

## **PLANT POLYPHENOLS WITH BROAD-SPECTRUM ANTIVIRAL ACTIVITY AS PROMISING THERAPEUTIC AGENTS**

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The COVID-19 pandemic demonstrated that drug repurposing—identifying active molecules among compounds with previously established antiviral activity—represents an effective strategy for discovering broad-spectrum antiviral agents. Clinical studies of Rutan conducted during the pandemic, a drug previously developed by our group for the treatment of influenza, demonstrated its safety and efficacy for the prevention and treatment of COVID-19, including in children, as well as for the prevention of post-COVID syndrome (long COVID). Rutan is a mixture of water-soluble polyphenols derived from sumac (*Rhus coriaria*). Studies of its mechanism of action demonstrated that Rutan polyphenols and their individual components inhibit the activity of key SARS-CoV-2 enzymes—the main protease (MPro, or 3CLPro) and RNA-dependent RNA polymerase (RdRp)—at micromolar concentrations.

The investigated polyphenols also exhibited antiviral activity against herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), human cytomegalovirus (CMV), Epstein–Barr virus (EBV), and hepatitis B virus (HBV). R5 inhibited HSV-1 and HSV-2 with comparable efficacy, whereas Rutan and R7 were more active against HSV-1, and geraniin showed greater activity against HSV-2. Rutan and R5 also inhibited the intracellular replication of CMV and EBV. Among the compounds evaluated against HBV, R5 and geraniin demonstrated the highest inhibitory activity, although Rutan itself and its other components were also active. Thus, for the first time, sumac polyphenols were shown to inhibit, in addition to HIV, influenza virus, and SARS-CoV-2, the replication of representatives of all three subfamilies of *Orthoherpesviridae*, as well as HBV, supporting their further development as broad-spectrum antiviral agents.

HSV-1 and HSV-2 are responsible for a largely overlooked and poorly controlled global epidemic; according to the latest WHO estimates, their prevalence in certain regions approaches 100%. Evidence also suggests their potential involvement in the development of multiple sclerosis, Alzheimer's disease, and several types of cancer. We therefore evaluated the ability of geraniin, Rutan, and its individual components (i) to inhibit drug-resistant strains of these viruses and (ii) to act synergistically with nucleoside and non-nucleoside antiviral agents. The simultaneous use of multiple

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## PLENARY PRESENTATIONS

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antiviral agents with different mechanisms of action may delay or potentially prevent the emergence of drug-resistant viral strains.

Our results demonstrated that Rutan and geraniin exhibit comparable activity against both nucleoside-sensitive and nucleoside-resistant strains of HSV-1 and HSV-2, including multidrug-resistant clinical isolates. We also identified synergistic effects of Rutan and geraniin in combination with acyclovir or glycyrrhizic acid in suppressing HSV-1 and HSV-2 replication. These findings provide a basis for the development of a new generation of antiherpetic therapeutics based on multicomponent combinations (“cocktails”), conceptually similar to combination therapies currently used for HIV infection.

The demonstrated efficacy of Rutan in the treatment of influenza and COVID-19, together with preliminary findings obtained in a cohort of patients with EBV infection, provides a rationale for investigating its potential application in hepatitis B therapy. At present, no available pharmacological treatment provides a definitive cure for HBV infection. Despite the availability of an effective prophylactic vaccine, approximately 250 million people worldwide are living with chronic hepatitis B. The development of new therapeutic agents capable of suppressing HBV replication therefore remains an urgent global medical need.