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Computational evaluation of quinones of *Nigella sativa* L. as potential inhibitor of dengue virus NS5 methyltransferase

Miah Roney[a,b], Amit Dubey[c,d], Muhammad Hassan Nasir[e], Akm Moyeenul Huq[b,f], Aisha Tufail[c], Saiful Nizam Tajuddin[a,b], Normaiza Binti Zamri[a] and Mohd Fadhlizil Fasihi Mohd Aluwi[a,b]

[a]Faculty of Industrial SCiences and Technology, Universiti Malaysia Pahang Al-Sultan Abdullah, Lebuhraya Tun Razak, Kuantan, Pahang Darul Makmur, Malaysia; [b]Centre for Bio-Aromatic Research, Universiti Malaysia Pahang Al-Sultan Abdullah, Lebuhraya Tun Razak, Kuantan, Pahang Darul Makmur, Malaysia; [c]Computational Chemistry and Drug Discovery Division, Quanta Calculus, Greater Noida, India; [d]Department of Pharmacology, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India; [e]Faculty of Medicine, University Sultan Zainal Abidin (UniSZA), Kuala Terengganu, Terengganu Darul Iman, Malaysia; [f]Department of Pharmacy, School of Medicine, University of Asia Pacific 74/A, Dhaka, Bangladesh

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ABSTRACT

Aedes aegypti is the primary vector for the transmission of the dengue virus, which causes dengue fever, dengue hemorrhagic illness and dengue shock syndrome. There is now no antiviral medication available to treat DENV, which kills thousands of people each year and infects millions of individuals. A possible target for the creation of fresh and efficient dengue treatments is the DENV-3 NS5 MTase. So, *Nigella sativa* quinones were examined using *in silico* methods to find natural anti-DENV compounds. The *in silico* docking was conducted utilising the Discovery Studio software on the quinones of *N. sativa* and the active site of the target protein DENV-3 NS5 MTase. In addition, the druggability and pharmacokinetics of the lead compound were assessed. Dithymoquinone was comparable to the reference compound in terms of its ability to bind to the active site of target protein. Dithymoquinone met the requirements for drug likeness and Lipinski's principles, as demonstrated by the ADMET analysis and drug likeness results. The current study indicated that the dithymoquinone from *N. sativa* had anti-DENV activity, suggesting further drug development and dengue treatment optimisation.

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anti-dengue; NS55; *in silico*; docking; DFT; MD simulation; *Nigella sativa*

Introduction

The mosquito vector *Aedes aegypti* spreads the tropical infectious illness dengue. The health of population in the tropical region where its vector lives is seriously threatened. Dengue illness is widespread in more than 100 countries and millions of new cases are reported each year. Globalisation and climate change are projected to cause the *A. aegypti* mosquito's infestation area to grow, thus causing even greater health problems. A half million cases of dengue infections are thought to occur annually on a global scale. Hospitalisation and symptoms such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) that can be fatal can result from this (Jarerattanachat et al., 2023).

Other diseases, including the chikungunya, zika and yellow fever viruses, are also spread by these lethal vectors. Rainfall, temperature, relative humidity and unplanned rapid urbanisation all affect the incidence of dengue disease. Dengue fever is widespread across the tropics. Intense joint and muscular agony that seems to be breaking bones is one of the symptoms, hence the term 'break-bone fever'. Dengue fever has been documented numerous times for more than 200 years. Four hundred million cases are anticipated per year, putting 3.97 billion people in 128 endemic countries at risk of contracting an illness (Miglani & Gakhar, 2022).

There are four distinct but closely related serotypes of Dengue virus (DENV), which is a genus of flavivirus and a member of the Flaviviridae family. These serotypes are DENV-I, DENV-II, DENV-III and DENV-IV. Seven non-structural (NS) proteins make up the dengue virus: NS-1, NS-2a, NS-2b, NS-3, NS-4A, NS-4B and NS-5 (Roney et al., 2023). The NS-5 exhibits methyltransferase activity at its N-terminus and RNA-dependent RNA polymerase (RdRp) activity at its C-terminus, making it a major drug target. The development of antiviral medication and their design should be improved with knowledge of NS-5 structural dynamics. The ideal target for developing inhibitors for flavivirus infections is NS-5 protease due to its significant role in viral replication. There are two types of DENV NS-5 RdRp inhibitors: nucleoside inhibitors, which serve as an RNA chain terminator by interfering with the polymerase's binding site, and non-nucleoside inhibitors, which exhibit enzymatic activity by acting at the allosteric site of the protease (NS-5) (Adawara et al., 2021).

New medications to treat a variety of ailments are increasingly being developed using natural items as a source. Over the past few decades, a variety of natural products with

CONTACT AKM Moyeenul Huq moyeenul@ump.edu.my; Mohd Fadhlizil Fasihi Mohd Aluwi fasihi@ump.edu.my
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