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Molecular docking and drug-likeness study of nirmatrelvir as promising drug candidates of dengue virus NS2B-NS3 protease

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ABSTRACT: *Aedes aegypti* is the primary vector for the transmission of the dengue virus (DENV), which causes dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). There is now no antiviral medication available to treat DENV, which kills thousands of people year and infects millions of individuals. Due to the current situation, effective and useful treatments for this virus urgently need to be developed. Therefore, the goal of the current work was to determine, using molecular docking and drug-likeness analysis, the anti-viral potential of Nirmatrelvir inhibitor against DENV (1-4) NS2B-NS3 protease. Nirmatrelvir shown robust and stable bonding in the binding pocket of DENV (1-4) NS2B-NS3 protease, as demonstrated by molecular docking. According to the drug-likeness study, Nirmatrelvir shown druggability and may function as possible inhibitor to halt DENV proliferation. To establish their action and other qualities, it is also necessary to research how substances behave in both *in-vitro* and *in-vivo* settings.

KEYWORDS: Nirmatrelvir; anti-dengue; NS2B/NS3 protease; molecular docking; drug-likeness.

1. INTRODUCTION

Around 2.5 billion people are infected with the mosquito-borne (spread by *A. aegypti* and *A. albopictus*) viral disease dengue, which causes nearly 25,000 fatalities annually and is becoming a major global health concern [1]. The symptoms of dengue virus (DENV) infection include headache, joint pain, rashes, low white blood cell count, mild asymptomatic dengue fever (DF), severe dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS), which is characterized by shock [2]. The World Health Organization (WHO) claims that because to the millions of illnesses that occur each year, dengue poses a risk to everyone on earth [3]. Recently, 20 endemic nations licensed the tetravalent dengue vaccine CYD-TDV (Dengvaxia, Sanofi Pasteur, Lyon, France). The WHO advises against using CYD-TDV outside of dengue-infected people aged 9 to 45 because seronegative people may develop severe dengue after receiving the vaccine [4]. Additionally, the restricted availability of the dengue vaccine in some nations suggested that new therapeutic options and an efficient next-generation vaccine, independent of prior dengue exposure, should be developed to combat this old disease. So, a promising approach to treating dengue would be drug-based anti-DENV therapy.

The virus genome of DENV is 11 kb in size, and it is encoded by seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) in addition to three structural proteins (capsid, membrane, and envelope glycoprotein) [2]. The location of these proteins is as follows: 5-CprM (M) -E-NS1- NS2A-NS2B-NS3-NS4A-NS4B-NS5-3 [1]. Nonstructural proteins are crucial for the structural organization of viruses and their entry into host cells, whereas structural proteins are crucial for viral replication and other cellular processes [5]. According to recent studies, a serine protease domain is found at the *N*-terminal region of NS3, and

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