

Rosmarinic Acid Inhibits Influenza Virus by Suppressing Cellular AKT Phosphorylation

Jim-Tong Horng^{1*}, Jia-Rong Jheng¹

¹. Chang Gung University

Background/Objective

Influenza A virus (IAV) is an important pathogen that has caused high human morbidity and mortality worldwide. In this study, we investigated the antiviral mechanism of a natural compound, rosmarinic acid (RA), which is found in several herbs, and possesses antimicrobial, antioxidant, and antiviral effects. We also demonstrated RA's efficacy *in vivo* using an animal model of influenza.

Method

Antiviral activity of RA was determined by neutralization assay (inhibition of virus-induced cell death) using MDCK cell line. Time-of-addition assay is used to examine RA's inhibitory effect at specific replication stages. Inhibition of phosphorylation of cellular AKT was determined by immunoblotting. Minigenome reporter assay was used to determine the viral polymerase activity. We examined the *in vivo* efficacy of RA using a mouse model.

Result

RA exhibited inhibitory activity against different influenza viruses including oseltamivir-resistant strains, with 50% inhibitory concentrations in the range of 7.6 – 89.6 μ M in Madin – Darby canine kidney cells. RA suppressed viral RNA expression, but without significantly affecting viral polymerase activity in a minigenome RNA assay. In addition, RA did not target hemagglutinin or neuraminidase, nor did it alter the subcellular localization of viral proteins. However, we found that it directly reduced the phosphorylated levels of the serine/threonine protein kinase AKT. We also further demonstrated the antiviral efficacy of RA in mouse models by increasing the survival rate of IAV-infected animals.

Conclusion

RA displayed a specific inhibitory activity against H1N1, including oseltamivir-resistant strains. This offers an alternative avenue for therapy when resistant viruses become prevalent. It thus has a potential for developing as therapeutic agent against influenza viruses.