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Research Article

Potential Inhibitor of Ten Medicinal Plant Active Compounds Against Covid 19 In Silico Study

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Abstract

SARS-COV-2 was identified in Wuhan city of China in December 2019, a new strain of the coronavirus family. There are no specific drugs available in the market and trials regarding the treatment of the COVID-19. Therefore, in silico screening for natural compounds was required to evaluate their antiviral effect. Molecular docking is the most common type of in-silico study which enables the visualization of binding conformation of ligand to target and produce quantitative in the form of binding energy. Remdesivir is the drug that showed promising results in some COVID-19 patients used as the control in the study. Ten medicinal plant active compounds were used to test their binding affinity towards the main protease and the spike protein using molecular docking. The results from molecular docking indicate that Andrographolide, Ellagic acid and Quercetin were able to fit into the binding pocket of the main protease and the spike protein of COVID-19 with highest binding affinity. The analysis obtained from molecular surface supports the postulation above. In conclusion, Andrographolide, Ellagic acid and Quercetin are shown to be ideal inhibitors compounds for SARS-COV-2. The ligands identified showed a promising result as an effective antiviral for covid-19 and it required further investigation in vitro and in vivo.

Keywords: SARS-COV-2; silico screening; molecular docking; Remdesivir

Introduction

Since the discovery of SARS-COV-2 in December 2019, the novel coronavirus-related pneumonia also known as COVID-19 has continued to spread worldwide, with the current case count close to 5,593,631 confirmed cases, and more than 353,334 deaths reported to the World Health Organization (WHO) as of 28 April 2020 (World Health Oorganization, 2020 ; Service, 2020)[1]. Recent study suggests that the median incubation period was estimated to be 5 days which is similar to SARS and in some cases (101 out of 10000 cases) patients start to develop symptoms after 14 days of active quarantine [2]. Moreover, recent research showed that 5% of Covid-19 patients suffer from mild symptoms or influenza-like symptoms unaccompanied by any risk factor which could be one of factors that increases the transmission rate [3]. SARS-COV-2 is a very contagious virus and life-threatening respiratory infection for humans, which is now prioritized for the global health research concern. The symptoms vary between infected patients such as cough, fatigue, sore throat, running nose, sneezing, fever, body aches, headache, diarrhoea, viral conjunctivitis, loss of smell and taste and shortness of breath [4, 5, 6]. The high percentage of infected individuals developed from viral pneumonia, consequent inflammation and acute respiratory distress syndrome arises by SARS-CoV-2 [7, 8]. In addition, severe pneumonia, secondary infections and

cardiovascular diseases were the main reason for death [9, 10]. Research has shown that remdesivir and chloroquine successfully suppressed the replication of SARS-CoV-2 in vitro and on January 19, 2020, one case of COVID-19 was successfully treated with remdesivir in the USA [11, 12]. After getting the desired result from the trials, there was no detectable nucleic acid of SARS-CoV-2 from specimens (serum and oropharyngeal swab), also there was no gene mutation after comparing it with the previously reported genome sequence of SARS-CoV-2 [13]. This will be useful in developing new therapies and clinical strategies against the COVID-19 infection.

At the present time, there is no approved drug for treating COVID-19 although there have been cases reported as having been treated successfully with compassionate use of remdesivir in the USA. Therefore, there is a need to develop new therapeutic drugs to suppress the virus replication.

Several plant molecules and compounds obtained from medicinal plants, herbal remedies, including Traditional Chinese Medicine, have been suggested as alternatives. These generally may be safer than chemical drugs and are less likely to encounter resistant viruses, because of their multivalent functions. In addition, certain herbal preparations can target both the virus itself and the symptoms The aim of this study is to test ten active compounds: Thymoquinone (CID: 10281), Andrographolide (CID: 5318517), Lauric acid (CID: 3893), Capric acid (CID: 2969), caprylic acid (CID: 379), Ellagic acid (CID: 5281855) and Pimpinella anisum (Anise seed) which consists of four active compound Anethol (CID: 637563), Coumarin(CID: 323), Quercetin (CID: 5280343) and (2R,3S,4S,5S)-6-[[(2R,3R,4R,5R,6S)-3,4,5-Trihydroxy-6-methyloxanyloxymethyl] oxane-2,3,4,5-tetrol (CID: 101552), may inhibit the novel corona viruses and provides scientists with information on compounds that may be effective [14, 15, 16].

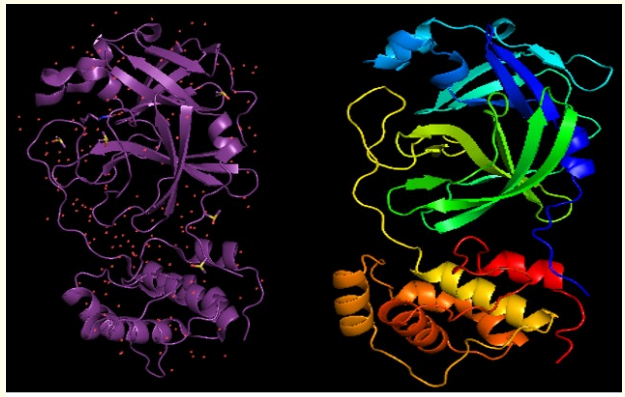
The two therapeutic targets options known as the main protease and the spike protein of SARS-COV-2 in silico using molecular docking method as both targets show promising drug targets to discovering new therapeutic approaches for COVID-19 [17, 18].

Auto Dock Vina was one of the docking engines used in molecular docking. It was an open source that was designed by Dr. Oleg Trott at The Scripps Research Institute. Auto Dock Vina was widely used as it was able to provide confirmation structures and the energy evaluation in prediction of target-ligand complexes. Auto Dock Vina and its predecessor, Auto Dock 4, both employ simplifications that may affect the result notably the rigidity of targets. The high rigidity of the targets reduces the size of conformation space allowing it to be searched more reliably [19]. However, according to Ng, Fong 2015 the result of a simulation showed that Auto Dock Vina has significantly improved the prediction accuracy and docking time when compared with Auto Dock [20].

Based on the review done by Pagadala, 2016 [21], unlike Auto Dock 4 that uses empirical scoring function and Genetic-Algorithm-based optimizer that searches for the lowest energy conformation search, Auto Dock Vina uses a knowledge-based scoring function with Monte Carlo sampling technique and the Broyden-Fletcher- Goldfard- Shanno (BFGS) method for optimization [21]. In Auto Dock Vina, Monte Carlo algorithm was used to perform global search whereas the algorithm of BFGS was used to perform local search. The introduction of local search contributes to the speed-up obtained where global search converges rapidly leading to shorter docking time [22].

Materials and Methods

The receptor was retrieved from Protein Data Base (https://www.rcsb.org). The SARS-COVID-19 main protease (figure 1a and 1b) (PDB ID: 7BUY) was used for docking as the receptor. The receptor preparation was using Discovery Studio 2017 software. The Heteroatom (carmofur and water) were selected and removed from the receptor. Polar hydrogen was added and optimized by a hydrogen bonding network. The receptor was saved in PDB format (SARS-COV19. PDB). Same procedure has been done for the spike protein (PDB ID: 7BZ5).



(a) (b)

Figure 1: (a) shows the SARS-COV-2 main protease docked with Carmofur; (b) shows Crystal structure of SARA-COV-2 main protease after optimization.

Ligand preparation

The ten ligands were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov) in SDF format and by using Pymol software the format was converted to PDB. The 3D structure of Thymoquinone (CID: 10281), Andrographolide (CID: 5318517), Lauric acid (CID: 3893), Capric acid (CID: 2969), caprylic acid (CID: 379), Ellagic acid (CID: 5281855) and Pimpinella anisum (Anise seed) which consists of four active compound Anethol (CID: 637563), Coumarin(CID: 323), Quercetin (CID: 5280343) and (2R,3S,4S,5S)-6-[[(2R,3R,4R,5R,6S)-3,4,5-Trihydroxy-6-methyloxan-2-yl]oxymethyl]oxane-2,3,4,5-tetrol (CID: 101552). In addition, hydrogen bonds were added to all ligands using Discovery studio 2017 software.

Docking procedure

The molecular docking process was done using PyRx software, the receptor and the ten ligands submitted in PDB format respectively. Vina search space was prepared as the following: Centre (X: -26.2348, Y:14.5426, Z:58.2395) and Dimensions angstrom (X: 46.5578, Y:62.0954, Z: 56.2231) (figure 2).

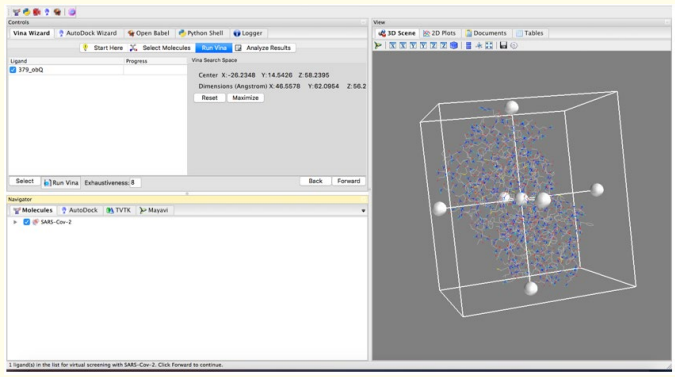


Figure 2: Show the Vina Wizard window ready for docking.

Prediction of ADMET of the ligands

ADME is known as Adsorption, Distribution, Metabolism and Excretion. It's an important component to analyse the pharmacodynamics of the proposed molecules which could be used as therapeutic drugs. While toxicology prediction of the ligands is an essential step to predict the degree to which overt adverse effects of a drug can be tolerated by a patient of the small molecules before being ingested and tested through the animal and human models. The online database pkCSM was used to predict ADMET of the ligands by submitting the SMILES strings of the small molecules [23]. The SMILES strings of the ligands obtained from PubChem, submitted into the website and ADMET mode was selected.

Results and Discussion

Binding Diagram Analysis

Based on the top three results obtained from AutoDock Vina result analysis, structures were extracted using PyMOL, Discovery studio, the binding site of experimental and control ligands to target were visualized.

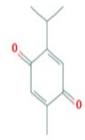
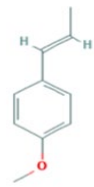
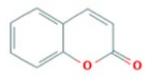
2D and 3D Interaction Diagram Analysis

2D and 3D interaction diagrams were obtained for the highest binding affinity complex result obtained from AutoDock Vina result analyse by using Discovery Studio 2017 and PyMOL. The list of interactions was obtained, the bond diagram was visualized and compared between control and experimental ligands.

Molecular Surface Analysis

Based on the Auto Dock Vina result analysis, one of the complexes that has the highest binding affinity result was used to conduct hydrophobicity analysis and hydrogen bonding analysis Discovery Studio 2017. The hydrophobic and hydrogen bonding analysis of experimental ligands were compared to that of control ligand.

Results of COVID-19 virus docked with different ligands

Ligand name	*Ligand 2D structure*	*Main protease Binding affinity (kcal/mol)*	*Spike protein Binding affinity (kcal/mol)*
Thymoquinone		5.2	5.6
Anethol		5.1	6.1
Coumarin		5.9	6.2

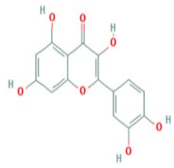
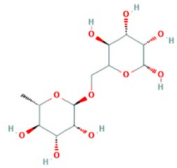
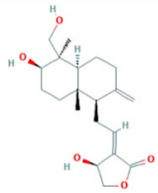
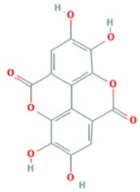
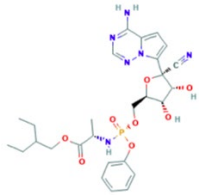
Quercetin		7.7	8.7
CID 101552		6.8	6.7
Andrographolide		7.2	7.7
Ellagic acid		7.5	7.9
Lauric acid		4.6	4.8
caprylic acid		4.3	4.8
Capric acid		4.5	5.1
Remdesivir		7.8	7.8

Table 1: Interaction data between the five ligands and one control docked with COVID-19 main protease.

Intermolecular interactions

2D and 3D Intermolecular interactions

The two-dimensional diagrams of intermolecular interaction for each lead with different proteins were created by Discovery Studios 2017 and PyMol.

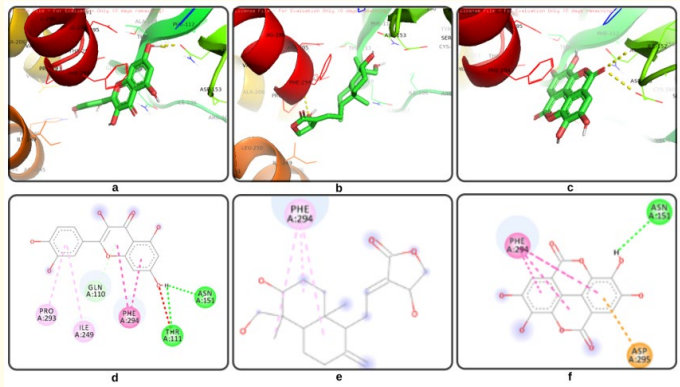


Figure 3: Molecular docking analysis of the SARS-COV-2 main protease. (a, b, c) shows the 3D interaction of (a) Quercetin, (b) Andrographolide, (c) Ellagic acid when successfully docked with the main proteases. (d, e, f) shows the 2D interaction (d) Quercetin, (e) Andrographolide, (f) Ellagic acid when successfully docked with the main proteases.

Quercetin, (b) Andrographolide, (c) Ellagic acid when successfully docked with the main proteases. (d, e, f) shows the 2D interaction (d) Quercetin, (e) Andrographolide, (f) Ellagic acid when successfully docked with the main proteases.

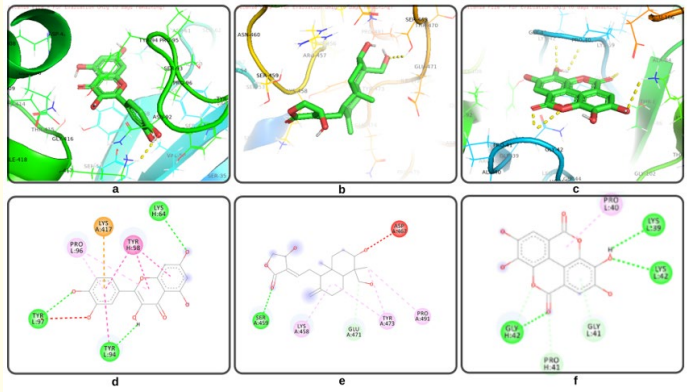


Figure 4: Molecular docking analysis of the Spike protein. (a, b, c) shows the 3D interaction of (a) Quercetin, (b) Andrographolide, (c) Ellagic acid when successfully docked with the spike protein. (d, e, f) shows the 2D interaction (d) Quercetin, (e) Andrographolide, (f) Ellagic acid when successfully docked with the spike protein.

Analysis of molecular surface

Analysis of the hydrophobicity degree

The analysis of hydrophobicity degree was performed using Discovery Studios 2017. It was performed on the molecular surface of ligands while binding to the targets as shown in figure 5. Based on these diagrams the colour of the molecular surface determines its

hydrophobicity. High intensity of brown colour signifies hydrophobic while high intensity of blue colour signifies hydrophilic. White colour signifies the balance of hydrophilicity and hydrophobicity at the surface.

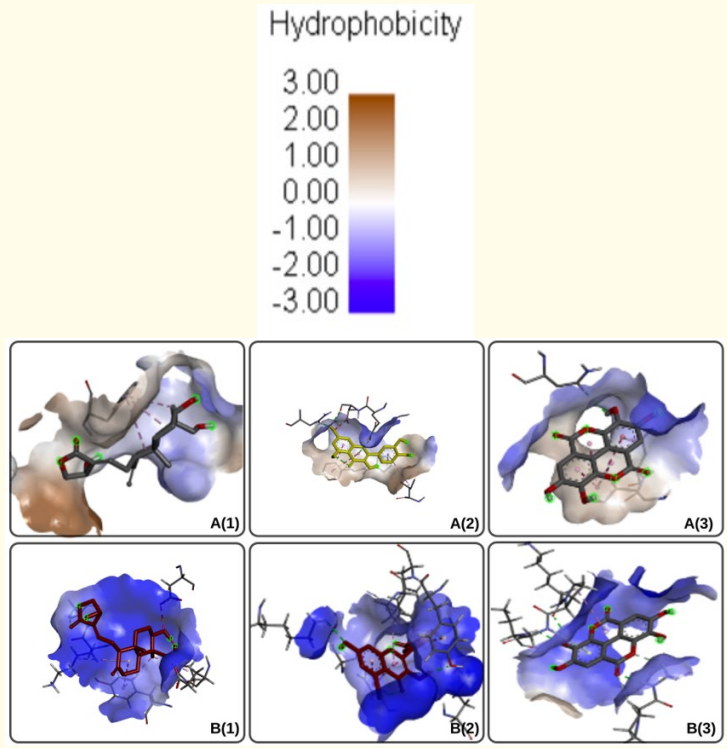


Figure 5: Hydrophobicity degree analysis of the main protease (A) and the Spike protein (B). (A1, A2, A3) shows the 3D interaction of (1) Andrographolide, (2) Quercetin, (3) Ellagic acid when successfully docked with the main protease. (B1, B2, B3) shows the 2D interaction shows the 3D interaction of (1) Andrographolide, (2) Quercetin, (3) Ellagic acid when successfully docked with the spike protein.

Analysis of hydrogen degree (kcal/mol)

The analysis of the hydrogen bond degree was performed using Discovery Studios 2017. It was performed on the molecular surface of ligands while docked to the respective targets as shown in figure 6. Based on these figures, the location and identity of hydrogen bond acceptors and hydrogen bond donors were determined.

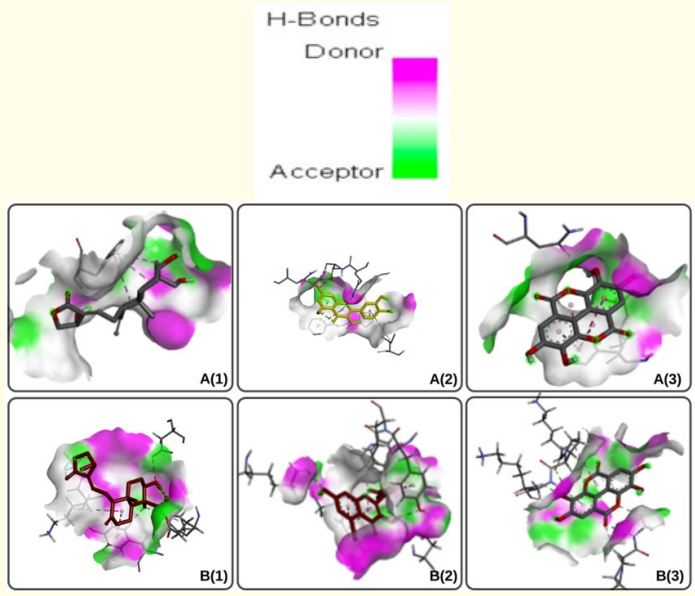


Figure 6: Hydrogen bond degree analysis of the main protease (A) and the Spike protein (B). (A1, A2, A3) shows the 3D interaction of (1) Andrographolide, (2) Quercetin, (3) Ellagic acid when successfully docked with the main protease. (B1, B2, B3) shows the 2D and the 3D interaction of (1) Andrographolide, (2) Quercetin, (3) Ellagic acid when successfully docked with the spike protein.

ADMET result

		Andrographolide	Quercetin	Ellagic acid
Absorption	Intestinal absorption	95.357 % High	77.207 % High	86.684 % High absorption rate
Distribution	VDss (human)	-0.286 Low	1.559 Moderate	0.375 (logL/kg) Low distribution rate
	BBB permeability	-0.598 BB Poor distribution	-1.098 BB Poor distribution	-1.272 log BB Poor distribution
Metabolism	CYP2D6 substrate	NO	NO	NO
	CYP3A4 substrate	YES	NO	NO
	CYP1A2 inhibitor	NO	YES	Yes
Excretion	Renal OCT2 substrate	NO	NO	NO

Toxicity	Max. tolerated dose (human)	0.128 Very low	0.499 Slightly high	0.476 (log mg/kg/day) low
	Oral Rat Chronic Toxicity (LOAEL)	2.162 (log mg/kg/day)	2.471 (log mg/kg/day)	2.698 (log mg/kg/day)
	T.Pyriformis toxicity	0.491 (log ug/L) Not toxic	0.288 (log ug/L) Not toxic	0.295 (log ug/L) Not toxic
	Minnow toxicity	1.37 (log mM) Not toxic	3.721 (log mM) Not toxic	2.11 (log mM) Not toxic

Discussion

The current need is to find an effective treatment for SARS-CoV-2 virus, various small molecules are in trial stage in order to provide a cure for this frightful outbreak such as Remdesivir [24]. Based on the results obtained from molecular docking using AutoDock Vina for SARS-COV-2 main protease and the Spike protein docked with ten natural compounds. By referring to Table 1, Andrographolide, Ellagic acid and Quercetin showed the highest binding affinity toward both receptors (main proteases and the spike protein) accompanied with the lowest binding energy needed while the binding affinity for example of Capric acid towards both receptors is much lesser compared to Andrographolide, Ellagic acid and Quercetin. The lower the binding energy between the ligands and the protein, the higher the possibility that they can bind to each other [25].

Molecular interactions analysis was accomplished using Discovery Studio visualizer 2017. All the results obtained using a fixed grid-box as mentioned above, in this way we can lower the variable that would affect the wanted results. The major types of intermolecular interactions are shown in figures 3 and 4, the main interaction format chosen for this experiment were hydrophobicity interaction test and hydrogen bond in Van Der Waals forces of interaction form. Docking results of Andrographolide, Ellagic acid and Quercetin with both receptors were compared to Remdesivir drug the FDA approved for treating Ebola virus [26]. *Remdesivir* drug has been shown to inhibit the replication of other human coronaviruses accompanied with high morbidness in vitro, such as Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 and severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 [27]. Moreover, on May 2020 remdesivir acquired an emergency use authorization by the EUA from FDA, according to the initial data showing that the recovery time is much faster for recovery of hospitalized patients with severe diseases. Other several antiviral agents, immunotherapies, and vaccines continue to be investigated and developed as potential therapies [28].

Quercetin docking result

The docking score of Quercetin is -7.7 and 8.7 kcal/mol with the main protease and the spike protein respectively. The good docking score elucidates that the inhibitor is strongly bound in the pocket with a favourable binding energy Value. When compared to the reference molecule Remdesivir, Quercetin shows better docking results when bound to the spike protein with only -7.8 kcal/mol.

A previous study demonstrated that quercetin could help in treating patients with H1N1 influenza A and Ebola virus, as it reduces the complications of the severe disease [29, 30].

Andrographolide docking result

The docking score of Andrographolide is -7.5 and 7.7 kcal/mol with the main protease and the spike protein respectively. Andrographolide docking result shows good score similar to Remdesivir elucidates that the inhibitor is strongly bound in the pocket with a favourable binding energy value. A recent study suggests that Andrographolide has shown to be a potential COVID-19 inhibitor when

successfully docked with the main protease as it supports our findings that andrographolide successfully binds to the spike protein which is one of the therapeutic targets [12, 31].

Ellagic acid docking result

Ellagic acid successfully docked to the main protease and the spike protein with docking score 7.5 kcal/mol and 7.9 kcal/mol respectively. The docking result of Ellagic acid shows a good indicator that it could work as an inhibitor that is strongly bound in the pocket with a favourable binding energy value when compared to Remdesivir. Studies have shown that ellagic acid possesses an antiviral effect toward human rhinovirus that could be used to prevent or treat HRV [32].

Analysis of Molecular Surface

There are a great number of parameters used for the analysis of molecular surfaces. In this project, the two most important parameters were used to analyse the molecular surface representation and assist in drug discovery and the process of development are the hydrogen bond and the degree of hydrophobicity.

Analysis of the degree of hydrophobicity

As stated by Patil 2010, hydrophobic interaction plays a vital role in the biologic action of the ligand, therefore the increase in the hydrophobic interactions within the ligand-protein complex interface, increases the drug stability and its biological activities. The analysis of main protease and spike protein for the degree of hydrophobicity were done (figure 5). When comparing Andrographolide, Ellagic acid, Quercetin and Remdesivir for their degree of hydrophobicity, Andrographolide, Ellagic acid and Quercetin showed large hydrophilic portions of their molecular surface and limited hydrophobic region.

Analysis of hydrogen bonding

Discovery Studio 2017 software was used to perform the H-bond analysis. This parameter was carried out on the molecular surface of the lead that docked to the respective receptor as illustrated from figure 6. The determination of the identity and the location of the H-bond acceptor and H-bond donor is based on the diagrams in the result section. The H-bond analysis is according to the colour intensity shown in the diagrams, pink colour means that specific area has hydrogen bond donor, green colour indicates hydrogen bond acceptor while white area indicates that the area has a balance number of hydrogen bond donor and acceptor. Based on the results Quercetin, Andrographolide and Ellagic acid all have many hydrogen bond donors and very few hydrogen bond acceptors. This further proves that all have more hydrophilic interactions than hydrogen bonding interactions with main protease and spike protein.

ADMET analysis

Andrographolide, Ellagic acid and Quercetin possess excellent properties of drug ability as well small biomolecules. According to the pkCSM pharmacokinetic properties results, the three ligands possess high absorption rate by using the human epithelial colorectal adenocarcinoma cells model. The lipophilicity of the ligands shows that the compounds have ideal properties for oral and intestinal absorption and are able to be absorbed sublingually as well. The ligand andrographolide unlike ellagic acid and quercetin, it does not inhibit liver metabolism by inhibiting CYP1A2 as a result it does not cause any adverse effect [33]. While quercetin and ellagic acid do not inhibit CYP3A4 substrate as it is responsible for drug metabolism that affects the pharmacokinetics effects. The toxicity prediction of the three ligands do not show any chronic or acute toxicity effect. The toxicity predicted was displayed in the website and the results is as follows, The Andrographolide does not have AMES toxicity, Maximum tolerated dose for human is about 0.128 log mg/kg/day, it does not inhibit hERG-I and hERG-II, Acute oral rat toxicity (LD50) was found to be 2.162 mol/kg, Chronic oral rat toxicity (LOAEL) was found to be 1 log mg/kg_bw/day, does not produce hepatotoxicity, it does not cause skin sensitivity, 0.491 log µg/L causes T. pyriformis toxicity and 1.37 log mM causes Minnow toxicity.

During the past few years, molecular docking has been used for the identification of synthetic and natural drug candidates against targets of MERS-CoV and SARS-CoV to find the suitable ligand that inhibit the replication of the virus. In this study, several drug candidates used against the main protease and the spike protein of SARS-CoV-2 by using virtual screening molecular docking in a silico approach. The ligands identified showed a promising result as an effective antiviral for covid-19 and it required further investigation in vitro and in vivo.

Conclusion

The current research was carried out to discover novel inhibitor molecules against the main protease and the spike protein. The ten ligands were tested and analysed by molecular docking techniques. The results of the top three ligands were compared with the reference molecules Remdesivir as it can bind more efficiently and act as inhibitors. According to the binding energy score obtained, Andrographolide, Quercetin and Ellagic acid can be tested against Coronavirus in vivo and in vitro to develop effective antiviral drugs.

References

1. World Health Organization. Coronavirus Disease (COVID-19) (2020).
2. Lauer SA., et al. "The incubation period of coronavirus disease 2019 (CoVID-19) from publicly reported confirmed cases: Estimation and application". Annals of Internal Medicine 172.9 (2020): 577-582.
3. Spellberg B., et al. "Community Prevalence of SARS-CoV-2 among Patients with Influenzalike Illnesses Presenting to a Los Angeles Medical Center in March 2020". JAMA - Journal of the American Medical Association 323.19 (2020): 1966-1967.
4. Centre for Disease Control and Prevention. (2020) Coronavirus Disease 2019.
5. Chan JFW., et al. "A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster". The Lancet 395.10223 (2020): 514-523.
6. Huang J., et al. "Pharmacological therapeutics targeting RNA-dependent RNA polymerase, proteinase and spike protein: From mechanistic studies to clinical trials for COVID-19". Journal of Clinical Medicine 9.4 (2020): 1131.
7. Heymann DL. "Data sharing and outbreaks: best practice exemplified". The Lancet 395.10223 (2020): 469-470.
8. Zhou P., et al. "A pneumonia outbreak associated with a new coronavirus of probable bat origin". Nature 579.7798 (2020): 270-273.
9. Chen N., et al. "Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study". The Lancet 395.10223 (2020): 507-513.
10. Li G and De Clercq E. "Therapeutic options for the 2019 novel coronavirus (2019-nCoV)". Nat. Rev. Drug Discov 19 (2020): 149-150.
11. Holshue ML., et al. "First Case of 2019 Novel Coronavirus in the United States". New England Journal of Medicine 382.10 (2020): 929-936.
12. Huang C., et al. "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China". The Lancet 395.10223 (2020): 497-506.
13. Lu R., et al. "Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding". The Lancet 395.10224 (2020): 565-574.
14. Gupta S, Mishra KP and Ganju L. "Broad-spectrum antiviral properties of andrographolide". Archives of Virology 162.3 (2017): 611-623.
15. Newman DJ and Cragg GM. "Natural Products as Sources of New Drugs from 1981 to 2014". Journal of Natural Products 79.3 (2016): 629-661.
16. Zakaryan H., et al. "Flavonoids: promising natural compounds against viral infections". Archives of Virology 162.9 (2017): 2539-2551.
17. Zhang L., et al. "Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors". Science 368 (2020): 409-412.

18. Li Q., et al. "Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia". New England Journal of Medicine 382.13 (2020): 1199-1207.
19. Forli S., et al. "Computational protein-ligand docking and virtual drug screening with the AutoDock suite". Nat. Protoc 11 (2016): 905-919.
20. Ng MCK, Fong S and Siu SWI. "PSOVina: The hybrid particle swarm optimization algorithm for protein-ligand docking". Journal of Bioinformatics and Computational Biology 13.3 (2015).
21. Pagadala NS, Syed K and Tuszynski J. "Software for molecular docking: a review". Biophysical Reviews 9.2 (2017): 91-102.
22. Handoko SD., et al. "QuickVina: Accelerating AutoDock Vina using gradient-based heuristics for global optimization". IEEE/ACM Transactions on Computational Biology and Bioinformatics 9.5 (2012): 1266-1272.
23. Pires DEV, Blundell TL and Ascher DB. "pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures". Journal of Medicinal Chemistry 58.9 (2015): 4066-4072.
24. Wang M., et al. "Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro". Cell Research 30.3 (2020): 269-271.
25. Binding Affinity (2016) Dissociation Constant.
26. Food, U. S., Administration, D. & Others. Search orphan drug designations and approvals. Lactobacillus acidophilus (2014).
27. Cennimo DJ. "What is the role of the antiviral drug remdesivir in the treatment of coronavirus disease 2019". Medscape.Com (2021): 2020-2022.
28. Rahaghi F. "Remdesivir for the Treatment of Covid-19 - Preliminary Report". New England Journal of Medicine 383.19 (2020): 992-994.
29. Qiu X., et al. "Prophylactic efficacy of quercetin 3-β-O-D-glucoside against Ebola virus infection". Antimicrobial Agents and Chemotherapy 60.9 (2016): 5182-5188.
30. Wu W., et al. "Quercetin as an antiviral agent inhibits influenza a virus (IAV) Entry". Viruses 8.1 (2015): 6.
31. Enmozhi SK., et al. Andrographolide as a potential inhibitor of SARS-CoV-2 main protease: an in silico approach. Journal of Biomolecular Structure and Dynamics 39.9 (2020): 3092-3098.
32. Park SW., et al. Antiviral activity and possible mode of action of ellagic acid identified in Lagerstroemia speciosa leaves toward human rhinoviruses. BMC Complementary and Alternative Medicine 14 (2014): 171.
33. Horn JR and Hansten PD. "Get to know an enzyme: CYP1A2". Pharm. Times (2007).

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