In silico screening of binding inhibitors targeting spike protein of SARS-CoV-2

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Abstract

The spread of SARS-CoV-2 has significantly impacted the treatment efficacy as the mutations manifested increasingly throughout the pandemic. New treatments have been urgently needed to combat the outbreak effectively. To this end, in silico screening methods and molecular docking have been employed to explore the potential of sesamin from sesame and marine natural product compounds in inhibiting the SARS-CoV-2 spike protein, a protein critical for viral entry. Several studies have indicated that sesame and natural product compounds contain numerous metabolites and potent antioxidants that are effective in antiviral activity and prevent allergic reactions. Therefore, this study aims to analyze the interactions and stability between sesamin derivatives and marine natural product compounds with the spike protein at the Tyr489 position. Molecular docking simulations and MM-PBSA binding energy calculations were employed to evaluate the compound potential as new SARS-CoV-2 inhibitors. A set of 6,142 compounds was obtained from the virtual chemical database, including 6,014 sesamin derivatives and 128 marine natural products. These compounds were then subjected to virtual screening, molecular dockings, and interaction analysis using molecular dynamics simulations. The studies revealed four ligand compounds, which are sesamin derivatives SE1 and SE2, and marine-derived natural products MA1 and MA2, showed the ability to bind to the spike protein, with ΔG_{bind} values ranging from -31.14 to -17.05 kcal/mol. Notably, SE1, with ΔG values of -31.14 kcal/mol exhibits the highest potential for the further development as an effective antiviral drug against SARS-CoV-2.

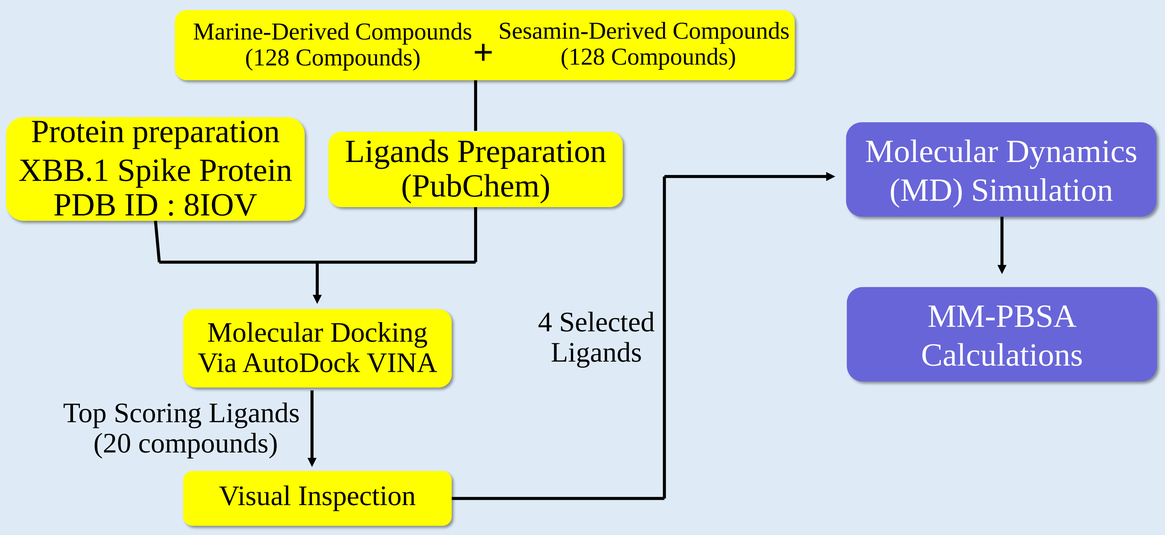
Introduction

The Omicron XBB.1 variant of the SARS-CoV-2 virus has undergone significant mutations in the spike protein, enabling it to evade immunity and spread more effectively. The spike protein plays a crucial role in facilitating the virus's entry into host cells by binding to the ACE-2 receptor. Despite the development of various vaccines and antiviral drugs, the emergence of new variants may reduce the effectiveness of these treatments. Therefore, there is an urgent need to discover new antiviral compounds for drug development.

This study focuses on Sesamin, found in sesame oil, which possesses anti-inflammatory, antioxidant, and antiviral properties. Additionally, marine natural products are a rich source of bioactive compounds with potent antiviral activities. Several studies have reported that both groups can modulate the immune system, inhibit viral infections, and reduce inflammation caused by viral infections.

Using in silico screening and molecular docking methods allows for the efficient identification of potential compounds, reducing the time and cost of drug development. This research aims to evaluate the potential of Sesamin derivatives and marine natural products and analyze their interactions in inhibiting the Omicron XBB.1 spike protein, to develop new antiviral drugs for future variants.

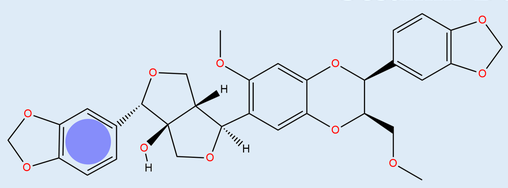
Methodology



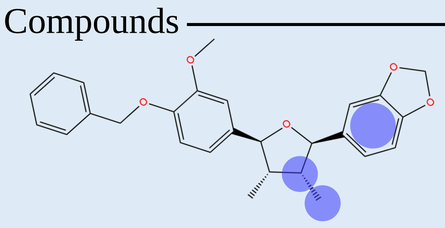
Results and Discussion

Molecular Docking

Sesamin-Derived Compounds



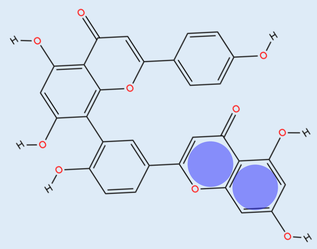
SE1
Binding Affinity : -7.3 kcal/mol



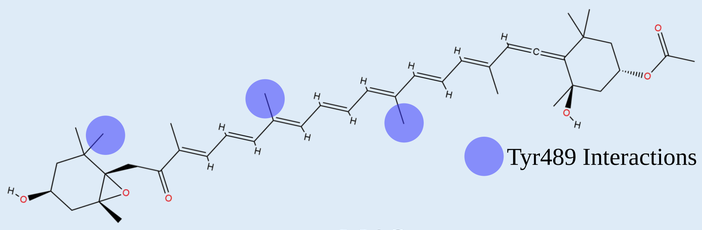
SE2
Binding Affinity : -6.8 kcal/mol

Tyr489 Interactions

Marine-Derived Compounds



MA1
Binding Affinity : -7.3 kcal/mol

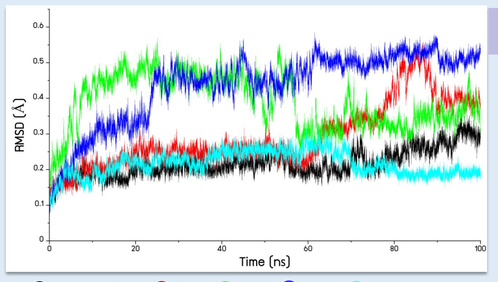


Tyr489 Interactions

MA2
Binding Affinity : -6.4 kcal/mol

The Molecular docking shows that derivatives of Sesamin and marine natural products exhibit potential in binding to target proteins with the lowest binding energy values, indicating stability in the form of Pi-Pi stacked interactions.

Molecular Dynamics

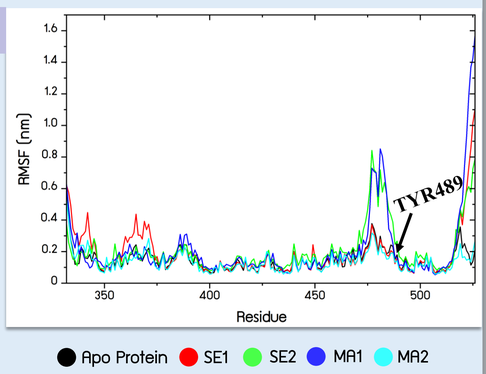


Root Mean Square Deviation (RMSD)

This RMSD graph presents the structural stability of proteins bound to different ligands over a 100 ns simulation period. The red line remains stable from 0 to 80 ns, indicating strong and consistent binding. The green line stabilizes later in the simulation, suggesting that binding is maintained over time. The blue line experiences initial fluctuations but stabilizes between 30 to 90 ns, indicating delayed binding. The cyan line remains stable throughout the entire simulation, making it a promising candidate for further drug developments.

Root Mean Square Fluctuation (RMSF)

The RMSF graph, focusing on the position of TYR489, demonstrates that SE1 exhibits a lower RMSF value compared to the other compounds. This indicates that SE1's contributes to greater protein stability than the other ligands, such as SE2, MA1, and MA2, which display relatively higher fluctuations. This finding suggests that SE1 may be a highly promising ligand for drug development.



MM-PBSA Calculations

Compounds	Contributing Energy (kcal/mol)						
	ΔE_{vdw}	ΔE_{elec}	$\Delta G_{nonpolar}$	ΔG_{polar}	ΔH	$-T\Delta S$	$\Delta G_{binding}$
SE1	-36.62 ± 2.72	-5.27 ± 1.33	-3.93 ± 0.16	10.80 ± 1.06	-35.01 ± 2.59	3.86 ± 0.05	-31.14± 2.59
SE2	-38.05 ± 3.18	-0.31 ± 1.62	-3.21 ± 0.23	4.61 ± 1.69	-36.96 ± 3.03	8.28 ± 0.05	-28.68 ± 3.03
MA1	-34.36 ± 2.44	-7.96 ± 3.16	-3.59 ± 0.15	17.31 ± 2.15	-28.60 ± 3.2	9.48 ± 0.05	-19.14 ± 3.20
MA2	-23.68 ± 2.79	-0.11 ± 0.93	-3.08 ± 0.23	4.18 ± 1.52	-22.69 ± 2.43	5.64 ± 0.04	-17.05 ± 2.43

According to the MM-PBSA table, SE1 exhibits the most favourable binding energy (-31.14 kcal/mol), followed by SE2 (-28.68 kcal/mol), attributed to strong van der Waals interactions and low entropy, which contribute to stable binding. In contrast, MA1 (-19.14 kcal/mol) and MA2 (-17.05 kcal/mol) display the least negative binding energies, accompanied by high polar solvation, indicating weak protein affinity.

Conclusions

- The results of molecular docking revealed that all four ligands interact with the protein at the TYR489 position, forming Pi-Pi stacked interactions. These interactions are stable, suggesting a high potential for further development into effective drugs.
- The simulations demonstrated that the selected compounds maintained structural stability, as evidenced by low RMSD and RMSF values. MM-PBSA results indicated that SE1 and SE2 exhibited the most favourable binding free energies, suggesting strong and stable interactions with the protein.

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