Mojdeh Heidary Navid
Dr. sc. hum.

The antiviral activity and mechanism of action of natural products against herpes simplex virus type 1 (HSV-1)

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Doktorvater: Prof. Dr. Paul Schnitzler

Natural products are an unlimited source for anti-herpetic drugs and since herpes simplex virus (HSV) might develop resistance to commonly used antiviral drugs, development of new drugs with novel mode of action are increasingly demanded. This study focused on the anti-HSV-1 activity of some essential oils and pentacyclic triterpenes in vitro. The antiviral activity of these natural products was tested by a plaque reduction assay. The 50% inhibitory concentration (IC_{50}) of Olbas oil and cajuput oil for HSV-1 was determined at 1.8 µg/ml and 7.5 µg/ml, respectively. Plaque formation was significantly reduced by 99% for Olbas oil and 66% for cajuput oil at noncytotoxic concentrations of these oils. The selectivity index of 150 for Olbas oil was superior to a rather low selectivity index of cajuput oil. The mode of antiviral action of these essential oils was assessed by time-on-addition assays. These results indicate that the essential oils affected the virus before adsorption, but not after penetration into the host cell, thus Olbas oil and cajuput oil exerted a direct antiviral effect on HSV-1. Considering the lipophilic nature of the Olbas mixture of essential oil which enables it to penetrate the skin, and a high selectivity index, Olbas oil might be suitable for topical treatment of herpetic infections.

In the second part of this study, the antiviral mechanism of action of a triterpene extract of birch bark and its major pentacyclic triterpenes, i.e. betulin, lupeol and betulinic acid was explored against acyclovir-sensitive HSV-1 (KOS) strain and acyclovir-resistant HSV-1 strains (1246-99, 496-02). TE, betulin, lupeol and betulinic acid exhibited high levels of antiviral activity against HSV-1 in viral suspension tests with IC_{50} values ranging between 0.2 to 0.5 µg/ml. Viral infectivity was significantly reduced by ~90% in both acyclovir-sensitive and clinical isolates of acyclovir-resistant HSV-1 strains.

The mode of antiviral action was assessed when TE and pentacyclic triterpenes were added at different times during HSV-1 infection cycle. Addition of these drugs to uninfected cells prior

to infection or to herpesvirus-infected cells during intracellular replication had a minor effect on virus multiplication. The immediate early, early and late protein expression was not affected during replication of HSV-1 when treated with TE, betulin, lupeol and betulinic acid. The early steps of viral infection, attachment and penetration were not affected when treated with TE, betulin, lupeol and betulinic acid. Virucidal activity of these triterpenes was marginal, however both TE and tested pentacyclic triterpenes exhibited high anti-herpetic activity when viruses were pretreated with these drugs prior to infection. Pentacyclic triterpenes inhibit acyclovir-sensitive and acyclovir-resistant clinical isolates of HSV-1 in the early phase of infection. Therefore, the direct interaction of triterpene extract and its isolated pentacyclic triterpenes on HSV-1 virions is a proposed mode of antiviral action of these natural products. So far, results obtained from this study revealed a promising application of triterpene extract and its isolated components as anti-herpetic agents.