Molecular Dynamics Simulation of Inhibitors Targeting Binding Between ACE2 Receptor and Spike Protein of SARS-CoV-2

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Abstract

In 2022, the emergence of the Omicron variant of SARS-CoV-2 intensified the COVID-19 pandemic in Thailand, significantly affecting both the economy and daily life. The virus enters host cells through its Spike (S) protein, which binds to the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell surface, leading to viral replication.This study aimed to identify compounds that could inhibit the interaction between the SARS-CoV-2 S protein and the ACE2 receptor using computational methods, thereby preventing viral entry. Two groups of compounds, marine-derived compounds (n=128) and sesamin-derived compounds, were screened using molecular docking, virtual screening, molecular dynamics (MD) simulations, and energy analysis through the Molecular Mechanics Poisson-Boltzmann Surface Area (MM/PBSA) approach.Virtual screening and molecular docking identified four ligands with the strongest predicted binding to the S protein, with binding scores of -7.6, -7.5, -8.3, and -7.4 kcal/mol. These ligands interact with Lys31 of ACE2, a key residue for Spike protein binding. Further analysis using MD simulations and MM/PBSA calculations showed that after 100 ns, ligand SC1 no longer interacted with Lys31, resulting in a free binding energy of -4.36 ± 5.24 kcal/mol. In contrast, three ligands—MC1, MC2, and SC2—maintained interactions with Lys31, with ΔG_{bind} values of -25.17 ± 1.57, -14.20 ± 3.29, and -29.69 ± 2.58 kcal/mol, respectively. These findings suggest that these three ligands have potential for further development as antiviral agents against SARS-CoV-2.

Introduction

The SARS-CoV-2 Omicron variant is the most highly mutated strain, allowing it to evade immune responses and spread rapidly. Although COVID-19 vaccines have been developed, no specific antiviral drug has been established. The rapid spread of highly transmissible variants highlights the need for additional antiviral strategies.

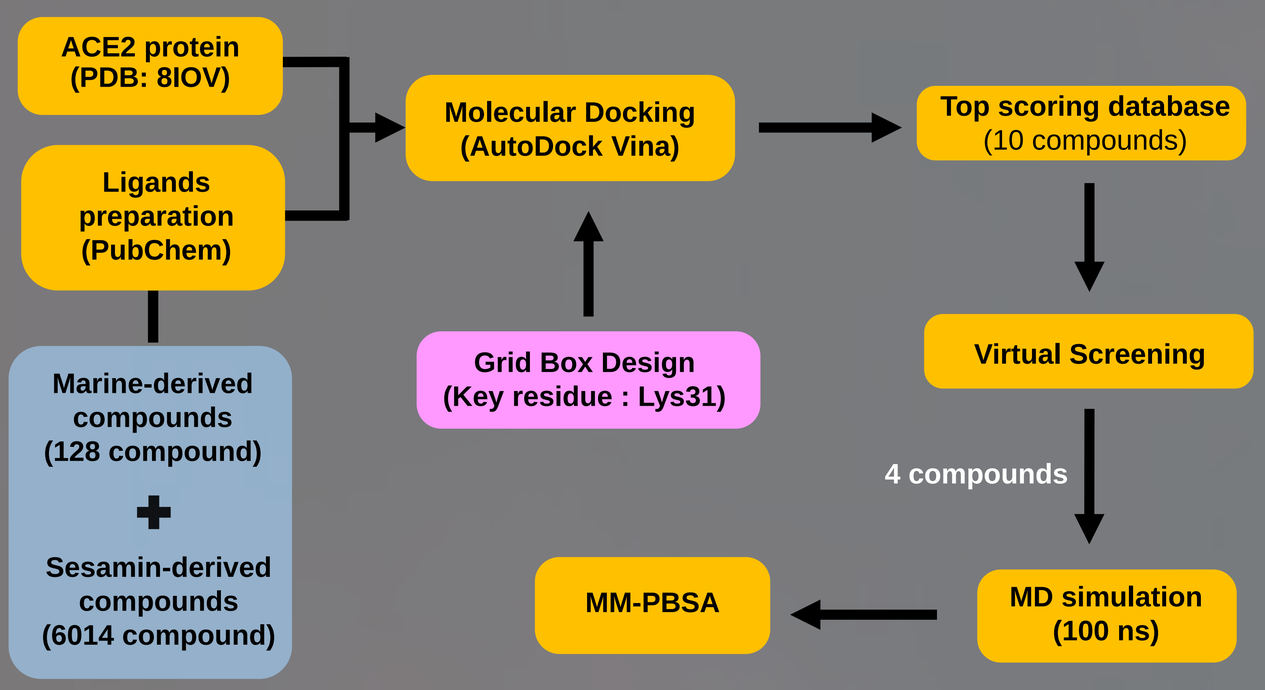
Marine-derived compounds and sesamin-derived compounds have shown high potential due to their unique structures, which can interfere with the binding of the spike protein to ACE2 at key amino acid residues, such as Lys31. ACE2 serves as the receptor for SARS-CoV-2, and its interaction with the spike protein leads to organ damage, particularly affecting the lungs, heart, and kidneys.

Inhibiting the spike protein-ACE2 interaction is an effective strategy for viral suppression, and computer-aided screening methods provide an efficient approach for identifying potential inhibitors. This study aims to discover inhibitors that disrupt the spike protein-ACE2 binding from both compound groups using a comprehensive computational approach, ultimately contributing to the development of effective antiviral drugs.

Objectives

- To explore compounds can inhibit the viral entry into host cells by interfering with the interaction between the spike protein of SARS-CoV-2 and ACE2.
- To study the interactions between compounds with the ACE2 receptor protein specific to the Lys31.
- To study ligands in a realistic simulation of the human body environment using molecular dynamics techniques.

Methodology



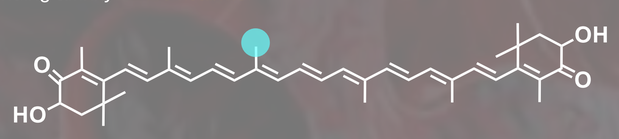
Results and Discussion

Molecular Docking

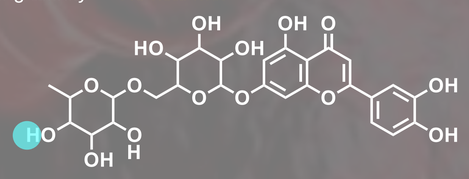
Marine-derived compounds

MC1 Binding affinity = -7.6 kcal/mol

Lys31 interaction



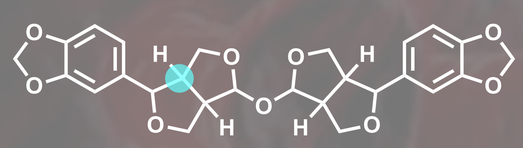
MC2 Binding affinity = -7.5 kcal/mol



Sesamin-derived compounds

SC1 Binding affinity = -8.3 kcal/mol

Lys31 interaction

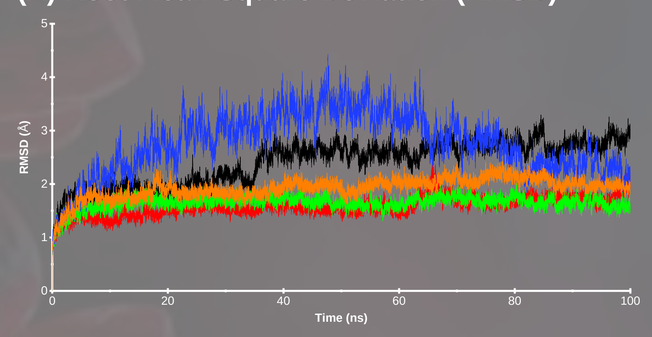


SC2 Binding affinity = -7.7 kcal/mol

The four compounds with the lowest binding affinity in each database and interact with Lys31.

MD Simulation

(A) Root Mean Square Deviation (RMSD)

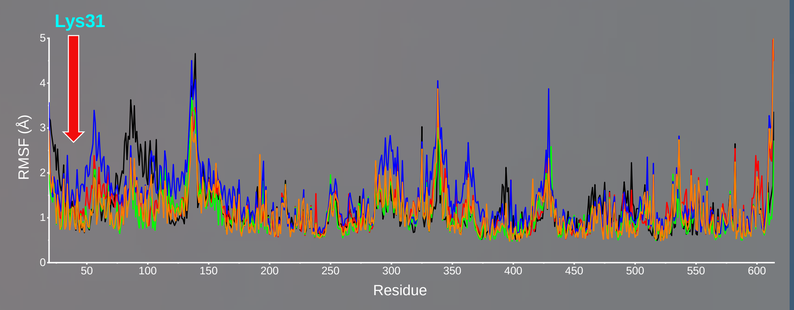


The RMSD analysis indicates that after 100 nanoseconds, SC1 exhibits greater fluctuations than the ACE2 protein in the absence of a ligand. This instability arises from the ligand's inability to interact effectively with the protein. In contrast, other compounds demonstrate significantly higher stability compared to the ligand-free protein. Notably, after 60 nanoseconds, the ligand shows an increase in stability.

(B) Root Mean Square Fluctuation (RMSF)

The RMSF graph comparison of the four ligands reveals that SC1 exhibits greater fluctuations than the apo-protein, whereas the other ligands generally follow a similar trend to that of the apo-protein.

Apo MC1 MC2 SC1 SC2



MM-PBSA calculation

Complex	MC1	MC2	SC1	SC2
$\Delta E_{nonpolar}$	-5.89 ± 0.03	-3.85 ± 0.01	-2.22 ± 0.00	-3.87 ± 0.03
ΔE_{polar}	16.75 ± 0.85	30.30 ± 0.85	6.33 ± 0.59	13.66 ± 0.20
ΔE_{elec}	-8.74 ± 2.81	-27.06 ± 3.02	-1.74 ± 0.39	-7.16 ± 0.44
ΔE_{vdW}	-44.95 ± 1.97	-27.92 ± 1.23	-19.60 ± 0.39	-39.57 ± 1.05
$T\Delta S$	17.66 ± 3.33	14.32 ± 0.05	12.87 ± 2.32	7.25 ± 0.77
$\Delta G_{binding}$	-25.17 ± 1.57	-14.20 ± 3.29	-4.36 ± 5.24	-29.69 ± 2.58

The MM-PBSA calculation results indicate that compounds MC1, MC2, and SC2 have binding free energies of -25.17 ± 1.57, -14.20 ± 3.29, and -29.69 ± 2.58 kcal/mol, respectively. These values suggest strong binding interactions between the protein and the ligands.

Conclusions

- Molecular docking and MD simulations suggest that compounds MC1, MC2, and SC2 have the potential to inhibit viral-host protein interactions.
- Molecular docking analysis revealed that all four compounds bind to the Lys31 position via hydrogen bonds and hydrophobic interactions.
- The MD simulation study indicated that SC1 binds to the protein structure, inducing instability, whereas the other ligands exhibit greater stability.
- The MM-PBSA calculation results show that SC2 has the lowest (most favorable) binding free energy, while SC1 exhibits the highest binding free energy.

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