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Targeting the Crimean-Congo haemorrhagic fever virus with natural compounds: an *in silico* study

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ABSTRACT

The Crimean-Congo haemorrhagic fever virus (CCHFV) is a highly transmissible pathogen capable of inducing severe haemorrhagic manifestations with high fatality rates. This study has aimed at demonstrating a virtual screening workflow and compound selection strategy to evaluate the potential of natural compounds to inhibit CCHFV through its ovarian tumor domain protease (vOTU); a key mediator of immune evasion. From a curated library of 5,749 natural compounds, five candidates met the selection criteria. Among these, 1,3,6-trigalloyl glucose exhibited the highest binding affinity (XP GScore: -9.351 kcal/mol) and geometric stability, as evidenced by a root mean square deviation (RMSD) of <4.5 Å in molecular dynamics simulations. The second most promising compound, 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl 6-O-(6-deoxy-α-L-gulopyranosyl)-β-D-talopyranoside, demonstrated an XP GScore of -7.909 kcal/mol and an RMSD <2.8 Å. These findings suggest that the identified natural compounds may serve as promising antiviral candidates against CCHFV. Further experimental validation is warranted in order to assess their therapeutic potential. Overall, this study underscores the utility of *in silico* approaches for the identification of novel antiviral agents derived from natural sources.

1. Introduction

The Crimean-Congo haemorrhagic fever (CCHF) is a severe zoonotic viral disease caused by infection with the Crimean-Congo haemorrhagic

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fever virus (CCHFV)[1]. Transmission occurs primarily through bites from infected *Hyalomma* ticks or *via* direct contact with the blood, tissues, or bodily fluids of infected animals[2]. First documented in the mid-twentieth century, CCHF is endemic across Africa, Asia, and Eastern Europe, posing a significant public health threat due to its high case fatality rate, which may exceed 30% in severe outbreaks[1].

The pathogenesis of CCHF involves complex interactions between CCHFV and the host immune system[3]. Viral infection activates the endothelial cells and the macrophages, triggering an excessive release of pro-inflammatory cytokines. This dysregulated immune response contributes to hallmark clinical features, including haemorrhage and multi-organ dysfunction[3]. Currently, the therapeutic options are limited; ribavirin remains the only antiviral agent with reported efficacy, though its clinical effectiveness remains controversial[2]. In response to the urgent need for novel antiviral strategies, researchers have increasingly turned to computational (*in silico*) drug discovery platforms[4].

This study has investigated the potential of natural compounds to inhibit CCHFV by targeting the viral ovarian tumor domain protease (vOTU); a deubiquitinating enzyme implicated in immune suppression[5]. Using molecular docking and molecular dynamics (MD) simulations, we have herein aimed to identify promising lead compounds for further experimental validation.

2. Methodology

This study employed an *in silico* approach to identify natural compounds capable of inhibiting CCHFV by targeting vOTU. The workflow included ligand preprocessing, protein optimization, molecular docking, and MD simulations. A phytochemical database was compiled from 200 Middle Eastern plant species, yielding 12,971 natural compounds. After deduplication, 5,749 unique ligand conformers were retained for analysis. Ligand preparation was performed using the Glide suite (Schrödinger), with optimization via the OPLS4 force field at physiological pH (7.0). Compounds exceeding 1,000 atoms were excluded in order to reduce computational overhead. Low-energy conformers were selected for virtual screening.

The crystal structure of CCHFV vOTU protease (Protein Data Bank ID: 5V5H) was prepared using the Protein Preparation Wizard in Glide. This included correction of bond orders, addition of hydrogen atoms, and energy minimization using the OPLS4 force field at pH 7. Structural integrity was confirmed *via* a root mean square deviation (RMSD) analysis, with a cutoff of 0.30 Å.

Molecular docking was performed using Glide's extra precision (XP) mode. The active site was defined based on key residues known to mediate ligand binding: Lys27, Asp39, Glu51, Asp52, Arg80, Leu81, and Val82. The XP GScores were used in order to rank ligand binding affinities. MD simulations were conducted in order to assess the stability of ligand-protein complexes and to characterize dynamic interactions. RMSD values were used for the evaluation of conformational stability. Binding modes and interaction types were analysed using Discovery Studio v20.1 (BIOVIA).

3. Results and Discussion

The virtual screening of 5,749 natural compounds identified five candidates with high binding affinities to vOTU, as indicated by XP GScores ranging from -9.351 to -7.909 kcal/mol (Figure 1). Among these, 1,3,6-trigalloyl glucose emerged as the top-performing ligand, with an XP GScore of -9.351 kcal/mol. This compound formed eight conventional hydrogen bonds, two carbon-hydrogen (C–H) bonds, one π-alkyl interaction, and one donor–donor interaction with vOTU.

MD simulations confirmed the stability of the 1,3,6-trigalloyl glucose–vOTU complex, with RMSD values consistently being below 4.5 Å. The second-ranked compound, 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl 6-O-(6-deoxy-α-L-gulopyranosyl)-β-D-talopyranoside, has exhibited an XP GScore of -7.909 kcal/mol and RMSD values below 2.8 Å. This compound formed three hydrogen bonds and ten C–H interactions with vOTU, thereby suggesting a strong inhibitory potential.

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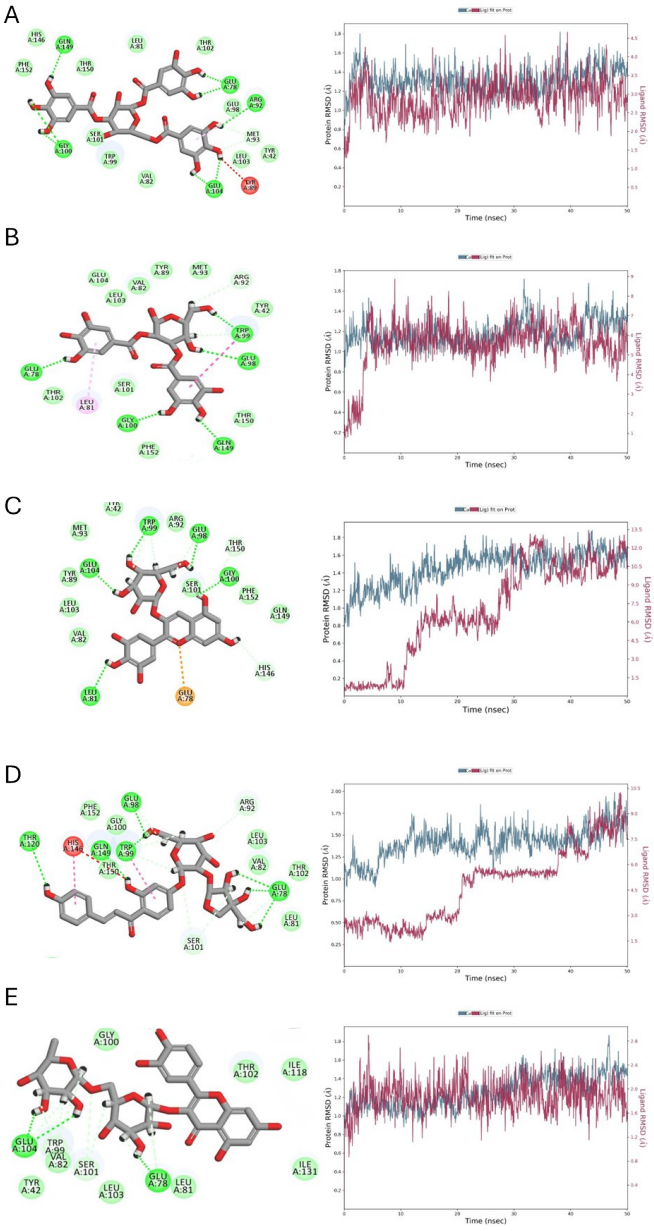

Figure 1. *Molecular docking and molecular dynamics (MD) analysis of natural compounds targeting the Crimean-Congo haemorrhagic fever virus (CCHFV) ovarian tumor domain protease (vOTU). (A): 1,3,6-Trigalloyl glucose exhibited the highest binding affinity (-9.351 kcal/mol), forming strong hydrogen bonds and hydrophobic interactions with key catalytic residues (Lys27, Asp39, Glu51), while RMSD analysis confirmed stable binding (<4.5 Å) over a 50-nsec simulation. (B–D): Other candidate compounds demonstrated binding affinities ranging from -7.986 to -7.909 kcal/mol, with diverse interaction profiles and comparatively lower conformational stability. (E): 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl 6-O-(6-deoxy-α-L-gulopyranosyl)-β-D-talopyranoside exhibited a favourable binding score (-8.556 kcal/mol), forming multiple hydrogen bonds and maintaining an RMSD >4 Å; indicative of high structural stability. The right panel illustrates RMSD fluctuations of ligand–protein complexes over time, confirming sustained ligand occupancy within the binding pocket. These findings suggest that compounds (A) and (E) are promising inhibitors of CCHFV vOTU and merit further experimental validation.*

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The observed ligand–vOTU interactions are significant, as vOTU plays a critical role in immune evasion by deubiquitinating and deISGylating host proteins[6]. Inhibiting vOTU may restore host antiviral responses and mitigate CCHFV pathogenesis. Given the limited efficacy of ribavirin[2], the identification of natural inhibitors targeting viral proteases represents a promising adjunct or alternative therapeutic strategy[7].

Natural products offer structural diversity and bioactivity, making them attractive candidates for antiviral drug development. Several phytochemicals have demonstrated inhibitory effects against the main protease (Mpro) of SARS-CoV-2, suggesting potential cross-viral applicability[8]. Further investigation into structure–activity relationships may enhance the potency and specificity of these compounds against CCHFV.

4. Conclusion

This study highlights the utility of *in silico* drug discovery for identifying natural compounds with inhibitory activity against CCHFV vOTU. Molecular docking and MD simulations revealed two lead compounds, namely 1,3,6-trigalloyl glucose and 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl 6-O-(6-deoxy-α-L-gulopyranosyl)-β-D-talopyranoside, with strong binding affinities and stable complex formation. These findings warrant further *in vitro* and *in vivo* validation in order to assess their therapeutic potential and safety profiles.

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Conflicts of interest

None exist.

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