulata Willd. (*Rhamnaceae*) It's a climbing and hanging vine wood plant that's perennial and semi-shrubby. It has been utilized as traditional medicine in several Southeast Asian and South Asian nations, including Thailand, India, and Bhutan, to lowering blood sugar and cholesterol [90,91]. Many medicinal active substances can be found in the plant. Friedelin and numerous anthraquinones found in the stem bark can be used to treat skin disorders and sprains. Ventinones A and B, anthraquinones found in the root, are used as a tonic for dyspepsia, moderate fever, and debility. Lupeol, beta-sitosterol, and its glucoside are all found in the leaves[92].

The *Ventilago denticulate* plant was valued for anti-herpes simplex virus type1 activity by (Lipipun *et al.*)[81], the results revealing that the extracts of *V. denticulata* displayed therapeutic antiviral ability in *vitro* and *in vivo*. In a plaque reduction assay, it suppressed HSV-1 by more than 50% at 100 g/ml, and it was also effective against thymidine kinase-deficient HSV-1 and phosphonoacetate-resistant HSV-1 strains. A cutaneous HSV-1 infection in mice was used in the *in vivo* investigation. *V.denticulata* extracts were found to be efficient in preventing the formation of skin damages ($P < 0.05$). In terms of the time it delay skin lesions to develop, There was no discernible difference between acyclovir and plant extracts, and extract toxicity was not found in treated mice.

Alternanthera Philoxeroides:

Alternanthera philoxeroides (Amaranthaceae) is a perennial herb that grows in water and endemic to South America, South Africa, China, and parts of Asia. *Alternanthera philoxeroides* has been claimed to have therapeutic benefits against influenza and the human immunodeficiency virus (HIV), as well as for the treatment of wounds, fever, and milk secretion [93-95]. The presence of several active substances such as alkaloids, glycosides, steroids, flavonoids, tannins, phenolic compounds, carbohydrates, amino acids, and proteins is related to these benefits [96].

Alternanthera philoxeroides produced Chikusetsusaponin Iva. (fig.1). In *vitro*, this substance inhibited HSV-1 and HSV-2 with SIs CC50/IC50 values of 29 and 30, respectively, while anti-HSV-2 ability was observed in *vivo* in a mouse model. The activity against HSV-2 of compound has been linked to virus particle destruction and the prevention of virus progeny from releasing outside the infected cells [97].

Aglaia Odorata:

The species type of the genus, *Aglaia odorata* (Meliaceae), is frequently used as traditional medicine for heart stimulant, febrifuge, cure of cough, inflammation, injuries, and toxicity by vomiting triggering. They also exhibit biological activities that are intriguing, such as anticancer, insects destructive, and anti-leukemic. *Aglaia odorata* phytochemical screening revealed the presence of terpenoid, steroid, phenol, alkaloid, aminopyrrolidine-diamides, essential oils, and saponin, all of which are involved in plant biological activities [98,99].

(Lipipun *et al.*) [81] tested the plant extract for anti-herpes simplex virus type 1 activities in *vivo*. In treated mice, the extract of *A. odorata* was likewise beneficial in reducing the size and progression of HSV-1 skin lesions. In terms of delaying the onset of skin lesions, there was no significant difference between acyclovir and the plant extract. In treated mice, the extract reduced mortality and improved survival time while causing no toxicity.

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