Computational Study of Northern Thai Natural Product Compounds as Inhibitors for Main Protease of SARS-CoV-2 Omicron Variant

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Abstract

The ongoing COVID-19 outbreak and the emergence of new variants, such as the Omicron variant, highlight the urgent need for identifying and developing effective inhibitory compounds or therapeutic drugs to combat the evolving virus and prevent further public health crises. A key target in developing antiviral treatments is the main protease of SARS-CoV-2, also known as M^{pro} or $3CL^{pro}$, which plays an essential role in viral replication. The enzyme is also absent in human cells, thus reducing the off-target effects arising from the antiviral inhibitors developed. This study evaluated the potential application of natural products from Northern Thailand in inhibiting M^{pro}, targeting the catalytic site at the His41 and Cys145 positions. A computational approach was employed, including molecular docking, drug-likeness analysis, MD simulations, and MMPBSA calculations. The results showed that Yokovanol has the lowest $\Delta G_{binding}$ of -28.81 ± 2.29 kcal/mol, better than the reference compound Baicalein, with $\Delta G_{binding}$ of -19.4 ± 2.38 kcal/mol. Energetic component analysis suggests that Yokovanol exhibits a strong potential to inhibit M^{pro}, highlighting its promise as a candidate for developing COVID-19 treatments. This study elucidates the potential and medicinal properties of plants from Northern Thailand, which have not been previously investigated in the context of antiviral drug development.

Introduction

The SARS-CoV-2 outbreak, especially the Omicron variant, remains a major public health challenge as mutations reduce treatment effectiveness. The main protease (M^{pro}), essential for viral replication and absent in human cells, is a key target for antiviral drug development. Natural compounds offer a promising source of new inhibitors. Northern Thailand's diverse medicinal plants have potential for antiviral drug discovery but remain underexplored for COVID-19 treatment. This study focuses on screening natural compounds from Northern Thai herbs to identify potential inhibitors of the main protease (M^{pro}), an essential enzyme for viral replication. Molecular docking and molecular dynamics simulations were employed to accelerate drug discovery while reducing time and cost. Herbs such as turmeric, galangal, Leech lime, and Millingtonia hortensis were investigated for their bioactive compounds, which could be developed into natural, effective, and safe antiviral drugs.

Objectives

- To identify and screen Northern Thai natural products with potential inhibitory effects against SARS-CoV-2 main protease of the Omicron variant using in silico methods
- To study the binding interactions of Northern Thai natural product compounds with SARS-CoV-2 main protease using molecular docking and MD simulation techniques

Methodology

STEP 1

PREPARATION

- ligand Northern Thai natural 127 compounds
- protein PDB ID:7TLL

STEP 2

MOLECULAR DOCKING

- using AutoDock vina

For predict the interaction between ligand and protein

STEP 3

DRUG-LIKENESS ANALYSIS

- Lipinski's Rule of Five

For properties to be a potential drug

STEP 4

MOLECULAR DYNAMICS SIMULATION

- using GROMACS (100 ns)

Study the movement and interactions of atoms and molecules over time

STEP 5

MM-PBSA CALCULATIONS

- Calculate of Binding free energy

For calculating the free energy of binding between a ligand and a protein.

STEP 6

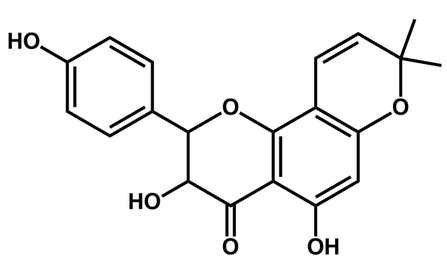
HITS

- Protein Stability
- Structural Behaviors
- Intermolecular Interaction
- Binding free energy

Results

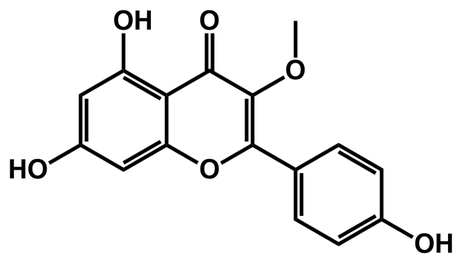
• MOLECULAR DOCKING

YUKOVANOL (C7)



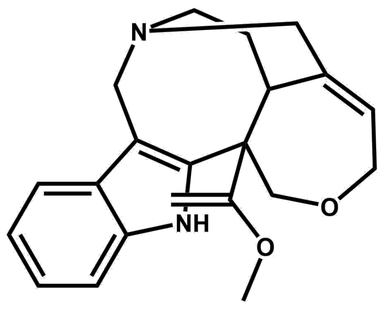
binding affinity = -7.9 Kcal/mol

KAEMPFEROL-3-METHYLETHER (C15)



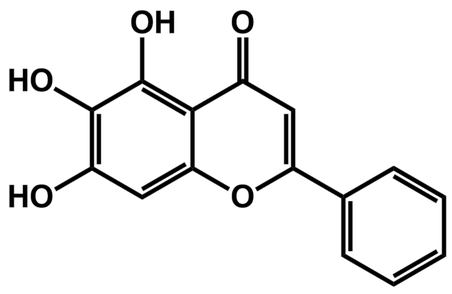
binding affinity = -7.6 Kcal/mol

ANGUSTILOBINE B (C24)



binding affinity = -7.7 Kcal/mol

BAICALEIN (Reference)



binding affinity = -7.4 Kcal/mol

Figure 1 All 3 compounds show better interactions than the reference compound, as reflected by their lower binding affinity values.

Yukovanol C7 shows the best inhibition of main protease of SARS-CoV-2 Omicron

• MOLECULAR DYNAMICS SIMULATION

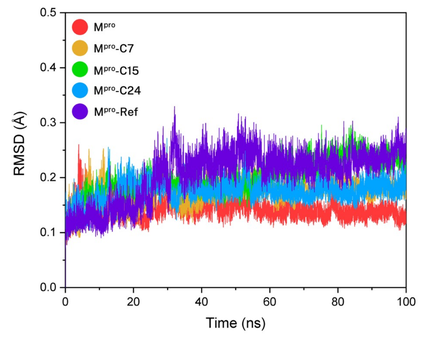


Figure 2 RMSD results confirm the high stability of the ligand-M^{pro} complex showing minimal structural fluctuations that are comparable to those of the apoenzyme.

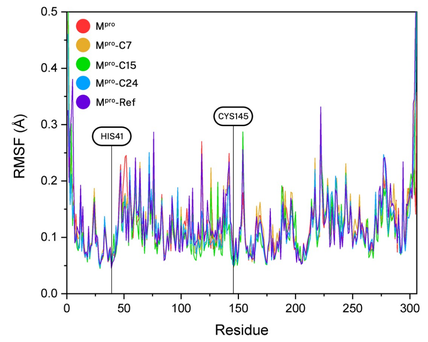
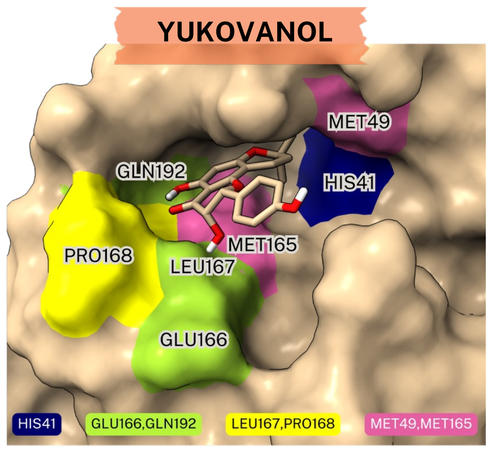
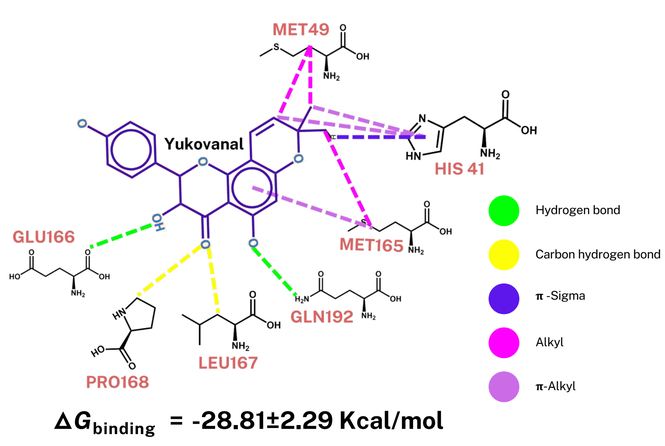


Figure 3 RMSF analysis shows minimal movement of key residues His41 and Cys145, confirming stable binding sites.





$\Delta G_{binding}$ = -28.81±2.29 Kcal/mol

Figure 4 The interaction between Yukovanol (C7) and M^{pro} is shown in the upper panel, highlighting key interactions with the crucial residue HIS41, which exhibits π-sigma and π-alkyl interactions. And the $\Delta G_{binding}$ is better than the reference compound, which is only -19.4 ± 2.38 kcal/mol.

Conclusions

- The top 3 candidate compounds Yukovanol, kaempferol-3-methylether, Angustilobine B exhibit strong binding affinities (predicted by molecular docking) of -7.9, -7.6, and -7.7 kcal/mol, respectively, and better than that of the reference (-7.4 kcal/mol).
- MM-PBSA binding energy analysis revealed that Yukovanol had the lowest binding energy (-28.81 ± 2.29 kcal/mol), followed by C15 (-17.02 ± 3.03 kcal/mol) and C24 (-16.63 ± 3.15 kcal/mol). and passed the drug-likeness analysis (Lipinski's Rule of 5).
- Key interactions observed included π-sigma and π-alkyl interactions with key residues HIS41, ensuring strong and stable binding.
- Yukovanol is natural compound from Northern Thailand, effectively inhibited the main protease of SARS-CoV-2 Omicron through strong interactions and low binding energy.

References

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