

The Efficacy and Mechanism of Herbals Action on Herpes Simplex Virus Type 1: A review

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ABSTRACT

HSV-1, a member of the Herpesviridae causes numerous diseases, including Herpes Labialis to deadly encephalitis. This review tried to provide more comprehensive and accurate data on the effects of different herbals on the HSV-1 as a probable alternative treatment for HSV-1. Further clarification of the herbals interactions with HSV is required which could provide valuable information about the chemical nature and mechanism(s) of action of the potential anti-HSV molecule(s) and all the most potential plant extracts must undertake further analysis and purification steps with the aim of identifying the active elements existing in the herbals.

KEY WORDS: Herbals, Herpes Simplex, HSV-1, Herpesviridae, Herpes Labialis.

1. INTRODUCTION

HSV-1, a member of the Herpesviridae causes various diseases, including Herpes Labialis to deadly encephalitis (Khajeh, 2011). This can occur in neonates, elderly, transplanted patients who are under immune suppression by medications or in patients with acquired immune deficiency syndrome (Khajeh, 2011). Herpes simplex viruses are also considered as the main etiology of acute infectious encephalitis (Sabouri, 2013). More than 90% of adults have experienced infection with at least one human herpes virus, during their life (Son, 2013). The efficient anti-herpes drugs, including acyclovir, ganciclovir, vidarabine, penciclovir, famciclovir, and valaciclovir are currently used for treatment. Continuing the current medication which does not improve the patients and also HSV resistance to anti-herpetic drugs are considered as a serious problem and has been increasingly focused attention (Khajeh, 2011). Emergence of drug-resistant strains of herpes virus following therapeutic treatment can be attributed to the mutation occurrence in either HSV DNA polymerases or thymidine kinase which leads to acyclovir and associated nucleoside analogues resistance. It has reported that virus strains correlated with clinical resistance are nearly defective in production of TK (Coen and Schaffer, 2003). Thus, it necessitates an investigation of developing new anti-herpes virus agents as therapeutic tools. With regard to the side effects that synthetic drugs might elicit, more increasing investigation for traditional medicine is urgently needed (Khajeh, 2011; Khan, 2005). This review tried to provide more comprehensive and accurate data on the effects of different herbals on the HSV-1 as a probable alternative treatment for HSV-1.

Evidence Acquisition: Data for this article were obtained via an initial Medline search and a systematic review of the references of relevant articles. Search terms used were "Herpes Simplex virus type 1" "herbals" and "therapy". English-language papers just were considered.

2. MEDICINAL HERBS AND MODE OF ANTIVIRAL ACTIVITY

2.1. *Glycyrrhiza glabra*: In our previous investigation, we reported more novel findings of the effect of anti-herpetic activity of methanolic and aqueous (Sabouri, 2014) extracts of Iranian *Glycyrrhiza glabra* which was obtained from Kermanshah city. The pretreatment of HSV-1 and Vero cells with the *Glycyrrhiza glabra* extract showed essential activity on the anti-viral effects of the methanolic extract (Sabouri, 2014). Furthermore, incubation of HSV-1 virus with a methanolic extract for one and two hours previous to viral infection and also pre-treatment of Vero cells with extract for two hours led to a significant decrease in TCID₅₀ quantity (Sabouri, 2014). Moreover, the aqueous extract effect of *Glycyrrhiza glabra* on the HSV-1 replication indicated various efficiency in the time course of extract and also pre-treatment of cells with the extract. In addition, virus incubation with aqueous extract presented remarkable anti HSV-1 activities among the groups under the research (Sabouri, 2014). Based on the current results, the suppression of HSV-1 replication in Vero cells occurs probably via the disruption of the expression stage by late genes but exact mechanisms need further investigation (Sabouri, 2014).

2.2. *Artemisia*: In another study, which we performed in Iran, seven species of *Artemisia* including *A. annua*, *A. chamaemelifolia*, *A. campestris*, *A. fragrans*, *A. incana*, *A. persica* and *A. vulgaris* were collected from different parts of Iran (Khajeh, 2011). Methanolic extracts were treated with HSV-1 at different concentrations *in vitro*. *A. annua* extracts indicated the strongest anti-HSV-1 activities among the extracts in comparison to the acyclovir at concentrations as 3.125, 6.25, 12.5, and 25 µg/mL. Nevertheless, the anti-HSV-1 activity of acyclovir was reported higher at 50 µg/mL in comparison to the *A. annua*. Moreover, *A. chamaemelifolia* presented the lowest anti-viral activity (Khajeh, 2011).

2.3. *Rheum officinale*, *Aloe barbadensis*, *Rhamnus frangula*, *Rhamnus purshianus*, and *Cassia angustifolia*: Different extracts of *Rheum officinale*, *Aloe barbadensis* (*Aloe vera*), *Rhamnus frangula*, *Rhamnus purshianus*, and *Cassia angustifolia* have been found to have anti HSV-1 activities (Sydiskis, 1991).

2.4. *Rhamnus frangula*, *Rhamnuspurshianus*, *Cassia angustifolia* and *Santolina insularis*: *Rhamnus frangula*, *Rhamnuspurshianus*, and *Cassia angustifolia* have been reported to present anti HSV-1 properties. Moreover, the current data supports a strong correlation between *Santolina insularis* essential oil and prevention of cell-to-cell virus spread and also in inactivation of HSV-1 (Sydiskis, 1991).

2.5. *Hypericum hookerianum*, *Usnea complanta*, *Holoptelia integrifolia* and *Nerium indicum*: Three extracts of Nepal traditional medicine, including *Hypericum mysorense*, *Hypericum hookerianum* and *Usnea complanta*, exhibited significant anti-HSV-1 activity at different concentrations and no toxic effects on cells were observed *in vitro* (Vijayan, 2004). Also, two species, *Holoptelia integrifolia* and *Nerium indicum* showed significant antiviral activity against the herpes simplex virus with no cytotoxic property (Vijayan, 2004).

2.6. *Gynura*: The ethanol extract of *Gynura procumbens* has exhibited a pivotal and elusive anti replicative and virucidal activities versus HSV-1 (Jarikasem, 2013).

2.7. *Vulgare (tansy)*, *Rosa canina* and *Urtica dioica (nettle)* (IMOD™): IMOD™ is a natural medicine, which is prepared as a mixture of herbal extracts including *Tanacetum vulgare* (tansy), *Rosa canina* and *Urtica dioica* (nettle) as well as selenium, flavonoids and carotenes (Paydary, 2012) that is manufactured by the Parsroos Company in Iran (Zabihollahi, 2012). IMOD has been reported that is able to suppress 50% of HSV replication (IC (50)) at 4.3×10^{-3} V/V concentrations. Virucidal assay indicated that IMOD could reduce the effectiveness of HSV particles to 54% of the controls. Also, it was shown that IMOD suppresses the replication of HSV in a phase following the entering of virions to the cells (Zabihollahi, 2012). Data obtained from the above mentioned study showed that IMOD had significant anti-viral activity against HIV and HSV (Zabihollahi, 2012; Ghobadi, 2013).

2.8. *Panax notoginseng* (Araliaceae): Steam-treated notoginseng, the roots of *Panax notoginseng* (Burk.) (Araliaceae), is reported as a famous Chinese ethnomedicine which has been utilized both in treated and raw forms. These investigations led to the isolation of a new dammarane-type from notoginseng which is a tetracyclic triterpene saponin (group of glycosides found in plants), that is namely notoginsenoside ST-4. The antiviral activity of notoginsenoside ST-4 has been investigated on HSV-1 which the activity was confirmed *in vitro*. The 50% effective concentration (EC(50)) values, evaluated by plaque reduction assay, as 16.47 +/- 0.67 μ M for HSV-1, while the 50% cytotoxic concentration (CC(50)) was measured by the XTT test on Vero cells as 510.64 +/- 4.56 μ M. The antiviral action of notoginsenoside ST-4 is generally thought to be correlated with the effects of penetration inhibition, and was determined via fluorescence microscopy observation. Thus, consistent with the data already presented, it may conclude that notoginsenoside ST-4 is a capable agent for herpes simplex virus therapy (Pei et al., 2011).

2.9. *Ficus carica*: The latex of fig fruit (*Ficus carica*) has been applied in classic medicine for the treatment of diseases with viral origin and also skin infections such as warts. To evaluate the capacity of the several extracts, they were studied *in vitro* for their probable antiviral potential activity against HSV-1. To confirm the antiviral action, observation of cytopathic effects was performed. The hexanic and hexane-ethyl acetate (v/v) extracts suppressed replication of HSV-1 at concentrations of 78 μ g/mL by experienced methods. In conclusion, these two extracts can be introduced as herbal medicines for HSV treatment. There was no report of the cytotoxic effect of extracts on Vero cells in the above mentioned tested concentrations (Lazreg, 2011).

2.10. *Paraguayan Scoparia dulcis* L: *Paraguayan Scoparia dulcis* L was shown that contain a beta-glucuronidase-inhibitory diterpene which is named scoparic acid A (SA). Moreover, scoparic acid B, scoparic acid C, and the aphidicolin-like tetracyclic diterpenes scopadulcic acid A (SDA) and scopadulcic acid B (SDB) were found in the plant (Hayashi, 2011). Analysis of diterpenes in the *Paraguayan dulcis* confirmed the existence of three chemotypes elements, including SA type, SDB type, and SDX type which contains fundamentally scopadiol and scopadulciol (SDC) (Hayashi, 2011). Moreover, SDB and SDC were shown to have multifunctional pharmacological effects like as inhibitory effects on HSV-1 (Hayashi, 2011).

2.11. *Eucalyptus maiden*: A report indicates that five new compounds have been detected along with analysis of the fresh fruits of *Eucalyptus maiden* including eucalmainosides A-E, phloroglucinol glycosides, with three hydrolyzable tannins, six simple phenolic and seven (+)-oleuropeic acid derivatives and also 15 flavonoids (Tian, 2010). The *in vitro* anti HSV-1 assessment showed weak anti-HSV-1 exertion of the flavonols, myricetin and quercetin, and also the ellagitannin isocoriariin F with TIC values of 0.31, 0.33, and 0.12 mM, in that order (Tian, 2010).

2.12. *Coptidis rhizomem*, *Ching-Wei-San*: *Ching-Wei-San*, *Coptidis Rhizoma* has shown to have the most effective antimicrobial activity among the Chinese herb medicine (Chin, 2010). To investigate the possible utilization of *Ching-Wei-San* against to HSV infection, the cytotoxicity, anti-HSV-1 function in Vero cells was assessed. The selectivity index of berberine, which is an alkaloid extraction from *Coptidis rhizome*, was about 1.2-1.5 times more than that of *Coptidis rhizome* extract and *Ching-Wei-San* in the liquefied solution (Chin, 2010). *Berberine* could

prevent the viral replication cycle following the virus penetration step and no further than the stage of viral DNA synthesis, and its activities were not influenced by the vigilance mechanisms. In conclusion, all *Coptidis rhizome*, *Ching-Wei-San* and *Berberine* revealed anti-HSV property (Chin, 2010).

2.13. *Nervilia fordii*: Five compounds of 7-O-methylkaempferol and quercetin glycosides, including *nervilia fordins* A-E, were secluded from the entire plant of *Nervilia fordii*, together with an identified coumarin and seven identified flavonoids. Their constructions were cleared on the basis of widespread spectroscopic studies, comprising HSQC, HMBC, ROESY, and chemical procedures. Compounds 1-3 and 6-13 were assessed for their anti HSV-1 action and cytotoxicity on African green monkey kidney cells (Vero cells) *in vitro*. Antiviral activity against HSV-1 was presented only by esculetin, while the aglycones indicated stouter cytotoxicity on Vero cells than their glycosides (Tian, 2009).

2.14. *Echinacea* (Echinaforce): The capability of a uniform preparation of the Echinacea (Echinaforce, an ethanol extract of herb and roots of *E. purpurea*, and covering identified concentrations of marker compounds) was assessed in hampering the HSV-1, introduction of various cytokines in a line of human bronchial epithelial cells (BEAS-2B), and in two other human cell lines. HSV-1 could induce significant secretion of IL-6 and IL-8 (CXCL8), additional to several other chemokines. The Echinacea preparation presented effective virucidal activity representing the multi-efficiency potential of the herb (Sharma, 2009).

2.15. *Stephania cepharantha*: Through screening water and MeOH extracts of 30 Chinese medicinal plants for their anti-HSV-1 activity, a MeOH extract of the root tubers of *Stephania cepharantha*. HAYATA revealed the most effective activity on the plaque reduction assay with an IC₅₀ value of 18.0 microg/ml. Of 49 alkaloids isolated from the MeOH extract, 17 alkaloids were found to be active against HSV-1, including 13 bisbenzylisoquinoline, 1 protoberberine, 2 morphinane and 1 proaporphine alkaloids, whereas benzylisoquinoline and hasubanane alkaloids were inactive. However, N-methylcrotosparine was active against HSV-1, as well as a HSV-1 thymidine kinase deficiency (acyclovir resistant type, HSV-1 TK-) and HSV-2 (IC₅₀ values of 8.3, 7.7 and 6.7 microg/ml, respectively), it was cytotoxic. FK-3000 was the most active against HSV-1, HSV-1 TK- and HSV-2 (IC₅₀ values of 7.8, 9.9 and 8.7 microg/ml) with *in vitro* therapeutic indices of 90, 71 and 81, respectively. FK-3000 was found to be a candidate as an anti-HSV agent against HSV-1, acyclovir (ACV) resistant-type HSV-1 and HSV-2 (Nawawi, 1999).

2.16. *Rhus javanica*: *Rhus javanica*, as a medicinal herb, exhibited oral therapeutic anti-HSV activity in mice. Two major anti-HSV compounds; moronic acid and betulonic acid were cleansed from the herbal extract by extraction with ethyl acetate at pH 10 followed by chromatographic separations and inspected their anti-HSV activity, *in vitro* and *in vivo* (Kurokawa, 1999). Moronic acid was quantitatively a major anti-HSV compound in the ethyl acetate-soluble part. The efficient concentrations for a 50% plaque reduction of moronic acid and betulonic acid for wild-type HSV type 1 (HSV-1) were 3.9 and 2.6 microgram/ml, respectively. The therapeutic index of moronic acid (10.3-16.3) was larger than that of betulonic acid (6.2). Susceptibility of acyclovir-phosphonoacetic acid-resistant HSV-1, thymidine kinase-deficient HSV-1, and wild-type HSV type 2 to moronic acid was similar to that of the wild-type HSV-1. When this compound was given orally to mice infected cutaneously with HSV-1 three times daily, it significantly slowed the progress of skin lesions and/or prolonged the mean survival times of infected mice without toxicity in relation to the control group. Moronic acid blocked virus yields in the brain more efficient than those in the skin. This was in line with the mean survival times. Thus, moronic acid was purified as a major anti-HSV compound from the herbal extract of *Rhus javanica*. The mode of the anti-HSV activity was different from that of ACV. Moronic acid revealed oral therapeutic efficacy in HSV-infected mice and possessed novel anti-HSV activity that was in line with that of the extract (Kurokawa, 1999).

The aqueous extract of *Geum japonicum* revealed prophylactic and therapeutic anti-herpes simplex virus (HSV) action in murine infection models. Eugeniin was purified as an anti-HSV compound from the extract and also was isolated from other herbal extract (*Syzygium aromaticum*) that had exhibited anti-HSV activity in mice. Thus the anti-HSV action of eugeniin was characterized. The effective concentration (5.0 microg/ml) for a 50% plaque reduction of eugeniin for wild HSV type 1 (HSV-1) on Vero cells was 13.9-fold lower than its 50% cytotoxic concentration determined by a yield-reduction assay. Eugeniin also inhibited the growth of acyclovir-phosphonoacetic acid-resistant HSV-1, thymidine kinase-deficient HSV-1 and wild HSV type 2. Eugeniin as well as phosphonoacetic acid inhibited viral DNA and late viral protein syntheses in their infected Vero cells, but not cellular protein synthesis at its inhibitory concentrations. Purified HSV-1 DNA polymerase activity was inhibited by eugeniin noncompetitively regarding dTTP. Its apparent K_i value for eugeniin was 8.2- and 5.8-fold lower than the K_i values of purified human DNA polymerases alpha and beta, respectively. Thus one of the major target sites of inhibitory action of eugeniin is viral DNA synthesis; the inhibitory action for viral DNA polymerase activity was novel compared with anti-HSV nucleoside analogs (Kurokawa, 1998).

Traditional herbal medicines with anti-herpes simplex virus type 1 (HSV-1) activity *in vivo* were studied for their prophylactic actions on recurring HSV-1 infection in mice. Mice were intradermally infected with HSV-1 in

the pinna and recurrent HSV-1 disease was induced by ultraviolet irradiation. Herbal extracts slowed the development of recurrent HSV-1 disease, reduced the incidence of severe erythema and/or vesicles in the pinna, and/or shortened the period of severe recurring lesions compared with water-administered mice ($P < 0.01$ or 0.05). Likewise, the prophylactic treatment of herbal extracts limited the development of recurrent skin lesions induced by stripping with cellophane tape physically. The prophylactic efficacy on recurrence was established by the absence of HSV DNA in the skin lesions. The HSV-1 genome was shown to exist in the trigeminal ganglia, but not in the pinna of latently infected mice before stimuli by a nested-polymerase chain reaction assay. After stimuli, the HSV-1 genome was detected in both pinna and trigeminal ganglia of latently infected mice administered with water. Though, prophylactic treatment reduced the rate of detection of HSV-1 genome in the stimulated pinna. Therefore, the herbal extracts exhibited prophylactic efficacy against recurrent HSV-1 disease in mice and modulated the recurrent HSV-1 infection (Kurokawa, 1997).

Nepeta coerulea, *Nepeta nepetella*, *Nepeta tuberosa*, *Sanguisorba minor magnolii* and *Dittrichia viscosa* showed clear antiviral activity against DNA and RNA viruses, i.e. HSV-1 (Jassim and Naji, 2003). *Nepeta coerulea*, *Nepeta nepetella*, *Nepeta tuberosa*, *Sanguisorba minor magnolii* and *Dittrichia viscosa* showed clear antiviral activity against HSV-1 (Abad, 2000).

3. CONCLUSIONS

In the current review, we offered results relating to the antiviral activity of several herbal medicine extracts and pure compound isolated from these resources to look for the probable effect of HSV-1. These novel results recommend that herbals could be one of the best choices for improvement of novel treatments for HSV infection, which may give synergistic anti-viral activity (Son, 2013).

We can conclude that extracts from plants in herbal medicine can reveal antiviral activity on HSV-1. Therefore, medicinal plants can be considered as a choice for the isolation of pure compounds acting against HSV-1. Regardless of the fact that the amount of evidence on anti-HSV plant extracts is very appropriate, nevertheless not all the bioactive anti-HSV molecules in charge for the activity of plant extracts have been recognized, isolated or tested (Khan, 2005).

Based on the specific assay system or screening approach, a large number of structurally unique antiviral compounds from medicinal plants (herbs) have been recognized (Kitazato, 2007). The advantages of natural compounds include fewer side effects in comparison to orthodox medical medications, and the production of synergistic effects for a more positive treatment result. Though, the potential beneficial effects of these natural compounds have to be established in large, rigorous trials (Kitazato, 2007). The continued discovery and development of novel formulations of herbal medicines, containing a combination of multiple ingredients that synergistically act to strongly and selectively inhibit virus replication at different stages and strengthen the impaired immune system, may be a possible therapeutic choice in the coming years (Kitazato, 2007). Further clarification of the herbals interactions with HSV is required which could provide valuable information about the chemical nature and mechanism(s) of action of the potential anti-HSV molecule(s) (Khan, 2005). This is extremely desirable and fundamental point, that all the most potential plant extracts must undertake further analysis and purification steps with the aim of identifying the active elements existing in the herbals.

Conflict of interest: There is no conflict of research in the current study.

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