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Molecular Docking Studies of Natural Alkaloids against SARS-CoV-2 Protease

Dr. Nidhi Tripathi
Head
Biotechnology and Biochemistry
Career College, Bhopal

Abstract

The emergence of SARS-CoV-2, the causative agent of COVID-19, has necessitated a global scientific effort to identify novel therapeutics capable of mitigating viral replication and disease progression. One promising avenue in antiviral research is the repurposing and screening of natural phytochemicals, particularly alkaloids, known for their vast chemical diversity and bioactivity. In this study, molecular docking simulations were conducted to evaluate the inhibitory potential of twelve selected natural alkaloids—such as berberine, quinine, and harmine—against the SARS-CoV-2 main protease (M^{pro}), a key enzyme in the viral life cycle. Using AutoDock Vina, binding affinities and interaction profiles were assessed, focusing on hydrogen bonding, van der Waals forces, and π–π stacking with catalytic residues like His41 and Cys145. Among the compounds screened, berberine demonstrated the strongest binding affinity and favorable molecular interactions. These findings indicate that certain alkaloids could serve as valuable leads for anti-COVID-19 drug development, pending experimental validation through biochemical assays and clinical trials.

Keywords: SARS-CoV-2 protease inhibition, COVID-19 therapeutics, molecular docking analysis, natural plant alkaloids, antiviral phytochemicals, AutoDock Vina simulation, berberine interactions, quinine bioactivity, virtual screening tools, in-silico drug discovery, bioinformatics, pandemic drug development

Introduction

The global health crisis caused by COVID-19 has triggered unprecedented scientific efforts to develop preventive and therapeutic strategies to curb the pandemic. While vaccines offer primary protection, antiviral drugs are critical to treating infected patients, especially in moderate and severe cases. SARS-CoV-2, a beta-coronavirus, relies on its main protease (M^{pro}) to process polyproteins into functional units necessary for viral replication. Inhibiting this enzyme blocks viral propagation at the molecular level, making M^{pro} a pivotal drug target.

Natural products, particularly alkaloids, have historically played a significant role in the development of therapeutic agents. Alkaloids such as quinine and berberine are known for their wide-ranging biological properties, including antimicrobial, anticancer, and antiviral effects. Their structural diversity and bioavailability make them suitable candidates for computational drug discovery.

This study seeks to bridge traditional phytochemical knowledge with modern bioinformatics tools by exploring the binding potential of various alkaloids with SARS-CoV-2 M^{pro}. Through molecular docking simulations, we aim to identify candidate molecules with high binding affinity, favorable interaction profiles, and therapeutic potential against COVID-19.

Methodology

This computational study involved multiple phases of molecular preparation, target identification, and docking simulation. A total of twelve alkaloids were chosen based on their reported antiviral and pharmacological properties from scientific literature and ethnobotanical databases. These included isoquinoline (berberine), indole (harmine), quinoline (quinine), and other structurally diverse alkaloids. Molecular structures of the selected compounds were downloaded in

.SDF format from the PubChem repository and converted into the .PDBQT format via Open Babel, ensuring appropriate torsion and 3D optimization.

For the protein target, the crystal structure of SARS-CoV-2 main protease (PDB ID: 6LU7) was retrieved from the RCSB Protein Data Bank. Pre-processing steps included removal of co-crystallized ligands, water molecules, and non-standard residues using PyMOL, followed by addition of Gasteiger charges and polar hydrogens in AutoDock Tools. The grid box was centered around the active site residues His41 and Cys145, based on previously validated coordinates.

Docking simulations were executed using AutoDock Vina under standard protocols. For each ligand, ten docking poses were generated, and the one with the lowest binding energy was selected for further analysis. Interaction visualization was performed using Discovery Studio Visualizer and PyMOL to assess hydrogen bonds, hydrophobic patches, salt bridges, and π-interactions. The docking protocol was validated through redocking of the co-crystallized inhibitor N3, which confirmed accurate active site targeting and RMSD values within acceptable limits (<2.0 Å).

Data Analysis

Docking results demonstrated that most selected alkaloids showed moderate to strong binding affinity toward the active site of SARS-CoV-2 M^{pro}. The strongest interaction was observed with berberine, which yielded a binding energy of -9.1 kcal/mol. Key residues involved in binding included His41, Cys145, and Met165, which form the catalytic dyad and S1/S2 substrate binding pockets. Hydrogen bonds and π–π stacking played crucial roles in anchoring the ligand to the active cavity.

Harmine and quinine also exhibited promising affinities of -8.7 kcal/mol and -8.4 kcal/mol, respectively, with interactions similar to those of known

inhibitors. Berberine's methoxy and aromatic groups allowed it to occupy the hydrophobic pocket efficiently and maintain strong non-covalent interactions.

The following table summarizes binding affinities and key interacting residues:

Compound	Binding Affinity (kcal/mol)	Key Interacting Residues
Berberine	-9.1	His41, Cys145, Met165
Harmine	-8.7	Glu166, His41, Phe140
Quinine	-8.4	Cys145, Gly143, His164

The docking data suggest that alkaloids possess pharmacophoric elements capable of mimicking or enhancing known M^{pro} inhibitors. Additional molecular dynamics (MD) simulations are recommended to assess complex stability in a dynamic environment.

Case Study: Berberine Interaction

Berberine, a natural isoquinoline alkaloid derived from *Berberis* species, has long been used in Ayurvedic and Chinese medicine for its antimicrobial and anti-inflammatory properties. In the current study, berberine exhibited the highest binding affinity to SARS-CoV-2 M^{pro} (-9.1 kcal/mol), suggesting strong potential as a lead compound.

Detailed interaction analysis revealed that berberine formed three hydrogen bonds with key active site residues—His41, Cys145, and Glu166. In addition, the aromatic rings of berberine were involved in π–π interactions with His163, enhancing binding stability. Hydrophobic interactions were observed with Met49 and Met165, helping anchor the ligand within the protease's S1 pocket.

Visual inspections of the docked complex indicated that berberine fits well into the catalytic cleft, forming a highly stable, energetically favorable complex. The molecule's planar structure and positive charge facilitate electrostatic interaction with negatively charged residues near the substrate-binding groove.

Given berberine's history of human use, pharmacokinetics, and safety, it stands as a viable candidate for further ADMET profiling, in vitro enzymatic inhibition assays, and structure-based optimization for COVID-19 therapeutic development.

Questionnaire and Tables

A knowledge-based questionnaire was distributed among 100 professionals including pharmaceutical researchers, medicinal chemists, and postgraduate students, aiming to assess awareness about molecular docking and natural antiviral compound use in COVID-19 research. The survey was conducted online using Google Forms and analyzed using descriptive statistics.

Table 1: Researcher Awareness on Phytochemical Antivirals

Survey Question	Yes (%)	No (%)
Are you familiar with molecular docking and its applications?	89%	11%
Do you believe natural alkaloids can serve as antiviral agents?	78%	22%
Have you personally worked with plant-derived molecules in research?	61%	39%
Are you aware of any alkaloids being tested against COVID-19?	35%	65%

Table 2: Preferred Methodologies for Initial Drug Screening

Drug Discovery Approach	% Preference
Molecular Docking & Dynamics	62%
In-vitro Bioassays	21%
High-throughput Screening (HTS)	10%
Traditional Herbal Knowledge	7%

Results indicate high confidence in computational tools, but also a significant knowledge gap regarding specific natural compounds. This suggests a need for interdisciplinary integration between ethnopharmacology and computational drug discovery to broaden the scope of antiviral screening.

Conclusion

This comprehensive molecular docking study highlights the inhibitory potential of natural alkaloids against the SARS-CoV-2 main protease. Among the twelve compounds tested, berberine, harmine, and quinine emerged as top candidates based on binding energy, active site coverage, and molecular interaction profiles. These alkaloids interacted favorably with the protease's catalytic dyad (His41 and Cys145), forming stable complexes capable of blocking enzymatic activity and thereby impeding viral replication.

The use of molecular docking as a virtual screening tool allows rapid, cost-effective identification of bioactive leads from natural sources. While in-silico methods cannot substitute laboratory confirmation, they significantly streamline drug discovery pipelines and inform structure-based optimization.

Further studies involving molecular dynamics simulation, ADMET prediction, in vitro protease inhibition assays, and in vivo antiviral efficacy trials are essential to validate and translate these findings into viable therapeutics. Given their established bioactivity, safety, and oral availability, alkaloids such as berberine represent promising scaffolds for the development of future COVID-19 antivirals.

References

1. Jin, Z., Du, X., Xu, Y., Deng, Y., et al. (2020). "Structure of M^{pro} from COVID-19 virus and discovery of its inhibitors." *Nature*, 582(7811), 289–293.
2. Trott, O., & Olson, A. J. (2010). "AutoDock Vina: improving the speed and accuracy of docking with a new scoring function." *Journal of Computational Chemistry*, 31(2), 455–461.
3. Ahmed, S., & Mehmood, A. (2021). "Natural products as potential inhibitors of SARS-CoV-2 main protease: a review of in-silico findings." *Biomedicine & Pharmacotherapy*, 138, 111850.
4. Kumar, S., & Singh, R. (2021). “Berberine and its derivatives as potential inhibitors for SARS-CoV-2 M^{pro}: A computational insight.” *Natural Product Research*, 35(16), 2678–2683.
5. NCBI PubChem Database. (2023). "Berberine, Quinine, Harmine: Compound Summary."
6. Wang, L., et al. (2020). "Pharmacological perspectives on natural alkaloids against viral infections." *Frontiers in Pharmacology*, 11, 583339.
7. WHO (2021). *COVID-19 Therapeutics Landscape Update*. Geneva: World Health Organization.