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Exploring active compounds of kelor (*Moringa oleifera* Lam.) leaves as an alternative medicine to improve immunity in facing Covid-19 via *in silico* study

Agus Mohammad Hikam[1], Nurul Jadid Mubarakati[1], Rasyadan Taufiq Probojati[2], Muhammad Hermawan Widyananda[3], Viol Dhea Kharisma[3*], Arif Nur Muhammad Ansori[4*]

[1]*Faculty of Mathematics and Natural Sciences, Universitas Islam Malang, Malang, Indonesia*
[2]*Faculty of Agriculture, Universitas Kadiri, Kediri, Indonesia*
[3]*Faculty of Mathematics and Natural Sciences, Universitas Brawijaya, Malang, Indonesia*
[4]*Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia*
**Correspondence: violdhea@student.ub.ac.id / arif.nma-17@fkh.unair.ac.id*

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Abstract

SARS-CoV-2 is a new strain of coronavirus (CoV) that was identified in Wuhan in 2019. This virus is known to have the ability to reduce human immunity. Kelor (*Moringa oleifera*) is a potential natural resource in Indonesia, which is very abundant and contains several metabolic compounds such as phenolics, flavonoids, saponins, cytokines, and caffeoylquinic acid, which was reported to show antioxidants, antibacterial and antiviral. This study aims to predict the biological activity, physicochemical properties, toxicity, and affinity-interactions of the active compounds of *M. oleifera* leave through in silico approach. The active compounds of *M. oleifera* were obtained from the KNApSAcK and PubChem databases. Analysis of the bioactivity of the compounds using the Way2Drug Pass Online webserver. Analysis of drug-likeness and toxicity using the Lipinski web server and pkCSM. Docking is done using Autodock vina software to analyze the interaction of the compounds with M^{pro}. Based on the physicochemical properties test, *M. oleifera* leaves' active compound has met the rules because it passed at least two Lipinski requirements. The compounds in *M. oleifera* leaves are known to have antiviral bioactivity with a pa value >0.3. As for its toxicity, aurantiamide acetate, chlorogenic acid, dibutyl phthalate, glucoputranjivin, linalool oxide, and vanillin have class IV toxicity, which means they are dangerous when ingested ($300<LD_{50}<2000$). While apigenin, astragalin, beta-sitosterol, chrysin, ellagic acid, ferulic acid, gallic acid, kaempferol, myricetin, niaziminin, quercetin, and rhamnetin have Class V toxicity properties, which means they may be harmful when ingested ($2000<LD_{50}<5000$). The results indicate that the compound astragalin is the compound with the highest affinity value, namely -8.7 (kcal/mol), compared to lopinavir as a

control compound with an affinity value -6.6 (kcal/mol). The types of bonds in astragalin compounds are hydrogen bonds with amino acids Glutamine 127 and Arginine 298. From these results, it is predicted that astragalin compounds have the highest potential as alternative drugs to increase body immunity against the COVID-19.

Keywords: Antiviral, COVID-19, *In silico analysis*, *M. Oleifera*

Introduction

COVID-19 is a new viral infection first reported in China in late December 2019, causing global health problems. WHO publicly declared the SARS-CoV-2 outbreak a pandemic on March 11, 2020[1]. The disease caused by SARS-CoV-2 is called COVID-19. Coronaviruses infect humans and other animals and cause various highly prevalent and severe diseases, including severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS). The SARS-CoV-2 genome comprises about 30,000 nucleotides: the replicase gene of SARS-CoV-2 encodes two overlapping polyproteins pp1a and pp1ab that are required for viral replication and transcription. The functional polypeptides are released from the polyproteins by extensive proteolytic processing, predominantly by the 33.8-kDa M^{pro} (also known as 3C-like protease). M^{pro} digests the polyprotein at least 11 conserved sites, starting with the autolytic cleavage from pp1a and pp1ab. The functional importance of M^{pro} in the viral life cycle, combined with the absence of closely related homologs in humans, identify M^{pro} as an attractive target for the design of antiviral drugs. To facilitate the rapid discovery of antiviral compounds with clinical potential, we developed a strategy that combines structure-assisted drug design, virtual drug screening, and high-throughput screening to repurpose existing drugs to target SARS-CoV-2 M^{pro}. This program focused on identifying drug leads that target the main protease (M^{pro}) of SARS-CoV-2: M^{pro} is a key enzyme of coronaviruses[2], which can spread from person to person. There are no specific antiviral drugs approved for the treatment of COVID-19. Currently, several clinical trials are being conducted to identify the drug. In this scenario, there is a need to identify new medicinal lead compounds to treat COVID-19[3].

Plants from genus *Moringa* were reported for many activities such as circulatory stimulant, anti-tumor, antipyretic, antiepileptic, anti-inflammatory, antiulcer, diuretic, antihypertensive, lowers cholesterol, antioxidants, antidiabetic, antibacterial, antifungal, and antiviral. The combination of the use of active components can contribute optimally to prevention to build the body's immune system and affect the treatment of certain diseases[4]. *M. oleifera* possesses remarkable inhibitory activities against viruses, such as HIV[5], HSV[6], HBV[7], FMDV[8] and NDV[9] and has a role as an immunostimulant because it can increase macrophages activity[10].

The explanation regarding the content of *M. oleifera* compounds which are very good for health and the results of phytochemical screening show that *M. oleifera* leaves have a protective effect against many infectious diseases (bacteria and viruses). Therefore, the researchers aimed to explore the active compound of *M. oleifera* as an alternative medicine to increase immunity against COVID-19 *in silico*.

Materials and methods

Data collection of *M. oleifera* bioactive compounds

Information about bioactive compounds of *M. oleifera* was obtained in two ways. The first is through the KNApSAcK webserver (http://www.knapsackfamily.com/KNApSAcK/) and the second form published research journal references. Bioactive compounds were downloaded from PubChem database (https://pubchem.ncbi.nlm.nih.gov/).

Bioactivity prediction

Bioactivity prediction of each compound was searched through the Way2Drug PASS Online web server (http://www.pharmaexpert.ru/passonline/) using SMILE code of each compound. The Pa (Probability Activity) value must be above 0.3, while the Pi (Probability Inhibition) value must not exceed the Pa value. The bioactivity taken is the potential of the compound as an antiviral. If Pa >0.7, the substance is very likely to exhibit the activity in the experiment, but the chance of the substance is the analog of a known pharmaceutical agent is also high. If 0.5<Pa<0.7, the substance is likely to exhibit the activity in an experiment, but the probability is less, and the substance is unlike known pharmaceutical agents. If Pa <0.5, the substance is unlikely to exhibit the activity in the experiment. However, if the presence of this activity is confirmed in the experiment, the substance might be a new chemical entity[11].

Lipinski test and toxicity

The Lipinski test is obtained through the Lipinski webserver (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) by entering the target compound file into it in pdb form. The parameters include molecular mass, hydrogen bonding, hydrogen bond acceptors, lipophilicity, and molar resistance. Both simple and complex filters have a role in combinatorial library design. Simple properties, for example, privileged building blocks and counting of structural properties (e.g. number of H-bond parameters) to complex calculations (e.g. regression or neural network-based models) explain the relationship of structural features to ADME properties. Drugs must contain adequate functionality to achieve acceptable receptor interactions. A single filter for under functionalization separates drug-like from non-drug-like compounds. Using retrospective analyses of known drugs, including simple property counting schemes, machine learning methods, regression models, and clustering methods, have all been employed to distinguish between drugs and non-drugs[12]. Meanwhile, the toxicity test is obtained through the pkCSM webserver (http://biosig.unimelb.edu.au/pkcsm/prediction), a novel method for predicting and optimizing small-molecule pharmacokinetic and toxicity properties which rely on distance-based graph signatures. We adapted the Cutoff Scanning concept to represent small molecule structure and chemistry (expressed as atomic pharmacophores–node labels) in order to represent and predict their pharmacokinetic and toxicity properties, building 30 predictors divided into five major classes: absorption (seven predictors), distribution (four predictors), metabolism (seven predictors), excretion (two predictors), and toxicity (10 predictors) by entering the SMILE code or compound .ile in the form of pdb. The parameters include the LD_{50} value test[13].

Molecular docking

The target protein in this study is M^{pro} SARS-CoV-2 obtained from NCBI database (https://www.ncbi.nlm.nih.gov/). Three-dimensional structure of M^{pro} (PDB ID: 7BQY) obtained from RCSB PDB database (https://www.rcsb.org/). Three-dimensional structure of bioactive compounds obtained from PubChem database. Proteins are prepared by removing contaminant molecules. Bioactive compounds are prepared by minimizing conformational energy. The purpose of molecular docking is to predict the interactions between proteins and ligands so that the effect of ligands on protein can be predicted. Docking between M^{pro} and bioactive compounds of *M. oleifera* performed using AutoDock Vina[14] integrated into PyRx. Visualization of docking results was conducted using the user-sponsored, open-source molecular visualization system PyMol 2.3.4.0 (Python). PyMOL supports most of the common representations for macromolecular structures: wire bonds, cylinders, spheres, ball-and-stick, dot surfaces, solid surfaces, wire mesh surfaces, backbone ribbons, and cartoon ribbons which are comparable to those generated by Molscript[15].

As a scientific discipline, structural biology drives the need for interactive molecular visualization and has dramatically developed over the last decades. Currently, small molecules with only thousands of atoms or short molecular dynamics simulations with only thousands of frames are rarely interesting for researchers anymore. The analysis focuses on very long simulations of structural

models, where several molecules can mutually interact with a macromolecular structure. A ligand, an interacting chemical compound, is often stimulated to interact with the studied macromolecule. Furthermore, the solvent molecules are also present in the simulation, raising new challenges for the visualization. Nowadays, it is no longer an issue to render several thousands of atoms interactively, even if they change over time. Now the challenge is to understand the dynamic behavior captured in several millions of timesteps. Direct playback of such a long molecular dynamics sequence is unsuitable for a visual analysis and more advanced techniques are required that convey several scales of dynamics[16]. Chemical compounds with the lowest binding energy were analyzed for the position of molecular interactions and the types of bonds formed at webserver protein plus (https://proteins.plus/)[17].

Results

Table 1. The value of Pa and Pi of active compounds of *Moringa* leaves as antiviral drugs

No	Compound	Pa	Pi	Biological Activity
1	Lopinavir (Control)	0.637	0.004	Antiviral
2	Apigenin	0.469	0.007	Antiviral
3	Astragalin	0.333	0.027	Antiviral
4	Aurantiamide Acetate	0.434	0.085	Antiviral
5	Beta Sitosterol	0.686	0.006	Antiviral
6	Chlorogenic Acid	0.303	0.035	Antiviral
7	Chrysin	0.468	0.007	Antiviral
8	Dibutil Phtalate	0.683	0.007	Antiviral
9	Ellagic acid	0.322	0.029	Antiviral
10	Ferulic Acid	0.501	0.022	Antiviral
11	Gallic Acid	0.342	0.025	Antiviral
12	Glucoputranjivin	0.569	0.009	Antiviral
13	Kaempferol	0.496	0.005	Antiviral
14	Linalool Oxide	0.427	0.025	Antiviral
15	Myricetin	0.334	0.026	Antiviral
16	Niaziminin	0.412	0.043	Antiviral
17	Quercetin	0.498	0.005	Antiviral
18	Rhamnetin	0.463	0.007	Antiviral
19	Vanillin	0.382	0.044	Antiviral

The LD_{50} is used to assess the potential short-term toxicity of a substance (Table 2).

Discussion

From the KNApSAcK analysis results, it was found that the active compounds of *M. oleifera* leaves were Rhamnetin and Glucoputranjivin. In comparison, from research journals[18] it was stated that *M. oleifera* leaves contain Apigenin, Astragalin, Aurantiamide Acetate, Beta-Sitosterol, Chlorogenic Acid, Chrysin, Dibutyl Phtalate, Ellagic Acid, Ferulic Acid, Gallic Acid, Kaempferol, Linalool Oxide, Myricetin, Niaziminin, Quercetin, and Vanillin. Furthermore, to determine the physicochemical properties of each compound, the Lipinski test was conducted. The Lipinski Rule helps in distinguishing between drug-like and non-drug-like molecules. The test predicts a high likelihood of success or failure due to drug resemblance for molecules obeying 2 or more rules. The 5 Lipinski rules include molecular mass less than 500 Daltons, high lipophilicity (expressed as LogP less than 5), less than 5 hydrogen bond donors, less than 10 hydrogen bond acceptors and the molar resistance must be between 40-130[19].

Table 2. Toxicity class of *Moringa* leaf active compound

No	Compound	Oral Rat Acute Toxicity LD_{50}	Toxicity Class
1	Lopinavir (Control)	2.340	V
2	Apigenin	2.450	V
3	Astragalin	2.540	V
4	Aurantiamide Acetate	1.960	IV
5	Beta Sitosterol	2.550	V
6	Chlorogenic Acid	1.970	IV
7	Chrysin	2.280	V
8	Dibutil Phtalate	1.800	IV
9	Ellagic acid	2.390	V
10	Ferulic Acid	2.280	V
11	Gallic Acid	2.210	V
12	Glucoputranjivin	1.880	IV
13	Kaempferol	2.440	V
14	Linalool Oxide	1.910	IV
15	Myricetin	2.490	V
16	Niaziminin	2.710	V
17	Quercetin	2.470	V
18	Rhamnetin	2.450	V
19	Vanillin	1.930	IV

From the PASS Online, it was found that all compounds have bioactivity as antiviral with a Pa value above 0.3. The Pa score of a compound must be higher than Pi because it will clarify the positive prediction of the potential of the query compound (Table 1). The results of the analysis show that compounds that have a probability activity (Pa) score >0.3 are less close to the fact because their potential is computationally proven, but this score suitable for screening, whereas if Pa >0.7 is seen as a positive predictor because its potential has been proven through previous research[20].

LD_{50} is defined as a statistical sign when giving a substance as a single dose that can cause the death of 50% of the tested animals. The classification of the toxicity class of compounds is based on the Globally Harmonized System (GHS), the toxicity class includes class I: fatal if ingested (LD_{50}<5 mg/kg), class II: fatal if swallowed (5<LD_{50}<50 mg/kg), class III: toxic if swallowed (50<LD_{50}<300), class IV: harmful if swallowed (300<LD_{50}<2000), Class V: may be harmful if swallowed (2000<LD_{50}<5000), Class VI: non-toxic (LD_{50}<5000)[21].

Molecular docking is the process of binding a ligand with a target protein and determining the binding energy formed in the stable molecular complex[22,23]. Ligands with lowest binding energy can affect the biological activity of a target protein. The lowest binding energy allows molecular complex formation in constant temperature and pressure[24]. Among the bioactive compounds of *M. oleifera* leaves, astragalin is the compound with the highest affinity value, which is -8.7 (kcal/mol), which is greater than the affinity value of Lopinavir as control compound with an affinity value of -6.6 (kcal/mol) (Table 3).

The position of astragalin interaction on the amino acid residues Arg298 and Gln127 with hydrogen bonds when Astragalin forms a molecular complex with M^{pro} (Figure 1).

The leaves of *M. oleifera* are predicted to act as antiviral agents because they have the bioactive compound astragalin capable of reaching targets by passing through cell membranes because they have high bioavailability refer to Lipinski Five Rule. In addition, astragalin has a low level of toxicity compared to other compounds. The binding energy produced by astragalin is more negative when it

binds to the specific Mpro domain, allowing the initiation of a direct inhibitory response to Mpro activity in SARS-CoV-2.

Table 3. Results of molecular docking of *Moringa* leaf active compounds

Ligand-Protein	Affinity (kcal/mol)	Chemical Bonds	Amino Acid
Lopinavir (Control) + 7BQY	-6.6	Hydrogen, Hydrophobic	Threonine 199, Lysine 137, Leucine 272, Tyrosine 237, Leucine 286, Methionine 276, Leucine 287
Apigenin + 7BQY	-7.8	Hydrogen, Hydrophobic	Aspartic Acid 187, Glutamin 192, Methionine 165, Glutamin 189.
Astragalin + 7BQY	-8.7	Hydrogen	Glutamin 127, Arginin 298
Aurantiamide Acetate + 7BQY	-7.7	Hydrogen, Hydrophobic	Histidine 41, Cysteine 145
Beta Sitosterol + 7BQY	-7.7	Hydrogen, Hydrophobic	Aspartic Acid 289, Leucine 287
Chlorogenic Acid + 7BQY	-7.1	Hydrogen	Asparagine 142, Histidine 163, Threonine 26
Chrysin + 7BQY	-7.5	Hydrogen, Hydrophobic	Proline 168, Leucine 167, Methionine 165, Glutamine 189, Aspartic Acid 187
Dibutil Phtalate + 7BQY	-5.3	Hydrogen, Hydrophobic	Phenylalanine 294, Arginine 298, Threonine 292
Ellagic Acid + 7BQY	-7.9	Hydrogen	Serine 158, Glutamine 110, Aspartic Acid 295, Threonine 292
Ferulic Acid + 7BQY	-5.7	Hydrogen, Hydrophobic	Methionine 165, Histidine 41
Gallic Acid + 7BQY	-5.7	Hydrogen	Asparagine 221, Phenylalanine 219, Serine 267, Aspagarine 274
Glucoputranjivin + 7BQY	-6.5	Hydrogen	Glutamine 166, Leucine 141, Aspagarine 142
Kaempferol + 7BQY	-7.9	Hydrogen, Hydrophobic	Aspartic Acid 187, Glutamine 189, Glutamic Acid 166, Methionine 165, Glutamine 192
Linalool Oxide + 7BQY	-5.0	Hydrogen	Threonine 111, Aspagarine 151
Myricetin + 7BQY	-7.5	Hydrogen	Glutamic Acid 166, Serine 144, Leucine 141, Histidine 163
Niaziminin + 7BQY	-7.2	Hydrogen, Hydrophobic	Threonine 111, Glutamine 110, Threonine 292, Phenylalanine 8, Arginine 298
Quercetin + 7BQY	-7.5	Hydrogen, Hydrophobic	Glutamine 189, Methionine 165, Histidine 163, Leucine 141
Rhamnetin + 7BQY	-7.7	Hydrogen, Hydrophobic	Glutamine 192, Glutamic Acid 166, Methionine 165, Glutamine 189
Vanillin + 7BQY	-5.1	Hydrogen, Hydrophobic	Glutamic Acid 270, Phenylalanine 219

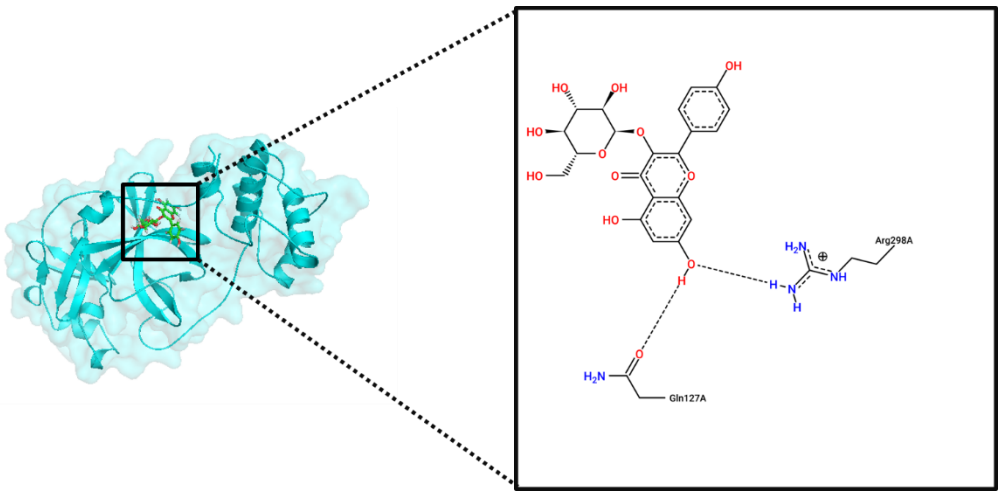

Figure 1. Visualization of Astragalin Docking Results using PyMol and Proteins Plus. This allows the binding domain to affect the M^{pro} protein inhibitor activity of SARS-CoV-2.

Conclusions

Our research demonstrated that all of these compounds have physicochemical properties that have met at least 2 out of 5 Lipinski test rules, also have biological activity that has potential as antiviral, aurantiamide acetate, chlorogenic acid, dibutyl phthalate, glucoputranjivin, linalool oxide, and vanillin have class IV toxicity properties. It means dangerous if swallowed. Apigenin, astragalin, beta-sitosterol, chrysin, ellagic acid, ferulic acid, gallic acid, kaempferol, myricetin, niaziminin, quercetin, and rhamnetin have Class V toxicity properties, which means they may be harmful if ingested. The docking results show that Astragalin CID 5282102 compound received the highest affinity value of -8.7 kcal/mol. From these results, it was predicted that astragalin compounds had the highest potential as an alternative medicine to increase body immunity against the SARS-CoV-2.

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Conflicts of Interest

There are not potential conflicts of interest.

References (AMA)

1. Ansori ANM, Kharisma VD, Muttaqin SS, Antonius Y, Parikesit AA. Genetic variant of SARS-CoV-2 isolates in Indonesia: Spike glycoprotein gene. *J Pure Appl Microbiol*. Published online 2020. doi:10.22207/JPAM.14.SPL1.35
2. Jin Z, Du X, Xu Y, et al. Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors. *Nature*. Published online 2020. doi:10.1038/s41586-020-2223-y

3. Zhang L, Lin D, Sun X, et al. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved a-ketoamide inhibitors. *Science (80-)*. Published online 2020. doi:10.1126/science.abb3405
4. Ahmad J, Khan I, Blundell R. Moringa oleifera and glycemic control: A review of current evidence and possible mechanisms. *Phyther Res*. Published online 2019. doi:10.1002/ptr.6473
5. Nworu, C S, Okoye, et al. Extracts of Moringa oleifera Lam. showing inhibitory activity against early steps in the infectivity of HIV-1 lentiviral particles in a viral vector-based screening. *African J Biotechnol*. Published online 2013. doi:10.5897/ajb2013.12343
6. Goswami D, Mukherjee PK, Kar A, Ojha D, Roy S, Chattopadhyay D. Screening of ethnomedicinal plants of diverse culture for antiviral potentials. *Indian J Tradit Knowl*. Published online 2016.
7. Feustel S, Ayón-Pérez F, Sandoval-Rodriguez A, et al. Protective Effects of Moringa oleifera on HBV Genotypes C and H Transiently Transfected Huh7 Cells. *J Immunol Res*. Published online 2017. doi:10.1155/2017/6063850
8. Imran I, Altaf I, Ashraf M, Javeed A, Munir N, Bashir R. In vitro evaluation of antiviral activity of leaf extracts of Azadirachta indica, Moringa oleifera, and Morus alba against the foot and mouth disease virus on BHK-21 cell line. *ScienceAsia*. Published online 2016. doi:10.2306/scienceasia1513-1874.2016.42.392
9. Okwor E.C., Okoye JO, Onah DN. Immunologic effects of Moringa oleifera methanolic leaf extract in chickens infected with Newcastle disease virus (kudu 113) strain. *African J Pharm Pharmacol*. Published online 2013. doi:10.5897/ajpp2013.3471
10. Biswas D, Nandy S, Mukherjee A, Pandey DK, Dey A. Moringa oleifera Lam. and derived phytochemicals as promising antiviral agents: A review. *South African J Bot*. Published online 2020. doi:10.1016/j.sajb.2019.07.049
11. Lagunin A, Stepanchikova A, Filimonov D, Poroikov V. PASS: Prediction of activity spectra for biologically active substances. *Bioinformatics*. Published online 2000. doi:10.1093/bioinformatics/16.8.747
12. Lipinski CA. Lead- and drug-like compounds: The rule-of-five revolution. *Drug Discov Today Technol*. Published online 2004. doi:10.1016/j.ddtec.2004.11.007
13. Pires DEV, Blundell TL, Ascher DB. pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. *J Med Chem*. Published online 2015. doi:10.1021/acs.jmedchem.5b00104
14. Trott O, Olson AJ. AutoDock Vina: Improving the speed and accuracy of docking with a new

scoring function, efficient optimization, and multithreading. *J Comput Chem*. Published online 2009. doi:10.1002/jcc.21334

15. Delano WL. The PyMOL Molecular Graphics System. *CCP4 Newsl protein Crystallogr*. Published online 2002.
16. Miao H, Klein T, Kouřil D, et al. Multiscale Molecular Visualization. *J Mol Biol*. Published online 2019. doi:10.1016/j.jmb.2018.09.004
17. Luqman A, Kharisma VD, Ruiz RA, Götz F. In silico and in vitro study of Trace Amines (TA) and Dopamine (DOP) interaction with human alpha 1-adrenergic receptor and the bacterial adrenergic receptor QseC. *Cell Physiol Biochem*. Published online 2020. doi:10.33594/000000276
18. Chadrakant Sangar V. In Silico Approach to Combat HIV Using Phytoconstituents of Moringa oleifera Lam. *Juniper Online J Immuno Virol*. Published online 2015. doi:10.19080/jojiv.2016.01.555558
19. Athar M, Lone MY, Jha PC. First protein drug target's appraisal of lead-likeness descriptors to unfold the intervening chemical space. *J Mol Graph Model*. Published online 2017. doi:10.1016/j.jmgm.2016.12.019
20. Kharisma VD, Ansori ANM, Widyananda MH, Utami SL, Nugraha AP. Molecular simulation: The potency of conserved region on E6 HPV-16 as a binding target of black tea compounds against cervical cancer. *Biochem Cell Arch*. Published online 2020. doi:10.35124/bca.2020.20.S1.2795
21. El-Din HMA, Loutfy SA, Fathy N, et al. Molecular docking based screening of compounds against VP40 from Ebola virus. *Bioinformation*. Published online 2016. doi:10.6026/97320630012192
22. Meng X-Y, Zhang H-X, Mezei M, Cui M. Molecular Docking: A Powerful Approach for Structure-Based Drug Discovery. *Curr Comput Aided-Drug Des*. Published online 2012. doi:10.2174/157340911795677602
23. Fu Y, Zhao J, Chen Z. Insights into the Molecular Mechanisms of Protein-Ligand Interactions by Molecular Docking and Molecular Dynamics Simulation: A Case of Oligopeptide Binding Protein. *Comput Math Methods Med*. Published online 2018. doi:10.1155/2018/3502514
24. Ramírez D, Caballero J. Is it reliable to use common molecular docking methods for comparing the binding affinities of enantiomer pairs for their protein target? *Int J Mol Sci*. Published online 2016. doi:10.3390/ijms17040525