Computational Drug Design of Cyclotide-Based Inhibitors Targeting Crimean–Congo Hemorrhagic Fever Virus: An Integrative Molecular Docking and Dynamics Approach

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ABSTRACT

Crimean–Congo haemorrhagic fever (CCHF) is a highly pathogenic zoonotic disease caused by a negative-sense single-stranded RNA virus of the *Nairoviridae* family and *Orthonairovirus* genus. The virus targets endothelial and immune cells, leading to immune evasion and vascular damage. This study employs computational modelling to evaluate cyclotides as potential antiviral agents targeting the glycoprotein of the CCHF viral envelope to mitigate its pathogenicity. The target protein (PDB ID: 8VVL) was retrieved from the Protein Data Bank, refined using PyMol, and its physicochemical properties were assessed via ProtParam. Cyclotides were obtained from the CyBase database, and 3D structures were modelled using Swiss Model for molecular docking analysis conducted via HDOCK. Toxicity and allergenicity predictions were performed, followed by molecular dynamics (MD) simulations for 100 ns using Desmond from Schrödinger LLC. The MMGBSA method was employed to estimate free binding energy. Physicochemical analysis indicated that the glycoprotein has a moderately hydrophilic nature (GRAVY: -0.113) with a theoretical isoelectric point of 8.06. Among the tested cyclotides, Kalata B7 demonstrated the highest docking score (-213.76 kcal/mol) and was identified as non-toxic and nonallergenic. MD simulations confirmed stable protein-ligand interactions, suggesting Kalata B7 as a promising therapeutic candidate. Further in vitro and in vivo studies are warranted to validate its potential for clinical application in combating CCHF.

Keywords: Crimean–Congo haemorrhagic fever (CCHF); Cyclotides; Molecular docking; Molecular dynamics simulations; Viral glycoprotein inhibition; Computational drug design

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