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Medicinal plants with anti-herpes viruses activity: A review

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Abstract

Several phytochemicals exhibited high level of antiviral activity. Medicinal plant possessed antiviral activity via many mechanisms included inhibition of viral replication, inhibition of the assembly of intracellular infectious virus particles, inhibition of viral infectivity, inhibition of RNA polymerase, DNA polymerase, viral neuraminidase, protease, reverse transcriptase and viral protein expression and many other mechanisms. Many natural products showed potent anti-herpes activity. The current research reviewed the medicinal with anti-herpes effect to encourage further research for development of future anti-herpes remedies.

Keywords: Medicinal plants; Antiviral; Anti-herpes; Pharmacology

1. Introduction

Herpes viruses (Herpesviridae) are enveloped viruses contained double-stranded DNA. Their life cycle characterized by two phases: lytic and latency phase. Herpes is a common viral infection of the skin or mucous membranes. Herpes infection is distributed worldwide, HSV-1 is more common than HSV-2, HSV-1 rate is 70-80% in populations of low socioeconomic status and 40- 60% in populations of improved socioeconomic status[1].

Cutaneous herpes simplex is characterized by painful, burning, or pruritic clusters of vesicles on the lips, oral mucous membranes, genital region, or other areas of the body. HSV infection of the eye results in keratoconjunctivitis, a serious condition that sometimes leads to corneal blindness. HSV may also cause encephalitis or other systemic infections, particularly in immune-compromised patients[2].

Prolonged treatment with conventional antiviral drugs is more likely to develop drug-resistant strains due to mutations of thymidine nucleoside kinase or DNA polymerase. Hence, the development of alternative treatments is clearly required. Several phytochemicals exhibited high level of antiviral activity. Medicinal plant possessed antiviral activity via many mechanisms included inhibition of viral replication, inhibition of the assembly of intracellular infectious virus particles, inhibition of viral infectivity, inhibition of RNA polymerase, DNA polymerase, viral neuraminidase, protease, reverse transcriptase and viral protein expression and many other mechanisms[3-9]. Many natural products showed potent anti- herpes activity[10-15]. The current review collected the medicinal which possessed anti-herpes effect to encourage further research for development of future anti-herpes remedies.

2. Medicinal plants with anti-herpes activity

2.1. *Allium sativum*

The antiviral activity of hydro-distilled essential oils of *Allium sativum* (bulbs) against (HSV1) was tested by using cytopathicity (CPE) assay. African green monkey kidney (Vero) cell line (virus infected cells) was incubated with

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different levels of essential oils. The antiviral activities were increased with increasing essential oils concentrations. The additions of 200, 500 and 1000 µg/ml of garlic essential oils increased antiviral activity percentages to 37.66, 72.94 and 93.81%, respectively[16-17]. Garlic extracts have been shown to have *in vitro* and *in vivo* antiviral activity against the human cytomegalovirus, influenza B, herpes simplex virus type 1, herpes simplex virus type 2, parainfluenza virus type 3, vaccinia virus, vesicular stomatitis virus, and human rhinovirus type 2. Ajoene was found to block the integrin-dependent processes in a human immunodeficiency virus-infected cell system[18-19].

2.2. *Ammi majus*

Ammi majus coumarins were evaluated for antiviral effects against two mammalian viruses, HSV-1 and VSV. The antiviral activity was determined by means of the end titration technique that depends on the ability of plant extract dilutions to inhibit the produced cytopathogenic effect**.** *Ammi majus* coumarins found to have no reliable antiviral activity against herpes simplex virus (HSV)[20-22].

2.3. *Aristolochia maurorum*

Antiviral properties of the plant extracts were determined by cytopathic effect inhibition assay and plaque reduction assay. *Aristolochia maurorum* extracts exhibited significant antiviral activity against HSV-1 and adenovirus type 5 at a concentration non toxic to the cell lines used. The extracts of *Aristolochia maurorum* showed great anti viral activity against HSV-1 and partial activity against adenovirus at higher concentrations[23].

2.4. *Asclepias curassavica*

The ethanolic extract (80%) of freeze dried entire plant showed no antiviral activity against Adeno virus, Coxsackie b2, Herpes type-1, Measles, Poliovirus-1 and Semlicki forest virus by cell cultured method[24-25].

2.5. *Calendula officinalis*

A tincture of the flowers suppressed the replication of herpes simplex, influenza A2 and influenza APR-8 viruses *in vitro*[26-27].

2.6. *Capparis spinosa*

In studying the antiviral and immune-modulatory properties of a methanolic extract of *C. spinosa* buds (CAP), it was found that CAP treatment interferes with HSV-2 replication in human peripheral blood mononuclear cells (PBMCs), inhibiting the extracellular virus release up-regulating their production of IL-12, IFN-α and TNF-α. Accordingly, CAP contribute in improving immune surveillance of PBMCs toward virus infection by up-regulating expression of peculiar pro-inflammatory cytokines, the authors postulated that it can be successfully employed for treatment of HSV-2 infections in immune-compromised hosts[28-29].

2.7. *Carthamus tinctorius*

The antiviral activity of *Carthamus tinctorius* (CT) was examined against gamma herpes virus infection. The results showed that treatment with CT extracts disrupted KSHV latency in the viral-infected host cells. n-Hexane and ethanol fractions of CT extracts critically affected at least two stages of the KHSV life-cycle by abnormally inducing KSHV lytic reactivation and by severely preventing KSHV virion release from the viral host cells. In addition to the effects on KSHV itself, CT extract treatments induced cellular modifications by dysregulating cell-cycle and producing strong cytotoxicity[30-31].

2.8. *Chrysanthemum cinerariaefolium*

Pyrethrins, complex esters extracted from *Chrysanthemum cinerariaefolium*, exhibited only minimal *in vitro* activity against herpes simplex virus (HSV). However, in employing a guinea pig model of HSV genital infection, no *in vivo* activity was recorded[32].

2.9. *Cicer arietinum*

The antiviral activities of the extracts from the seed, fruit skin and aerial parts of ten varieties of *Cicer arietinum* (Chickpea) were evaluated against Herpes *simplex* type 1 (HSV-1) and *Parainfluenza-3* (*PI*-3) viruses. Madin-Darby Bovine Kidney and Vero cell lines were employed for antiviral assessment of the *Citer arientinum L.* extracts, in which acyclovir for *HSV*-1 and oseltamivir for *PI*-3 were tested as reference drugs. *Cicer arietinum* seed extracts (Aydin 92 variety) possesses significant antiviral activity against both DNA (max to min CPE inhibitory conc: 32-4 µg/ ml) and RNA (max to min CPE inhibitory conc.: 32-16 µg/ ml) viruses compared to the fruit skin and aerial part extracts as well

as the controls. Besides, the extracts of fruit skin (Menemen 92 variety) and aerial parts (Aydin 92 variety) showed remarkable activity against DNA viruses at 32 - 1 µg/ ml concentration[33-34].

2.10. *Cuminum cyminum*

The essential oils of *Cuminum cyminum* showed antiviral activities against herpes simplex virus 1 (HSV-1) using cytopathicity (CPE) assay. At concentration of 1000 µg the antiviral activity reached 91.60 ± 1.93[35-36].

2.11. *Cupressus sempervirens*

Ethanol extracts of *Cupressus sempervirens, C. semipervirens* var. *horizontalis* and *Cupressus sempervirens* var. *cereiformis* were used to test their influence on herpes viruses (HSV-1). HeLa cells monolayers were infected with herpes viruses (HSV-1). Antiviral activity of the plant extracts assessed using Hematoxylin & Eosin method and observed under a light microscope. All tests were compared with a positive control, acyclovir. Results showed that all three plants have antiviral activity against HSV-1 virus. The most active extract was the extract obtained from *C. semipervirens.* Among the different parts tested, the fruit's extract possessed the strongest anti- HSV activity[37-38].

2.12. *Cyperus rotuntdus*

Cyperus rotundus exerted virucidal effect against HSV[39-40].

2.13. *Dactyloctenium aegyptium*

The antiviral activity against HSV-2, HSV-1 and HAV-10 of *Dactyloctenium aegyptium* aerial parts extracts was investigated using cytopathic effect inhibition assay. The ethyl acetate showed weak antiviral activity, *n*-butanol extracts of *Dactyloctenium aegyptium* showed moderate antiviral effects against HAV-10 and HSV-1. The *n*-hexane extract showed strong antiviral activity against all viruses tested[41-42].

2.14. *Datura metel*

The antiviral activity of atropine was evaluated by plaque reduction test against herpes simplex virus, influenza virus, Newcastle Disease virus, sindbis, vaccinia, adenovirus and Japanese encephaitis virus. Viruses were cultivated on primary chick embryo (CE), HeLa S3, primary monkey kidney cells (MK). Atropine inhibited only the growth of enveloped viruses independent of the nucleic acid content of the virus. It also blocked the glycosylaton of viral proteins of *Herpes* virus and hence the production of new virions. Virions formed in the presence of atropine were non infectious[43-45].

2.15. *Dianthus caryophyllus*

Crude extract of *Dianthus caryophyllus* was tested for their antiviral activity against herpes simplex virus-1 (HSV-1) and hepatitis A virus-27 (HAV-27). Non-toxic concentration (20 µg/ml) of *Dianthus caryophyllus* seed extract to both Vero and HepG2 cells showed potent antiviral activity against HSV-1 and HAV-27 using plaque infectivity count assay. No effect was detected for the extract on adsorption or on the stages of virus replication. A comparison has been done between the antiviral activity of two therapeutic drugs (acyclovir and amentadine used as controls for HSV-1 and HAV-MBB, respectively) and the tested seed extract. The results revealed that the seed extract was more efficient in its inhibitory activity than synthetic chemical drugs against the same viruses[46-47].

2.16. *Erodium cicutarium*

Extracts from *Erodium cicutarium* were tested for antiviral and interferon inducing properties. Both water extract and methanol extract as well as its fractions exerted antiviral effect in relation to myxoviruses, herpes virus type 1, vesicular stomatitis and vaccinia virus. None of these extracts did induce interferon in a suspension of human leukocytes[48-50].

2.17. *Eucalyptus* species

The antiviral effect of the leaf essential oil of *Eucalyptus camaldulensis* was studied against many viruses. Rotavirus Wa strain, Coxsackievirus B4, and herpes virus type 1 were affected by essential oil with percentage of reduction 50%, 53.3%, and 90% respectively, but no effect was found against adenovirus type 7[51-52].

2.17.1. *Glycyrrhiza glabra*

Glycyrrhiza glabra extracts and glycyrrhizic acid inhibited the replication of several viruses included Epstein-Barr virus, Herpes simplex virus, hepatitis A virus, hepatitis B virus, hepatitis C virus, human cytomegalovirus, human immunodeficiency virus, influenza virus, SARS coronavirus and varicella zoster virus[53-63].

Many studies have demonstrated that glycyrrhizin was responsible for the antiviral activity of licorice. The possible antiviral mechanisms of this compounds were (HCV): affected release step while infectious HCV particles are infecting cells. Inhibited HCV full length viral particles and HCV core gene expression; (HSV): reduced adhesion force and stress between CCEC and PMN, (CVB3): blocked the degradation of nuclear factor κB inhibitor IκB; (DHV): activated T lymphocyte proliferation; (H5N1): weakened H5N1-induced production of CXCL10, IL-6 and CCL5, and suppressed H5N1-induced apoptosis, (influenza virus): reduced HMGB 1 binding to DNA, and inhibited influenza virus polymerase activity, (CVA16 EV71): inactivated CVA16 directly, while the effect of anti-EV71 was associated with an events during the virus cell entry, (HSV1): established a resistance state to HSV1 replication and (Rotavirus): reduced the levels of viral proteins VP2, VP6 and NSP2 at a step or steps subsequent to virus entry[64-65].

2.18. *Gossypium* species

Gossypol has been reported to possess antiviral properties against enveloped viruses, including HIV-1, HSV-2, influenza, and parainfluenza[66-70].

2.18.1. *Hibiscus sabdariffa*

The aqueous extract of *Hibiscus sabdariffa* (AEHS) and its bioactive constituent protocatechuic acid (PCA), were evaluated *in vitro* for their antiviral activity against HSV-2 clinical isolates and anti-enzymatic activity against urease. PCA showed potent anti-HSV-2 activity compared with that of acyclovir, with EC_{50}values of 0.92 and 1.43 μg/ml, respectively, and selectivity indices > 217 and > 140, respectively. AEHS exerted anti-urease activity, with an IC_{50} value of 82.4 μg/ml[71-72].

2.18.2. *Jasminum sambac*

Anti-herpes simplex viruses (HSV-1 and HSV-2) and antiadenoviruses (ADV-3, ADV-8 and ADV-11) activities of hot water extract of *Jasminum sambac* flowers was evaluated using XTT-based colorimetric assay. The results revealed that hot water extracts exhibited anti-HSV and anti-ADV activities[73-74].

2.18.3. *Lallemantia royleana*

The essential oils from Lallemantia royleana were screened for their inhibitory effect against herpes simplex virus type 1 (HSV-1) *in vitro* on Vero cell line CCL-81-ATCC using a plaque reduction assay. Results showed that the inhibitory concentration (IC_{50}) was determined at 0.011% for *L. royleana* oil with a high selectivity index (6.45)[75-76].

2.18.4. *Mangifera indica*

The antiviral effect of mangiferin, extracted from the leaves of mango (*Mangifera indica*) was tested against herpes simplex virus type 2 (HSV-2) *in vitro*. The EC_{50} of mangiferin against HSV-2 plaque formation in HeLa cells was 111.7 micrograms.ml-1, and the concentrations of 33 and 80 micrograms.ml-1 reduced the virus replicative yields by 90% (EC_{90}) and 99% (EC_{99}), respectively. The therapeutic index (IC_{50}/EC_{50}) was 8.1[77].

Four methods were used to evaluate the antiviral effect of mangiferin and isomangiferin against type I herpes simplex virus (HSV-I) (*in vitro* direct action, simultaneous addition of drug-virus-inoculum to cell bottle, virus inoculation preceding drug addition, and drug addition followed by virus inoculation). It was found that isomangiferin somewhat exceeded such control drugs as acyclovir, idoxuridine, and cyclocytidine, and that mangiferin was lower than isomangiferin. The average plaque reduction rates of mangiferin and isomangiferin were 56.8% and 69.5% respectively. The antiviral effect of mangiferin and isomangiferin was due to their capability of inhibiting virus replication within cells[78].

2.18.5. *Matricaria chamomilla*

Camomile essential oils were screened for antiviral effect against herpes simplex virus type 2 (HSV-2) *in vitro* on RC-37 cells using a plaque reduction assay. A clearly dose-dependent virucidal activity against HSV-2 was demonstrated for camomile essential oils. The inhibitory concentrations (IC_{50}) were determined at 0.003%. In order to determine the mode of the inhibitory effect, essential oils were added at different stages during the viral infection cycle. They afected

HSV-2 mainly before adsorption probably by interacting with the viral envelope. Camomile oil exhibited a high selectivity index and seemed to be a promising candidate for topical therapeutic application as virucidal agents for treatment of herpes genitalis[79-80].

2.18.6. *Melia azedarach*

Limonoid 1-cinnamoyl-3,11-dihydroxymeliacarpin was isolated from the ethyl acetate extract of leaves of Melia azedarach. showed IC_{50} values of 6 microM and 20 microM for vesicular stomatitis (VSV) and herpes simplex (HSV-1) viruses, respectively[81].

Meliacine, isolated from leaves of *Melia azedarach* exhibited potent antiviral activity against herpes simplex virus type 1 (HSV-1) by inhibiting specific infected-cell polypeptides produced late in infection which involved in DNA synthesis and in the assembly of nucleocapsids. It also affected a late event in the multiplication cycle of HSV-1. It diminished the synthesis of viral DNA and inhibited the spread of infectious viral particles[82].

2.18.7. *Melissa officinalis*

When hot water extracts of *Melissa officinalis* injected into embryonated eggs, it protected them against the lethal action of Semliki Forest, Newcastle, vaccinia, and herpes simplex viruses. Plaques produced by these viruses in chick embryo cell monolayers can be suppressed by applying melissa extract-impregnated antibiotic-sensitivity discs to the agar overlay surface. Injection of 10% gelatin into eggs before or after injection of melissa extract largely eliminates the antiviral effect. It is suggested that the active antiviral moiety of the extract was a tannin or tannin-like polyphenol that perhaps acts at the cell surface[83].

The effects of the volatile oil components of *Melissa officinalis* (25, 50, 100, 150 and 200 microg/ ml) on Herpes simplex virus type 2 (HSV-2) replication were studied in HEp-2 cells. The replication of HSV-2 was inhibited, which indicated that the *Melissa officinalis* extract contained an anti-HSV-2 substance. However, *Melissa officinalis* volatile oil was found to be non-toxic to HEp-2 cells up to a concentration of 100 micro/ml[84].

The aqueous extract of *Melissa officinalis* as well as phenolic extract compounds (caffeic acid, p-coumaric acid and rosmarinic acid) were examined for their antiviral activity against herpes simplex virus type 1 (HSV-1) *in vitro*. The Melissa extract showed high virucidal activity against HSV-1, even at very low concentrations of 1.5 μg/ml, whereas similar results for phenolic compounds were only achieved at 100 times higher concentrations. Furthermore, the Melissa extract and rosmarinic acid inhibited HSV-1 attachment to host cells in a dose-dependent manner[85].

The virucidal and antiviral effects of *Melissa officinalis* extracts (M1: 50 ethanol extract, M2: ethanol extract, M3: , M3: ethyl acetate and M4: aqueous extract) were studied against Herpes simplex virus type 1 (HSV-1). Virucidal effect was registered within 3 and 6 hours of treatment using M4 administered in maximum tolerable concentrations. The remaining extracts inactivate the virus at the 12^{th} and 24^{th} hour[86].

The antiviral effect the essential oil of *Melissa officinalis* was examined against herpes simplex virus *in vitro* on monkey kidney cells using a plaque reduction assay. At noncytotoxic concentrations of the oil,plaque formation was significantly reduced by 98.8% for HSV-1 and 97.2% for HSV-2, higher concentrations of the oil abolished viral infectivity nearly completely. In order to determine the mode of antiviral action of this essential oil, time-on-addition assays were performed. Both herpesviruses were significantly inhibited by pretreatment with the oil prior to infection of cells, it appeared that Melissa oil affected the virus before adsorption, but not after penetration into the host cell[87].

The nontannin polyphenol fraction possessed antiviral effect against herpes simplex and vaccinia viruses in egg and cell-culture systems. The presence of gelatin did not eliminate the antiviral activity of aqueous extracts of *Melissa officinalis* against herpes simplex and vaccinia viruses in disc plaque-suppression tests, suggesting that a second, nontannin, antiviral substance was present[88].

The antiviral activity of a hydroalcoholic extract of *Melissa officinalis* leaves extract against the Herpes simplex virus type 2 (HSV-2) was assessed by the cytopathic effect inhibition assay on Vero cells (ATCC CCL-81), in comparison with acyclovir. *Melissa officinalis* leaves extract reduced the cytopathic effect of HSV-2 on Vero cells, in the range of non-toxic concentrations of 0.025-1 mg/ml. The maximum inhibiting effect (60%) was obtained with 0.5 mg/ml. The viral binding assay showed that the extract does not prevent the entry of HSV-2 in the cells[89].

A double-blind, placebo-controlled, randomized trial was carried to investigate the efficacy of standardized cream contained 1% dried extract of *Melissa officinalis* leaves, in the treatment of herpes simplex labialis. The cream was

smeared on the affected area four times daily over five days. The tested formulation was effective for the treatment of herpes simplex labialis. There was a significant difference in the values of symptoms score on day 2 of therapy[90].

A multicentric studies provided the proof that dried extract from *Melissa officinalis* gave protection against herpes simplex infections. The activity was very high when the treatment was intiated in the very early stages[91].

2.18.8. *Momordica charantia*

Momordica charantia possessed *in vitro* anti-viral activity against numerous viruses, including Epstein-Barr, herpes, and HIV viruses. The leaf extract showed an increased resistance to viral infections and possessed immunostimulant effect in humans and animals, and increased the interferon production and natural killer cell activity. The anti-viral compounds of the plant were proteins or glycoprotein (lectins) in nature, therefore, oral intake of the plant didn't slow down the HIV multiplication in infected people due to its poor absorption. In one preliminary clinical trial, an enema form of a bitter gourd extract showed some benefits in people infected with HIV[92].

The lyophilized *Momordica charantia* extracts prepared from accessions collected in Togo showed high antiviral activity (<5 µg/ml) against Sindbis and Herpes simplex type 1 viruses[93].

2.18.9. *Morus alba*

The antiviral and antibacterial of phenolic compounds of *Morus alba* root bark were evaluated. The antiviral activity was determined by the plaque number reduction assay and by the titer reduction assay and the antibacterial effect was tested using broth microdilution method. Six compounds (five prenylated compounds and a simple phenolic ester) exhibited inhibitory activity against the replication of herpes simplex virus 1 (HSV-1) or herpes simplex virus 2 (HSV-2), with IC_{50} values ranging from 0.64 to 1.93 µg/ml, and EC_{50} values 0.93 and 1.61 µg/ml. Molecular docking studies demonstrated the effects of the active compounds was mediated by targeting HSV-1 DNA polymerase and HSV-2 protease. Four compounds showed antibacterial activity, they diminished the growth of all of the Gram-positive strains tested, with MIC values of 1-16 µg/ml[94].

Leachianone G, isolated from the root bark of *Morus alba* showed potent antiviral activity (IC_{50}) = 1.6 microg/ml), whereas mulberroside C showed weak activity (IC_{50}) = 75.4 microg/ml) against herpes simplex type 1 virus (HSV-1)[95].

2.18.10. *Nerium oleander*

The antiviral activity of hot and cold extract of *Nerium oleander* was studied against six different viruses [herpes simplex virus type 1 (HSV-1), polio virus type 1 (Sb-1), vesicular stomatitis virus (VSV), reovirus type-1 (Reo-1), human immunodeficiency virus type-1 (HIV-1), and yellow fever virus (YFV)]. The results of plaque reduction assay demonstrated that both, hot extract and cold extract inhibited Sb-1 viral infection. they exerted their effect after infection period, particularly during the first two hours post infection[96].

2.18.11. *Ocimum basilicum*

Extracts and purified components of *Ocimum basilicum* were tested for antiviral activity against DNA viruses (herpes viruses (HSV), adenoviruses (ADV) and hepatitis B virus) and RNA viruses (coxsackievirus B1 (CVB1) and enterovirus 71 (EV71)). The crude aqueous and ethanolic extracts and some selected purified compounds (apigenin, linalool and ursolic acid), exhibited broad spectrum antiviral activity. Ursolic acid showed the strongest activity against HSV-1 (EC_{50} = 6.6 mg/l, selectivity index (SI) = 15.2), ADV-8 (EC_{50} = 4.2 mg/l, SI = 23.8), CVB1 (EC_{50} = 0.4 mg/l, SI = 251.3) and EV71 (EC_{50} = 0.5 mg/l, SI = 201). Apigenin showed the highest activity against HSV-2 (EC_{50} = 9.7 mg/l, SI = 6.2), ADV-3 (EC_{50} = 11.1 mg/l, SI = 5.4), hepatitis B surface antigen (EC_{50} = 7.1 mg/l, SI = 2.3) and hepatitis B e antigen (EC_{50} = 12.8 mg/l, SI = 1.3), while linalool showed strongest activity against AVD-II (EC_{50} = 16.9 mg/l, SI = 10.5)[97].

2.18.12. *Olea europaea*

The *in vitro* antiviral effects of olive leaf extract (OLE) and propolis alone or in combination were investigated for their antiviral efficacy in HSV-1 in comparison with acyclovir.The antiviral efficacy was observed both with one-hour and three-hour incubation at a concentration of 10 µg/ ml for propolis and 1.2 mg/ml for olive leaf extract. The duration and concentration of the greatest decrease in viral quantity were in the first one hour and 10 µg/ml for propolis, and in the first one hour and 1.2 mg/ ml for olive leaf extract. Combination of propolis and olive leaf extract with acyclovir caused no cytopathic effects, and the combination of extracts led to delayed cytopathic effect[98-99].

2.18.13. *Origanum vulgare*

Twenty-one phenolic compounds isolated from *Origanum vulgare* were also subjected to *in vitro* antiviral evaluation against RSV, CVB3 and HSV-1 with CPE reduction assay. Only apigenin showed moderate to weak inhibitory activity against RSV Long strain with IC_{50} value of 23.1 μM, and compound (acacetin 7-O-[4000-O-acetyl-b-D-apiofuransyl-(1→3)]- b-D-xylopyranoside) exhibited weak activity against RSV A strain with IC_{50} value of 81.7 μM. Compounds (acacetin-7-O- [6‴-O-acetyl-b-D-galactopyranosyl-(1→2)]-b-D-glucopyranoside and 2,5-dihydroxybenzoic acid) also exhibited weak effects against HSV-1 with IC_{50} values of 38.5 and 32.7 μM, respectively[100].

2.18.14. *Pimpinella anisum*

Lignin-carbohydrate-protein complexes isolated from a hot water extract of seeds of *Pimpinella anisum* showed antiviral activities against herpes simplex virus types 1 and 2 (HSV-1 and -2), human cytomegalovirus (HCMV) and measles virus. They were interfered with virus adsorption to the host cell surface and directly inactivate viruses. They were also enhanced nitric oxide (NO) production by inducing iNOS mRNA, protein expression in RAW 264.7 murine macrophage cells and enhanced mRNA expression of cytokines including IL-1β and IL-10[101].

2.18.15. *Punica granatum*

In studying the effect of tannin from the pericarp of *Punica granatum* against genital herpes virus (HSV-2). The tannin inhibited HSV-2 replication, and killing virus by blocking its adsorption on to cells[102].

The purified polyphenol extract of pomegranate inhibited influenza virus and possessed a synergistic effect with oseltamivir. On the other hand, hydroalcoholic extract of whole fruits showed potent antiviral activity against the influenza virus[103-105].

2.19. *Quercus* species

The antiviral effect of hydroalchoholic extract of *Quercus persica* against HSV-1 replication was studied in baby hamster kidney cells. There was significant relationship between the concentration of the extract and cell death ($P<0.01$). IC_{50}s of the extract on HSV-1, before and after attachment to BHK cells were 1.02 and 0.257 μg/ml, respectively. There was significant relationship between the concentration of the extract and inhibition of cytopathic effect[106].

The inhibitory effect of crude ethanol extract and 4 corresponding fractions of *Quercus brantii* on adsorption and/or post-adsorption stages of HSV-1 replication cycle were determined. The chloroform fraction and the crude extract possessed the highest effect against HSV-1 with selectivity indices of 53.8 and 48.4, respectively. The n-hexane, n-butanol, and chloroform fractions inhibited HSV-1 replication in postadsorption stage ($P < .001$)[107].

2.19.1. *Ranunculus sceleratus*

Compounds isolated from *Ranunculus sceleratus* were tested for inhibitory effects on hepatitis B virus (HBV) and Herpes simplex virus type-1 (HSV-1). The results showed that apigenin 4'- O- alpha-rhamnopyranoside, apigenin 7- O- beta-glucopyranosyl-4'- O- alpha-rhamnopyranoside, tricin 7- O- beta-glucopyranoside, tricin, and isoscopoletin possessed inhibitory activity against HBV replication. Protocatechuyl aldehyde exhibited an inhibiting activity on HSV-1 replication[108].

2.19.2. *Rheum ribes*

The ethanol extract of *Rheum ribes* was evaluated for antiviral activities against herpes simplex virus (HSV) and Sindbis virus (SINV). The extract showed potent anti-HSV effect and weak anti-SINV activity[109].

2.19.3. *Ricinus communis*

The antiviral potential of *Ricinus communis* leaves was investigated against three viruses [Coxsackie B virus type 4 (COXB4), herpes simplex virus type 1 (HSV1), and hepatitis A virus (HAV)]. The leaves extracts possessed antiviral activity. Evaluation of the anti-replicative activity showed that all extracts possessed high anti-replicative activity against HAV especially methanol and methylene chloride fractions and moderate activity against COXB4; butanol > methylene chloride and ethyl acetate > methanol. All extracts showed protective activity against HAV, especially butanol extract, while methanol extracts showed higher non-significant antiviral protective activity against HSV1 vs Acyclovir[110].

2.19.4. *Robinia pseudoacacia*

Robinia pseudoacacia cv. Idaho 70% ethanol percolate was evaluated for antiviral effect. The percolation produced significantly inhibitory effects on HSV-1 and EV-71 viruses with the therapeutic index TI values 113.8 and 46.2, respectively[111].

2.19.5. *Sambucus ebulus*

The antiviral effects of hydroalcoholic extract of *Sambucus ebulus* was investigated against HSV-1. The postexposure assay of HSV-1 with *Sambucus ebulus* extract at the highest nontoxic concentration (75 µg/ml), *Sambucus ebulus* extract led to 2.6 log10 $TCID_{50}$ reduction in infectious virus titer. At the highest nontoxic concentration, the *Sambucus ebulus* extract led to inhibition rates of 91.2%, ($P<0.001$). A significant reduction was observed in fluorescence emission intensity in HSV-1-infected cell treated with *Sambucus ebulus* extract compared to the control group[112].

2.19.6. *Teucrium chamaedrys*

The chloroform and methanol extracts of *Teucrium chamaedrys* were tested for antiviral activity against Herpes simplex virus type 2. The studied extracts inhibited the replication of Herpes simplex virus type 2 (HSV-2) in MDBK cells significantly without apparent cytotoxicity. The EC_{50} of the chloroform extract was 350 µg/ml. The replication of the virus was suppressed over 82% at maximum tolerable concentration. The methanol extract showed weak antiviral effect (EC_{50} = 680 µg/ml). The extracts applied in MTC inactivated extracellular virus, viral adsorption and entry of Herpes simplex virus type 2[113].

2.19.7. *Thuja occidentalis*

The antiviral effect of *Thuja occidentalis* was investigated by using the plaque reduction assay with herpes simplex (HSV-1; strain Elstree). Besides a microscopical examination on degenerative cell growth, the influence of the fractions and substances on the DNA metabolism of Helacells was also determined. The extracts were obtained using absolute ethanol, 96 vol.% ethanol and methanol, and lyophilized. Further steps in the purification procedure included gelchromatography using sephadex G-50 or sephadex LH-20. By purification, the required amount of active substance for more than 90% plaque reduction, was reduced from 1,000 µg/ml to 50 µg/ml. The 50% cytotoxic dose in the highly purified fractions was 400 µg/ml and the minimal antiviral dose was smaller than 50 µg/ml[114].

2.19.8. *Thymus kotschyanus*

The crude aqueous extract of *Thymus kotschyanus* was screened for antiviral property on HSV-1. The antiviral effect of the extract was determined by cytopathic effect inhibition assay. Thymus kotschyanus extract inhibited HSV-1 multiplication at concentrations of 200-900µg/ml. Its EC_{50} and IC_{50} was 48.36 µg/ml and 1.12 $x10^2$ µg/ml[115].

The antiviral effect of the aqueous extract of *Thymus kotschyanus* was investigated on HSV-1 multiplication. Antiviral properties of the plant extract was determined by cytopathic effect inhibition assay at one, two and three hours after inoculation of HSV-1. The result showed that the extract possessed potent antiviral effect at nontoxic concentrations after an hour of virus inoculation that decreased at two and three hours[116].

2.19.9. *Vitis vinifera*

The antiviral activity of *Vitis vinifera* leaf extract was studied against two human viruses: the Herpes simplex virus type 1 (HSV-1) and the coronavirus 2 (SARS-CoV-2). Leaf extract was able to inhibit both HSV-1 and SARS-CoV-2 replication in the early stages of infection by directly blocking the proteins enriched on the viral surface, at a very low concentration of 10 µg/ml[117].

2.19.10. *Zizyphus spina-christi*

Different extracts and fractions of the leaves, fruits and seeds of *Zizyphus spina-christi* were investigated *in vitro* for their antiviral activities against herpes simplex type 1 (HSV1), Measles Edmondston A (MEA), Poliomyelitis virus type 1 (polio 1) and Vesicular stomatitis virus (VSV). The ethyl acetate fraction of the fruits and the aqueous extract of the leaves showed significant antiviral properties against Herpes simplex type 1 (HSV-1) which correspond to a reduction of the viral titre of 10^4 and 10^3, respectively. The chloroform and petroleum ether extracts of the leaves, fruits and seeds were inactive against the tested viruses[118].

3. Conclusion

In this review, we have discuss the previous literature regarding medicinal plants extracts and pure compounds with promising antiviral activity against herpesvirus infections. Natural product are safe and effective in inhibiting different stages of different types of herpesviruses. The current review aims to encourage further research for development of future anti-herpes remedies.

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