Virtual Screening-Based Identification of Potent DENV-3 RdRp Protease Inhibitors via In-House Usnic Acid Derivative Database

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ABSTRACT

Dengue virus (DENV) is the causative agent of dengue fever, dengue hemorrhagic disease and dengue shock syndrome (DSS), transmitted predominantly in tropical and subtropical regions by *Aedes aegypti*. It infects millions of people and causes thousands of deaths each year, but there is no antiviral drug against DENV. Usnic acid lately piqued the interest of researchers for extraordinary biological characteristics, including antiviral activity. Based on high larvicidal activities against *Aedes aegypti*, this study aims to search usnic acid derivatives as novel anti-DENV agents through a combination of ligand-based and pharmacophore-based virtual screening. One hundred and sixteen (116) usnic acid derivatives were obtained from a database of 428 in-house usnic acid derivatives through pharmacophore filtering steps. Subsequent docking simulation on DENV-3 NS-5 RdRp afforded 41 compounds with a strong binding affinity towards the enzyme. The pharmacokinetics and drug likeness prediction resulted in seven hit compounds, which eventually undergo cytochrome P450 enzyme screening to obtain the lead compound, labelled as **362**. In addition, molecular dynamic (MD) simulation of lead compound **362** was performed to verify the stability of the docked complex and the binding posture acquired in docking experiments. Overall, the lead compounds have shown a high fit value of pharmacophore, strong binding affinity towards RdRp enzyme, good pharmacokinetics, and drug likeness properties. The discovery of a new usnic acid derivative as a novel anti-DENV agent targeting RdRp could lead to further drug development and optimization to treat dengue.

KEYWORDS: Anti-DENV; usnic acid; pharmacophore; docking; virtual screening; molecular dynamic simulation

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