Phytochemicals as Potential Drug Candidates for SARS Cov-2: An RDRp Based In-Silico Drug Designing

Christy Joy(✉) and Marria C. Cyriac

Department of Biotechnology, Sahrdaya College of Engineering and Technology, Thrissur, Kodakara, Kerala, India
joychristy114@gmail.com

Abstract. The global pandemic that the world is currently witnessing, COVID-19, even with vaccines available, the test positivity rate (TPR) tends to remain highly threatening. This research focuses on identifying phytochemicals, previously known for their broad-spectrum antiviral properties which can be potential drug candidates for theSARS-CoV-2. A total of 225 phytocompounds (downloaded from PubChem database) are docked against targetprotein (downloaded from PDB database) of SARS-CoV-2using the POAP pipeline. The target protein is the RDRp complex. They are screened according to their binding affinity values and the filtered phytochemicals are then subjected to various analyses including ADME properties (preADMET, swissADME), bioactivity score, and molecular properties (molinspiration), drug-likeness (preADMET), lipophilicity, water solubility, and pharmacokinetics (swissADME). The receptor-ligand interactions and the amino acid positions are obtained using Discovery Studio Visualiser. Molecular dynamic simulation studies are performed to reveal key receptor-drug interactions that must be formed to achieve tight drug binding and also to predict stability. Out of the 225, 10 phytochemicals showed the best scores and more probability of drug action. Compounds that showed promising drug action potential include oriciacridone, corilagin, cinchophyllamine, sophaline D, amentoflavone, cryptomisrine, ginkgetin, hypericin, pseudojervine, dieckol, hinokiflavone, robustaflavone, solamargine. The research herein provides new possibilities for in vitro and in vivo analyses of the proposed ligands to develop new drugs againstSARS-CoV-2.

Keywords: NSP · ADME · receptor-ligand interaction · binding site pockets · MD simulation

1 Introduction

Late in December 2019, the coronavirus outbreak in China led to a series of horrifying events globally. As of 15 April 2022, 6:00 am, the pandemic has claimed 6190349 lives [1]. Not just lives, the global economy, and peace were shattered within a year. The coronavirus primarily affects the respiratory system in humans. The SARS-CoV-2 and MERS-CoV are considered to be major public health threats. The incubation period of

V. Agarwal et al. (Eds.): BIOSANGAM 2022, ABSR 24, pp. 58–69, 2023.
https://doi.org/10.2991/978-94-6463-020-6_7

the virus is found to be nearly 5–6 days and then the symptoms of the infection start to occur [2]. SARS-CoV-2 is a group of positive sense, single-stranded viruses. They are highly diverse and the researchers say, based on genetic sequence similarity that this particular virus is likely to be originated from bats [3]. The similarity in the nucleic acid sequence shows that SARS-CoV-2 is a beta-coronavirus. Their RNA genome is composed of 29891 nucleotides and 9860 amino acids. The viral genome has 10 open reading frames (ORF). They encode the structural and non-structural proteins of the virus [4]. The spike protein (S), membrane protein (M), an envelope protein (E), and nucleocapsid protein are important structural proteins and are located at the 3' end of the genome. The non-structural proteins like NSP1-NSP10 and NSP12-NSP16 are located at the 5' end of the viral genome [5].

The common symptoms of covid 19 infection as brought down to fever, cough, and shortness by US Centers for Disease Control and Prevention (CDC). The symptoms are gravely similar to influenza-like illnesses. The list got longer as the pandemic progressed. Ageusia, anosmia, headache, sore throat, and chills topped the list [6]. The covid 19 transmission was believed to be through respiratory droplets. But advanced research shows potential for additional routes like the ocular route, sexual route, vertical route, and indirect transmission [7]. Oral antivirals and antibody therapy has been a major milestone in the treatment of SARS-CoV-2. But there poses a need for more antiviral compound discoveries [8, 9]. Because the symptoms and the range of infection differ in different people. And with the virus manipulating us with its different forms, we need to find non-toxic, preferably phytochemical compounds to solve the root cause of this viral infection.

The study looks at 250 phytocompounds, which were previously known for their broad-spectrum antiviral effects, as prospective drug candidates against the RdRp protein (PDB ID:6M71) ofSARS-CoV-2, which is a therapeutic target [10–14, 16, 17, 17–46]. The compounds were chosen from data in the literature. Each of these chemicals possesses drug-like characteristics and has previously been used to treat a variety of viral diseases. A comparison study focuses solely on molecular docking and molecular dynamics simulation to find prospective natural compounds with greater binding affinity and stability, as well as favourable physicochemical characteristics, than control compounds.

2 Materials and Methods

2.1 Protein Preparation

The Protein Data Bank was used to obtain three-dimensional structures of target proteins (PDB). The target protein structure is that of an RNA-dependent RNA polymerase (PDB ID: 6M71), i.e., NSP 12. To optimize the structure, unnecessary hetero groups and homologous chains were eliminated from the proteins. Finally, using Auto Dock, these structures were fine-tuned for stereochemical inaccuracies by adding Kollman charges and polar hydrogen atoms [47]. These improved and energy-minimized structures were saved in the PDBQT format [48].

2.2 Ligand Preparation

PubChem and Chemspider databases were used to retrieve the three-dimensional structures of the selected small molecules. For virtual screening investigations, the structure data file (SDF) formats were employed as the input format [49–51].

2.3 Binding Pocket Prediction

The Discovery Studio Visualizer was used to identify the binding sites of all of the specified target proteins [52]. Various counter maps with X, Y, and Z coordinates were obtained, as well as the size of the active site with corresponding amino acids. Finally, the best binding pockets were ranked and used for docking studies based on the score [53–57].

2.4 Comparative Virtual Screening of Anti-viral Compounds

Parallelized Open Babel and Auto dock suite Pipeline is a bash shell script-based pipeline for optimizing and minimizing small molecules using Open Babel, as well as performing virtual screening with Auto dock Vina. The ligands were developed using the Open Babel tool and the POAP ligand preparation module. The conformers were created once the 3-D coordinates for the ligands were determined. The 50 conformers for each ligand were generated using the weighted rotor approach, and the best conformer with the lowest energy was chosen for further minimization. The ligands were energy minimized using the conjugate gradient method with 5000 steps and default parameters. After energy minimization, the ligand was converted to a pdbqt file format for virtual screening against the targets [58].

The POAP multiple receptor virtual screening module of AutoDock Vina was used to perform virtual screening of the targets. By adding polar hydrogens and gastieger charges using the MGLTOOLS-1.5.6, the receptors were constructed. Each target's active site configuration file was produced and presented as input to the POAP. AutoDockVina was utilised to perform the Virtual screening with exhaustiveness of 8. The POAP performed a virtual screening of the ligands against the targets and filed the results in a separate directory containing protein-ligand complexes and docking energy scores. The combined score of ligands with the receptor was taken further for analysis.

2.5 ADME Filtrations

Drug molecules' ADME (absorption, distribution, metabolism, and excretion) qualities are crucial for them to pass clinical trials. The Swiss Institute of Bioinformatics' SwissADME programme allows users to compute physicochemical descriptors and estimate ADME parameters, pharmacokinetic features, druglike nature, and medicinal chemistry friendliness of one or more small compounds. Thus, for the screened compounds, physicochemical descriptors such as molecular weight (MW), rotatable bonds (RB), hydrogen bond donor count (HBD), hydrogen bond acceptor count (HBA), Total Polar surface area (TPSA), octanol-water partition coefficient (ilogP), blood-brain barrier permeant (BBBp), and Lipinski's rule of five violation (LPV) were computed [59]. The FAF4 Drug web server was used to predict other physicochemical characteristics such as oral bioavailability (OBV) and phospholipidosis [60–64].

2.6 Toxicity Analysis

The toxicity of the chemicals tested is also significant in establishing a compound's efficacy as a drug. As a result, all of the compounds in silico toxicity predictions were made using the Toxtree tool, which assesses toxic risks using a decision tree technique. The technique examines the presence of numerous functional moieties in the chemical structure to estimate the probability of toxicity [65].

2.7 Molecular Dynamics Simulation

The stability of the docked complexes was studied by implementing molecular dynamics simulations using the Desmond package with Optimized Potentials for Liquid Simulations (OPLS) forcefield [66]. The protein structure (PDB ID: 6M71) was pre-processed using Proteinprep wizard in which bond order was assigned, hydrogen atoms were added, and zero-order bonds to metals and disulphide bonds were created. The complete system for MD simulation was built on a predefined SPC water model in a cubic boundary box with a distance of 10Å and minimized volume. Further, Na+ counter ions were added to neutralize the system, and energy was minimized. The energy minimized full system was set for the production run at a temperature of 300K and pressure of 1 bar. The isotherm-isobar (NPT) ensemble was selected and simulation was carried out for 100 ns [29, 34, 43, 67].

3 Results and Discussion

3.1 Post Docking Analysis

The docking results were analysed and ranked based on the binding energy for short-listing the best potential hits. Table 1 shows the results of docking in terms of binding energy. The compounds remdesivir and favipiravir were considered as a control for comparison of the binding energy. Remdesivir showed binding energy values with a minimum binding energy of −8.4 kJ/mol with RdRp protein. Further, favipiravir was docked and the binding energy was found between a range of −5.4 kJ/mol to −4.0 kJ/mol. Thus, considering the binding energy a cut-off of −10.0 kJ/mol was selected to identify the best-docked complex. Oriciacridone showed binding energy of −11.4 kJ/mol. Cryptomisrine was ranked two, with −10.8 kJ/mol followed by Cinchophyllamine and Corilagin, with a binding energy of −10.1 kJ/mol each.

3.2 ADME Filtration and Toxicity Analysis

These compounds were also submitted to ADME calculations based on physio-chemical characteristics. The computed descriptors describing ADME qualities for the top selected chemicals did not fall within the required range. Additionally, the highest docking score compounds were discovered to pass the blood-brain barrier, and the results revealed phospholipidosis warnings. Lipinski's rule of five was likewise broken by the majority of compounds. Toxicity experiments were used to screen for multiple mutagenic and carcinogenic functional groups, and the chemical sophaline D was determined to fit with high confidence. For molecular dynamics simulation, the sophaline D-6M71 complex was chosen.

Table 1. Docking score of best hits

Ligand	Binding Affinity (KJ/mol)
Oriciacridone	−11.4
Cryptomisrine	−10.8
Corilagin	−10.1
Cinchophyllamine	−10.1
Sophaline d	−7.5

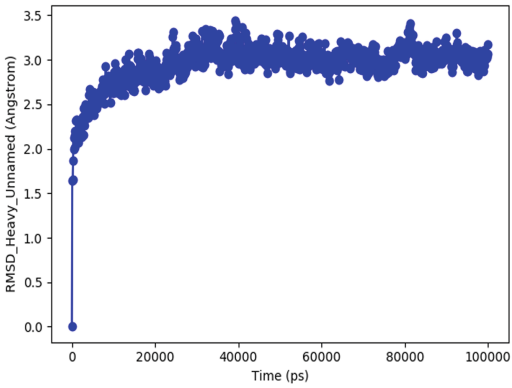

Fig. 1. RMSD for RDRp-Sophaline D complex

3.3 Molecular Dynamic Simulation

The system was solvated using (Simple Point-Charge) SPC water molecule model and the total system had been neutralized with 7 NA+ ions. In the trajectory analysis, the backbone RMSD for the apoenzyme was found within the range of 3.16Å with a standard deviation of 0.141Å and for the holoenzyme was found within the range of 3.06Å with a standard deviation of 0.249Å for 100 ns simulation, and the system converged at 80 ns and sustained throughout the simulation run with minimum conformational changes as shown in Fig. 1. The residues-wise fluctuation differences in apo and holo form were inferred by analysing the root mean square fluctuation (RMSF) plot. It revealed that the holo forms remained stable throughout the simulation and were in close range to that of the apo form as given in Fig. 2. The radius of gyration for the apoenzyme was found within the range of 21.84Å with a standard deviation of 0.055Å and for the holoenzyme was found within range of 22.73Å with a standard deviation of 0.065Å.

In the RDRp-Sophaline Dcontact histogram (Fig. 3), a value of 0.7 recommends that the specific interaction is retained during 70% of the simulation time. Values above 1.0 are probable as some protein residue may make multiple contacts of the same subtype with the ligand. The ligand-protein interactions in two dimensions are given in Fig. 4.

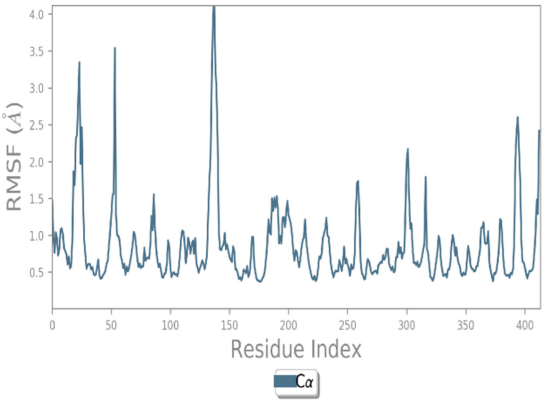

Fig. 2. Root mean square fluctuation (RMSF) plot

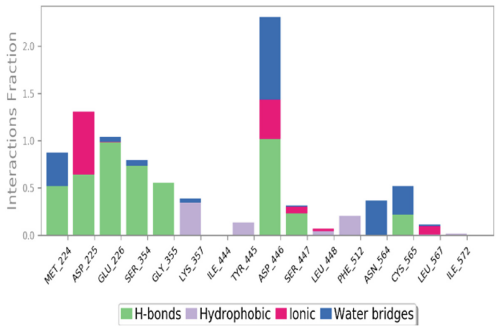

Fig. 3. The RDRp-Sophaline D contact histogram

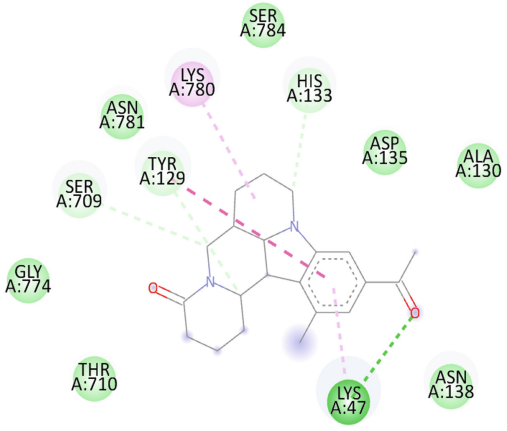

Fig. 4. Ligand-protein interactions in 2D diagram

4 Conclusion

After performing different levels of virtual screening- Docking, ADME properties, Toxicity studies, pharmacophore modelling, and Molecular Dynamics simulations the best compound identified is sophaline D. It is an alkaloid isolated mainly from the roots of Sophora*alopecuroides*. In-silico drug discovery helps a great deal in the primary screening for drugs. The prediction of toxicity and the characterization of the side effects of each compound helped get a better idea about the compounds. The work suggests sophaline d as a promising inhibitor to the RdRp protein of the SARS-CoV-2 virus. The phytochemical will also show great results in further wet lab studies.

References

1. "Coronavirus disease (COVID-19)." https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (accessed Apr. 15, 2022).
2. H. A. Rothan and S. N. Byrareddy, "The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak," *J. Autoimmun.*, vol. 109, p. 102433, May 2020, doi: https://doi.org/10.1016/J.JAUT.2020.102433.
3. F. He, Y. Deng, and W. Li, "Coronavirus disease 2019: What we know?," *J. Med. Virol.*, vol. 92, no. 7, pp. 719–725, Jul. 2020, doi: https://doi.org/10.1002/JMV.25766.
4. S. Satarker and M. Nampoothiri, "Structural Proteins in Severe Acute Respiratory Syndrome Coronavirus-2," *Arch. Med. Res.*, vol. 51, no. 6, p. 482, Aug. 2020, doi: https://doi.org/10.1016/J.ARCMED.2020.05.012.
5. R. Yadav *et al.*, "Role of Structural and Non-Structural Proteins and Therapeutic Targets of SARS-CoV-2 for COVID-19," *Cells 2021,* vol. 10, no. 4, p. 821, Apr. 2021, doi: https://doi.org/10.3390/CELLS10040821.
6. B. E. Dixon *et al.*, "Symptoms and symptom clusters associated with SARS-CoV-2 infection in community-based populations: Results from a statewide epidemiological study," *medRxiv*, Oct. 2020, doi: https://doi.org/10.1101/2020.10.11.20210922.
7. K. P. Patel *et al.*, "Transmission of SARS-CoV-2: an update of current literature," *Eur. J. Clin. Microbiol. Infect. Dis. 2020 3911*, vol. 39, no. 11, pp. 2005–2011, Jul. 2020, doi: https://doi.org/10.1007/S10096-020-03961-1.
8. P. D. Monk *et al.*, "Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial," *Lancet. Respir. Med.*, vol. 9, no. 2, p. 196, Feb. 2021, doi: https://doi.org/10.1016/S2213-2600(20)30511-7.
9. M. Cevik, J. L. Marcus, C. Buckee, and T. C. Smith, "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Transmission Dynamics Should Inform Policy," *Clin. Infect. Dis. An Off. Publ. Infect. Dis. Soc. Am.*, vol. 73, no. Suppl 2, p. S170, Aug. 2021, doi: https://doi.org/10.1093/CID/CIAA1442.
10. A. Nag, R. Banerjee, R. R. Chowdhury, and C. K. Venkatesh, "Phytochemicals as potential drug candidates for targeting SARS CoV 2 proteins, an in silico study," *VirusDisease 2021 321*, vol. 32, no. 1, pp. 98–107, Apr. 2021, doi: https://doi.org/10.1007/S13337-021-00654-X.
11. S. Hiremath *et al.*, "In silico docking analysis revealed the potential of phytochemicals present in Phyllanthus amarus and Andrographis paniculata , used in Ayurveda medicine in inhibiting SARS-CoV-2," *3 Biotech 2021 112*, vol. 11, no. 2, pp. 1–18, Jan. 2021, doi: https://doi.org/10.1007/S13205-020-02578-7.

12. A. Kumar *et al.*, "Identification of phytochemical inhibitors against main protease of COVID-19 using molecular modeling approaches,", vol. 39, no. 10, pp. 3760–3770, 2020, doi: https://doi.org/10.1080/07391102.2020.1772112.
13. J. O. Oladele, O. M. Oyeleke, O. T. Oladele, and A. T. Oladiji, "Covid-19 treatment: Investigation on the phytochemical constituents of Vernonia amygdalina as potential Coronavirus-2 inhibitors," *Comput. Toxicol.*, vol. 18, p. 100161, May 2021, doi: https://doi.org/10.1016/J.COMTOX.2021.100161.
14. R. Abdizadeh, F. Hadizadeh, and T. Abdizadeh, "In silico analysis and identification of antiviral coumarin derivatives against 3-chymotrypsin-like main protease of the novel coronavirus SARS-CoV-2," *Mol. Divers. 2021*, vol. 1, pp. 1–24, Jul. 2021, doi: https://doi.org/10.1007/S11030-021-10230-6.
15. S. Kumar, P. Kashyap, S. Chowdhury, S. Kumar, A. Panwar, and A. Kumar, "Identification of phytochemicals as potential therapeutic agents that binds to Nsp15 protein target of coronavirus (SARS-CoV-2) that are capable of inhibiting virus replication," *Phytomedicine*, vol. 85, p. 153317, May 2021, doi: https://doi.org/10.1016/J.PHYMED.2020.153317.
16. G. Joshi *et al.*, "Recent efforts for drug identification from phytochemicals against SARS-CoV-2: Exploration of the chemical space to identify druggable leads," *Food Chem. Toxicol.*, vol. 152, p. 112160, Jun. 2021, doi: https://doi.org/10.1016/J.FCT.2021.112160.
17. A. Majeed, W. Hussain, F. Yasmin, A. Akhtar, and N. Rasool, "Virtual Screening of Phytochemicals by Targeting HR1 Domain of SARS-CoV-2 S Protein: Molecular Docking, Molecular Dynamics Simulations, and DFT Studies," *Biomed Res. Int.*, vol. 2021, 2021, doi: https://doi.org/10.1155/2021/6661191.
18. H. M. Wahedi, S. Ahmad, and S. W. Abbasi, "Stilbene-based natural compounds as promising drug candidates against COVID-19," *J. Biomol. Struct. Dyn.*, vol. 39, no. 9, pp. 3225–3234, 2021, doi: https://doi.org/10.1080/07391102.2020.1762743.
19. I. Muhammad *et al.*, "Screening of potent phytochemical inhibitors against SARS-CoV-2 protease and its two Asian mutants," *Comput. Biol. Med.*, vol. 133, p. 104362, Jun. 2021, doi: https://doi.org/10.1016/J.COMPBIOMED.2021.104362.
20. A. B. Gurung, M. A. Ali, J. Lee, M. A. Farah, and K. M. Al-Anazi, "Unravelling lead antiviral phytochemicals for the inhibition of SARS-CoV-2 Mpro enzyme through in silico approach," *Life Sci.*, vol. 255, p. 117831, 2020, doi: https://doi.org/10.1016/j.lfs.2020.117831.
21. S. Nallusamy *et al.*, "Shortlisting Phytochemicals Exhibiting Inhibitory Activity against Major Proteins of SARS-CoV-2 through Virtual Screening," pp. 1–26, 2020, doi: https://doi.org/10.21203/rs.3.rs-31834/v1.
22. S. Kumar, P. Kashyap, S. Chowdhury, S. Kumar, A. Panwar, and A. Kumar, "Identification of phytochemicals as potential therapeutic agents that binds to Nsp15 protein target of coronavirus (SARS-CoV-2) that are capable of inhibiting virus replication," *Phytomedicine*, vol. 85, no. July, p. 153317, 2021, doi: https://doi.org/10.1016/j.phymed.2020.153317.
23. K. K. Varshney, M. Varshney, and B. Nath, "Molecular Modeling of Isolated Phytochemicals from Ocimum sanctum Towards Exploring Potential Inhibitors of SARS Coronavirus Main Protease and Papain-Like Protease to Treat COVID-19." Mar. 14, 2020, Accessed: Jul. 25, 2021. [Online]. Available: https://papers.ssrn.com/abstract=3554371.
24. C. N. Patel, D. Goswami, P. K. Sivakumar, and H. A. Pandya, "Repurposing of anticancer phytochemicals for identifying potential fusion inhibitor for SARS-CoV-2 using molecular docking and molecular dynamics (MD) simulations", 2021, doi: https://doi.org/10.1080/07391102.2021.1902393.
25. S. Muthumanickam, A. Kamaladevi, P. Boomi, S. Gowrishankar, and S. K. Pandian, "Indian Ethnomedicinal Phytochemicals as Promising Inhibitors of RNA-Binding Domain of SARS-CoV-2 Nucleocapsid Phosphoprotein: An In Silico Study," *Front. Mol. Biosci.*, vol. 8, p. 1, Jul. 2021, doi: https://doi.org/10.3389/FMOLB.2021.637329.

26. S. Mahmud *et al.*, "Plant-Based Phytochemical Screening by Targeting Main Protease of SARS-CoV-2 to Design Effective Potent Inhibitors," *Biol. 2021*, vol. 10, no. 7, p. 589, Jun. 2021, doi: https://doi.org/10.3390/BIOLOGY10070589.
27. C. Vicidomini, V. Roviello, and G. N. Roviello, "In Silico Investigation on the Interaction of Chiral Phytochemicals from Opuntia ficus-indica with SARS-CoV-2 Mpro," *Symmetry 2021*, vol. 13, no. 6, p. 1041, Jun. 2021, doi: https://doi.org/10.3390/SYM13061041.
28. A. Basu, A. Sarkar, and U. Maulik, "Molecular docking study of potential phytochemicals and their effects on the complex of SARS-CoV2 spike protein and human ACE2," *Sci. Rep.*, vol. 10, no. 1, pp. 1–15, 2020, doi: https://doi.org/10.1038/s41598-020-74715-4.
29. P. K. Parida, D. Paul, and D. Chakravorty, "The natural way forward: Molecular dynamics simulation analysis of phytochemicals from Indian medicinal plants as potential inhibitors of SARS-CoV-2 targets," *Phyther. Res.*, vol. 34, no. 12, pp. 3420–3433, 2020, doi: https://doi.org/10.1002/ptr.6868.
30. 32.S. Beura and P. Chetti, "In-silico strategies for probing chloroquine based inhibitors against SARS-CoV-2," *J. Biomol. Struct. Dyn.*, vol. 39, no. 10, pp. 3747–3759, 2021, doi: https://doi.org/10.1080/07391102.2020.1772111.
31. R. Islam *et al.*, "A molecular modeling approach to identify effective antiviral phytochemicals against the main protease of SARS-CoV-2", vol. 39, no. 9, pp. 3213–3224, 2020, doi: https://doi.org/10.1080/07391102.2020.1761883.
32. S. S. Swain, S. K. Panda, and W. Luyten, "Phytochemicals against SARS-CoV as potential drug leads," *Biomed. J.*, vol. 44, no. 1, pp. 74–85, Feb. 2021, doi: https://doi.org/10.1016/J.BJ.2020.12.002.
33. K. Kousar, A. Majeed, F. Yasmin, and W. Hussain, "Phytochemicals from Selective Plants Have Promising Potential against SARS-CoV-2: Investigation and Corroboration through Molecular Docking, MD Simulations, and Quantum Computations", vol. 2020, 2020.
34. R. P. Vivek-Ananth, S. Krishnaswamy, and A. Samal, "Potential phytochemical inhibitors of SARS-CoV-2 helicase Nsp13: a molecular docking and dynamic simulation study," *Mol. Divers. 2021*, vol. 1, pp. 1–14, Jun. 2021, doi: https://doi.org/10.1007/S11030-021-10251-1.
35. M. B. Majnooni, S. Fakhri, G. Bahrami, M. Naseri, M. H. Farzaei, and J. Echeverría, "Alkaloids as Potential Phytochemicals against SARS-CoV-2: Approaches to the Associated Pivotal Mechanisms," *Evidence-based Complement. Altern. Med.*, vol. 2021, 2021, doi: https://doi.org/10.1155/2021/6632623.
36. R. Islam *et al.*, "A molecular modeling approach to identify effective antiviral phytochemicals against the main protease of SARS-CoV-2," *J. Biomol. Struct. Dyn.*, vol. 39, no. 9, pp. 3213–3224, 2021, doi: https://doi.org/10.1080/07391102.2020.1761883.
37. A. Kumar *et al.*, "Identification of phytochemical inhibitors against main protease of COVID-19 using molecular modeling approaches," *J. Biomol. Struct. Dyn.*, vol. 39, no. 10, pp. 3760–3770, 2021, doi: https://doi.org/10.1080/07391102.2020.1772112.
38. Y. E. Sherif, S. A. Gabr, N. M. Hosny, A. H. Alghadir, and R. Alansari, "Phytochemicals of Rhus spp. as Potential Inhibitors of the SARS-CoV-2 Main Protease: Molecular Docking and Drug-Likeness Study," *Evidence-based Complement. Altern. Med.*, vol. 2021, 2021, doi: https://doi.org/10.1155/2021/8814890.
39. M. Merarchi, N. Dudha, B. C. Das, and M. Garg, "Natural products and phytochemicals as potential anti-SARS-CoV-2 drugs," *Phyther. Res.*, 2021, doi: https://doi.org/10.1002/PTR.7151.
40. A. Basu, A. Sarkar, and U. Maulik, "Molecular docking study of potential phytochemicals and their effects on the complex of SARS-CoV2 spike protein and human ACE2," *Sci. Rep.*, vol. 10, no. 1, 2020, doi: https://doi.org/10.1038/s41598-020-74715-4.

41. U. R. Surya and N. Praveen, "A molecular docking study of SARS-CoV-2 main protease against phytochemicals of Boerhavia diffusa Linn. for novel COVID-19 drug discovery," *VirusDisease 2021 321*, vol. 32, no. 1, pp. 46–54, Mar. 2021, doi: https://doi.org/10.1007/S13337-021-00683-6.
42. J. Natesh, P. Mondal, B. Kaur, A. A. Abdul Salam, S. Kasilingam, and S. M. Meeran, "Promising phytochemicals of traditional Himalayan medicinal plants against putative replication and transmission targets of SARS-CoV-2 by computational investigation," *Comput. Biol. Med.*, vol. 133, p. 104383, Jun. 2021, doi: https://doi.org/10.1016/J.COMPBIOMED.2021.104383.
43. P. K. Parida, D. Paul, and D. Chakravorty, "The natural way forward: Molecular dynamics simulation analysis of phytochemicals from Indian medicinal plants as potential inhibitors of SARS-CoV-2 targets," *Phyther. Res.*, vol. 34, no. 12, pp. 3420–3433, Dec. 2020, doi: https://doi.org/10.1002/PTR.6868.
44. A. B. Gurung, M. A. Ali, J. Lee, M. A. Farah, and K. M. Al-Anazi, "Unravelling lead antiviral phytochemicals for the inhibition of SARS-CoV-2 Mpro enzyme through in silico approach," *Life Sci.*, vol. 255, p. 117831, Aug. 2020, doi: https://doi.org/10.1016/J.LFS.2020.117831.
45. V. Umashankar, S. H. Deshpande, H. V. Hegde, I. Singh, and D. Chattopadhyay, "Phytochemical Moieties From Indian Traditional Medicine for Targeting Dual Hotspots on SARS-CoV-2 Spike Protein: An Integrative in-silico Approach," *Front. Med.*, vol. 8, no. May, pp. 1–20, 2021, doi: https://doi.org/10.3389/fmed.2021.672629.
46. S. Mahmud *et al.*, "Efficacy of Phytochemicals Derived from Avicennia officinalis for the Management of COVID-19: A Combined In Silico and Biochemical Study," *Mol. 2021*, vol. 26, no. 8, p. 2210, Apr. 2021, doi: https://doi.org/10.3390/MOLECULES26082210.
47. O. Trott and A. J. Olson, "AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading," *J. Comput. Chem.*, p. NA-NA, 2009, doi: https://doi.org/10.1002/JCC.21334.
48. M. M. Jaghoori, B. Bleijlevens, and S. D. Olabarriaga, "1001 Ways to run AutoDock Vina for virtual screening," *J. Comput. Aided. Mol. Des.*, vol. 30, no. 3, pp. 237–249, Mar. 2016, doi: https://doi.org/10.1007/S10822-016-9900-9.
49. S. Kim *et al.*, "PubChem substance and compound databases," *academic.oup.com*, vol. 44, 2016, doi: https://doi.org/10.1093/nar/gkv951.
50. W. D. Ihlenfeldt, E. E. Bolton, and S. H. Bryant, "The PubChem chemical structure sketcher," *J. Cheminform.*, vol. 1, no. 1, 2009, doi: https://doi.org/10.1186/1758-2946-1-20.
51. Q. Li, T. Cheng, Y. Wang, S. B.-D. discovery today, and undefined 2010, "PubChem as a public resource for drug discovery," *Elsevier*, Accessed: Apr. 25, 2022. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S1359644610007737.
52. B. Jejurikar, S. R.-A. J. R. Chem, and undefined 2021, "Drug designing in discovery studio," *ajrconline.org*, Accessed: Apr. 25, 2022. [Online]. Available: https://ajrconline.org/HTML_Papers/AsianJournalofResearchinChemistry__PID__2021-14-2-8.html.
53. V. Temml, T. Kaserer, Z. Kutil, P. Landa, T. Vanek, and D. Schuster, "Pharmacophore modeling for COX-1 and-2 inhibitors with LigandScout in comparison to Discovery Studio," *Future Med. Chem.*, vol. 6, no. 17, pp. 1869–1881, Nov. 2014, doi: https://doi.org/10.4155/FMC.14.114.
54. D. S.-A. [2.1] and undefined 2008, "Discovery Studio," *researchgate.net*, Accessed: Apr. 25, 2022. [Online]. Available: https://www.researchgate.net/profile/Tanweer-Alam-2/post/hi_can_somebody_plz_tell_me_how_to_import_a_database_into_Discovery_Studio_for_a_3D_database_search/attachment/59d63bb879197b8077998bbd/AS%3A412232203685889%401475295224962/download/ds-overview-20.pdf.
55. V. Temml, T. Kaserer, Z. Kutil, P. Landa, T. Vanek, and D. Schuster, "Pharmacophore modeling for COX-1 and -2 inhibitors with LigandScout in comparison to Discovery Studio", vol. 6, no. 17, pp. 1869–1881, Dec. 2014, doi: https://doi.org/10.4155/FMC.14.114.

56. L. Design, "Pharmacophore and ligand-based design with Biovia Discovery Studio®," 2014, Accessed: Jun. 12, 2022. [Online]. Available: https://www.3ds.com/fileadmin/PRODUCTS-SERVICES/BIOVIA/PDF/Pharmacophore-Ligand-based-Design-with-BIOVIA-Discovery-Studio.pdf.
57. "Introduction to the Discovery Studio Visualizer."
58. A. Samdani and U. Vetrivel, "POAP: A GNU parallel based multithreaded pipeline of open babel and AutoDock suite for boosted high throughput virtual screening," *Comput. Biol. Chem.*, vol. 74, pp. 39–48, Jun. 2018, doi: https://doi.org/10.1016/J.COMPBIOLCHEM.2018.02.012.
59. A. Daina, O. Michielin, V. Z.-S. reports, and undefined 2017, "SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules," *nature.com*, Accessed: Jun. 12, 2022. [Online]. Available: https://www.nature.com/articles/srep42717.
60. P. Tripathi, S. Ghosh, S. T.-W. S. News, and undefined 2019, "Bioavailability prediction of phytochemicals present in Calotropis procera (Aiton) R. Br. by using Swiss-ADME tool," *yadda.icm.edu.pl*, Accessed: Apr. 25, 2022. [Online]. Available: https://yadda.icm.edu.pl/yadda/element/bwmeta1.element.psjd-6a4a6eed-dbd4-4e3f-9a9e-d2da448d1fbf.
61. S. Mishra, R. D.-J. of drug delivery and therapeutics, and undefined 2019, "In vitro ADME studies of TUG-891, a GPR-120 inhibitor using SWISS ADME predictor," *jddtonline.info*, 2011, doi: https://doi.org/10.22270/jddt.v9i2-s.2710.
62. A. Daina, O. Michielin, V. Z.-S. reports, and undefined 2017, "SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules," *nature.com*, Accessed: Apr. 25, 2022. [Online]. Available: https://www.nature.com/articles/srep42717.
63. R. Yaligar ICAR -Krishi Vigyan Kendra, I. R. Jyothi ICAR -Krishi Vigyan Kendra, I. G. Narappa ICAR -Krishi Vigyan Kendra, I. M. Ravi ICAR -Krishi Vigyan Kendra, and R. Yaligar, "Swiss ADME prediction of phytochemicals present in Butea monosperma (Lam.) Taub," *phytojournal.com*, vol. 9, no. 3, pp. 1799–1809, 2020, Accessed: Apr. 25, 2022. [Online]. Available: https://www.phytojournal.com/archives/2020/vol9issue3/PartAD/9-3-296-345.pdf.
64. B. Bakchi, A. Krishna, … E. S.-J. of M., and undefined 2022, "An Overview on Applications of SwissADME Web Tool in the Design and Development of Anticancer, Antitubercular and Antimicrobial agents: A Medicinal Chemist's," *Elsevier*, Accessed: Apr. 25, 2022. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0022286022003854.
65. G. Patlewicz, N. Jeliazkova, R. J. Safford, A. P. Worth, and B. Aleksiev, "An evaluation of the implementation of the Cramer classification scheme in the Toxtree software," *SAR QSAR Environ. Res.*, vol. 19, no. 5–6, pp. 495–524, Jul. 2008, doi: https://doi.org/10.1080/10629360802083871.
66. J. Bhachoo and T. Beuming, "Investigating protein–peptide interactions using the schrödinger computational suite," *Methods Mol. Biol.*, vol. 1561, pp. 235–254, 2017, doi: https://doi.org/10.1007/978-1-4939-6798-8_14.
67. M. S. Kalbhor, S. Bhowmick, A. M. Alanazi, P. C. Patil, and M. A. Islam, "Multi-step molecular docking and dynamics simulation-based screening of large antiviral specific chemical libraries for identification of Nipah virus glycoprotein inhibitors," *Biophys. Chem.*, vol. 270, p. 106537, Mar. 2021, doi: https://doi.org/10.1016/J.BPC.2020.106537.