

Antiviral activity of caffeic acid against Ilheus virus

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Ilheus virus (ILHV) is a neglected arbovirus belonging to the *Flaviviridae* family, *Flavivirus* genus. The ILHV is transmitted to humans by the biting of infected vectors, especially mosquitoes belonging to *Psorophora* and *Ochlerotatus* genera. The infection could cause disease characterized by an acute febrile illness, like dengue fever, with typical clinical symptoms such as fever, headache, muscle, joint pain, and skin rash, which may develop into meningitis and/or encephalitis. Currently, no specific vaccine and treatment against this virus are available; therefore, it is essential to research effective antiviral molecules to mitigate the impact of the infection in the endemic areas. In this line, a novel antiviral approach (economical, simple to use, and environmentally friendly) is using natural compounds. In this study, we tested the antiviral potential of caffeic acid present in plants and natural products, such as wine and coffee, against ILHV. The cytotoxicity of the compound was evaluated by the MTT assay, and the *in vitro* prophylactic and therapeutic effect of caffeic acid on ILHV replication in A549 cells was investigated by administering it under post-treatment conditions. The antiviral activity was determined by titration using plaque-forming unit assay. The molecular mechanism of inhibitory action was further proposed using *in silico* molecular docking studies. The *in vitro* experiments revealed CC₅₀ > 1000 µM, EC₅₀, and EC₉₀ values as 100.7 and 906.1 µM, respectively, under post-treatment conditions. Besides, the molecular docking indicated that the caffeic acid could efficiently interact with the specific allosteric binding site cavity of the NS2B-NS3 proteases. Our results indicate that the caffeic acid had low cytotoxicity and significant antiviral effects on ILHV multiplication in A549 cells, providing a new candidate drug to treat this neglected arbovirus infection.

Palavras-Chaves: Antiviral; flavivirus; arbovirus

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