Full Length Research Article
Advancements in Life Sciences – International Quarterly Journal of Biological Sciences

ARTICLE INFO

Date Received: 21/09/2020;
Date Revised: 20/02/2022;
Date Published Online: 25/05/2022;

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How to Cite:
Saif R, Ashfaq K, Ali G, Iftekhar A, Z Saeeda, Yousaf MZ (2022). Computational Prediction of Cassia angustifolia Compounds as a potential Drug Agents against Main Protease of SARS-nCov2. Adv. Life Sci. 9(1): 36-40.

Keywords:
Molecular docking; 6LU7; Auto-Dock Vina; SARS-nCov2

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Computational Prediction of *Cassia angustifolia* Compounds as a potential Drug Agents against Main Protease of SARS-nCov2

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Abstract

Background: In November-December 2019, a plethora of pneumonia like cases were reported in Wuhan, China. After some time, the causative agent of this ailment was identified and named as a novel coronavirus 2. This novel virus spread over the world with no time and declared as pandemic by WHO. To develop antiviral drugs, different clinically used drugs were used as a trial but went in vain. In the current study, we choose an herb with already known therapeutic effects to check its antiviral properties against this virus too.

Methods: Cassia angustifolia is a well-known herb for pharmaceutical industries as its different compounds are already used in different medicines. Here we performed molecular docking of main compounds of Cassia angustifolia against the main protease of SARS-nCoV2 and were compared with different drugs that are already being used on commercial bases to obtain the lowest energy complex. Auto-Dock vina and its packages were used for molecular docking of SARS-nCov2.

Results: Molecular docking of Cassia angustifolia compounds represent very promising binding energies complexes, e.g., Sennoside B gives -9.05kcal/mol and Aloe-Emodin give -4 Kcal/mol of energy against the main protease of coronavirus. In contrast, a couple of commercially used antiviral drugs were also evaluated against the selected protein of coronavirus e.g., Hydroxychloroquine and Ribavirin complexes appeared with -5.2 Kcal/mol and -6.3 Kcal/mol of energy respectively.

Conclusion: Many compounds of Cassia angustifolia showed the promising energy complexes even better than the commercially used antiviral drugs e.g., Sennoside B which has the best energies against main protease of coronavirus. Further, *in-vivo* and *in-vitro* studies are needed to validate this hypothesis with advanced MD simulations and wet-lab experimentations.

Introduction

Wuhan, the capital city of Hubei Province and the major transportation hub of China started dealing with severe pneumonia with unknown causes in local hospitals at the beginning of December 2019. China informed about the outbreak of this disease to the WHO on December 31st. Most of the patients were exposed to the famous Hunan wholesale sea market of Wuhan. Consequently, Hunan sea market was closed on 1st January [1]. The virus spread rapidly across all over the world. On March 11, WHO announced it as a Pandemic disease. Effective prevention and treatment were essential in this situation. Some of the studies showed the herbal remedies to prevent Coronavirus [2]. *Cassia Senna L. (Cassia angustifolia)* is a well-known curative herb cultivated in areas near Somalia, Sudan, Arabian Peninsula and upper Nile as well as India and Pakistan. *Cassia angustifolia* is considered as a medicinal herb due to its therapeutic properties: i)Anti-Oxidative [3] ii) Anti-Diabetic [4] iii)Anti-obesity [5] iv)Anti-Cancer [3] . The medical importance of *Cassia angustifolia* has motivated researchers to investigate its therapeutic effect against CoVID19.

In the current study, we report the results of the molecular docking of *Cassia angustifolia* with the main protease protein of coronavirus. For the comparison of binding energies, commercially available drugs used against the SARS-nCov2 were selected (Hydroxychloroquine, Ribavirin, Favipiravir, Remdesivir) and compared with *Cassia angustifolia* [6,7]. All of these were selected according to Lipinski's physiochemical properties.

Methods

Curative Herb Choice

On regional review, we stated that *Cassia Senna L.* (*Cassia angustifolia*) usually known as *Alexandrian Senna*, Indian Senna or Senna Makki leaves has been conventionally suggested during the COVID-19 pandemic for their expected antiviral effects. Historically, Senna leaves have been used as early as the 9th century when Arabian physicians treated constipation by using both its leaves and pods.

Selection of Target Protein

The crystal structure of COVID-19's main protease in complex with an inhibitor N3 (PDB ID: 6LU7) was acquired from Protein Data Bank-RCSB (PDB) (https://www.rcsb.org/). (Table 1)

Molecular Structure and Selection of Ligands

The 2D structure of the ligand *Sennoside B* and 3D structure of *6-Hydroxymusicin, Tinnevellin Glucoside, Aloe-Emodin, Kaempferol* were acquired from PubChem (https://pubchem.ncbi.nlm.nih.gov) [8,9] which were used as a potential drug agent taken from *Cassia angustifolia* (Figure 2) **.** There are some other Sennoside compounds available in this Herb which includes Sennoside A, C and D having similar structures to *Sennoside B* (Figure 1).

Enzyme	PDB ID	Organism	Resolution	Classification	Expression System	Total Structure weight (DA)	Chaine	Method
Main protease of SARS-nCov2	6LU7	Bat SARS-like coronavirus	2.1Å	Viral Protein	*E. coli* BL21(DE3)	34506.34	A	X-RAY Diffraction

Table 1: Crystallographic properties of Main Protease of Coronavirus

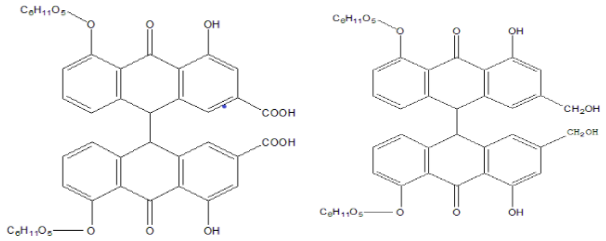


Figure 1: Structure of sennoside A and B (Left) and Structure of Sennoside C and D (Right).

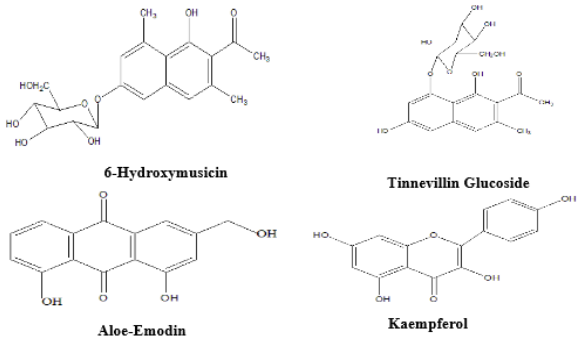


Figure 2: 2D structure of major compounds of *Cassia angustifolia*

All of the compounds selected for *Cassia angustifolia* were chosen according to Lipinski's physiochemical parameter rule [10,11] obtained from PubChem. (Table 2)

Ligand	Molecular Weight (g/mol)	Hdonn	Hacc	TPSA (Å²)	LogP
Sennoside B	862.75	12	20	348	1.2
6-Hydroxymusicin	392.4	5	8	137	1.6
Tinnevellin Glucoside	408.4	5	9	146	1.2
Aloe-emodin	270.24	3	5	94.8	1.8
Kaempferol	286.24	4	6	107	1.9

Table 2: Properties of compounds according to Lipinski's Parameter Rule

Commercial drugs were chosen to compare the binding energies with the obtained docking results and their molecular 2D structures were prepared using chem Draw. (Figure 3). The drugs were chosen following the properties of Lipinski's Physiochemical parameters, which were obtained using PubChem (https://pubchem.ncbi.nlm.nih.gov). (Table 3)

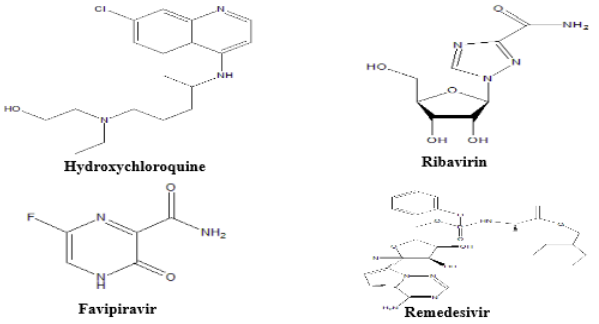


Figure 3: Chemical structure of commercially drugs used against SARS-nCoV2.

Ligand	Molecular Weight (g/mol)	Hdonn	Hacc	TPSA (Å²)	LogP
Hydroxychloroquine	335.9	2	4	48.4	3.6
Ribavirin	244.2	4	7	144	-1.8
Favipiravir	157.1	2	4	84.6	-0.6
Remdesivir	602.6	4	13	204	1.9

Table 3: Commercially used drugs and properties according to Lipinski's physiochemical parameters.

Software/Platform used for Molecular Docking

The tools that were used for protein docking are AutoDock Vina-ADT (version 1.5.7) package [12] and Discover Studio 2020. Different tools were deployed for docking purposes (MGL tool, Python, CADD, Vision).

Preparation of Protein and Ligands

For the preparation of protein receptor, some important steps were carried out. Preliminary query protein molecule was purified using Discovery Studio. Protein sequence was extracted from PDB (ID:6LU7) in the PDB format. Protein sequence was read through the Discovery Studio to visualize and edit protein structure in order to remove the water molecules and other bound ligands. The protein was purified and was saved as a PDB format file.

For the preparation of Ligands, Structure of ligand such as *Sennoside B* was extracted from PubChem. The 2D/3D structure of the ligand was mined in SDF file. Using Discovery Studio, the structure was visualized and the format of SDF was changed into PDB file format.

Recognition of Active Site

Molecular docking of *Main Protease in complex with inhibitor N3* was a blind Docking (Docking without knowing binding and active site) computed using *AutoDock Vina*. The active site of the protein was designated automatically by the software. In order to make the process more efficient, different tools and references can be used for the conformation of the active site in proteins before docking.

Synchronize Grid Box

After the automated recognition of Active site, polar molecules of hydrogen were added successfully by using MGL Tool. Using the MGL tool to customize the 3D grid box, the number of points were set according to the three dimensions i.e., X, Y and Z (Figure 4). Figure 4 depicts that the number of points in the three dimensions are set to 26 by default, and then spacing (angstrom) is set to be at 1.000 so that it can cover the maximum area of the protein. Centre of grid box for X, Y and Z are set automatically by the tool. After setting of grids, the file was saved in the PDBQT format.

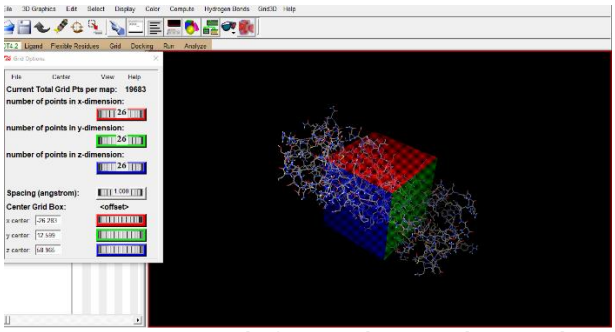


Figure 4: Using MGL tool of AutoDock vina package to adjust values of grid.

Finalizing Ligand Preparation

For the preparation of ligand, angle of torsion must be defined. Open the ligand file in MGL tool and set the number of torsion angle by default for the fewest atom. Save this file in the PDBQT format.

Results

Obtained results shows that *Sennoside B* has greater energy complex of -9.05 kcal/mol in a result of Docking with Main protease of a coronavirus protein which is considered as best docking score when compared to all other compounds of *Cassia angustifolia* given in (Table 4). Commercially used drugs have lower energies as compared to the compounds of *Cassia angustifolia* such as *Hydroxychloroquine* gives the docking score of -5.2 kcal/mol. Interaction with the other compounds and commercially used drugs docking score is given in the (Table 5).

Ligand	Docking score
Sennoside B	-9.05
6-Hydroxymusicin	-6.5
Tinnevellin Glucoside	-6.3
sAloe-Emodin	-7.4
Kaempferol	-6.6

Table 4: Docking score of compounds with 6LU7

Ligand	Docking Score
Hydroxychloroquine	-5.2
Ribavirin	-6.3
Favipiravir	-5.7
Remdesivir	-6.0

Table 5: Docking results of commercially used drugs

By using Discovery studio visualize the 2D interaction between the compounds and the main peptidase protein of SARS-nCov2. (Table 8)

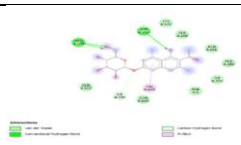
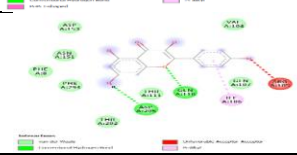
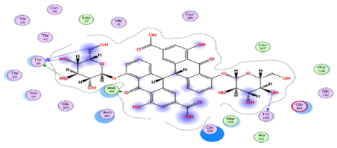
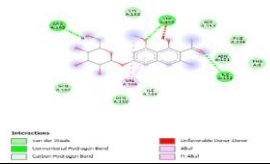
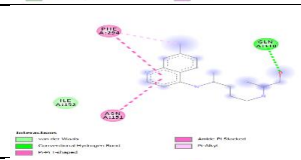
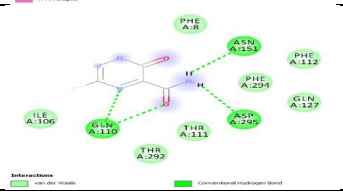
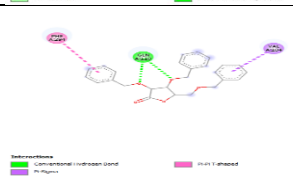
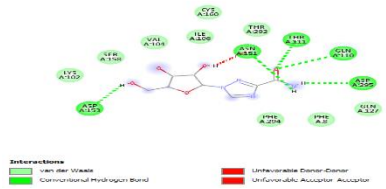
Ligand	2D Interaction	Type of Interaction
6-Hydroxymusicin		Two hydrogen interaction possible with: -Amino acid ARG A: 105 with the distance of 2.04. -Amino acid ASP A:153 with the distance of 2.88
Aloe - Emodin		Three Hydrogen interactions possible with -Amino acid THR A:111 with the distance of 1.89 -Amino acid SER A:158 with the distance of 2.13 -Amino acid LYS A:102 with the distance of 2.54
Kaempferol		Two hydrogen interaction possible with -Amino acid GLN A:110 with the distance of 2.57 -Amino acid ASP A:295 with the distance of 2.57
Sennoside B		There are non-perceptible interactions, only electrostatics (Van der Waals) interactions are perceptible.
Tinnevellin Glucoside		Three hydrogen interaction possible with -Amino acid ARG A:105 with the distance of 2.13 -Amino acid SER A:158 with the distance of 2.26 -Amino acid ILE A:152 with the distance of 3.07
Hydroxychloroquine		One hydrogen interaction possible with -Amino acid GLN A:110 with the distance of 2.69
Favipiravir		Three hydrogen interaction possible with -Amino acid GLN A:110 with the distance of 2.08 -Amino acid ASP A:295 With the distance of 2.39 -Amino acid ASN A:151 with the distance of 2.23
Remdesivir		Two hydrogen interactions possible with -Amino acid GLN A:110 with the distance of 2.92 and 2.14
Ribavirin		Two hydrogen interactions possible with -Amino acid GLN A:110 with the distance of 2.97 -Amino acid ASP A:295 with the distance of 2.38

Table 6: 2D Interactions of Compounds of *Cassia angustifolia* and commercial drugs used

Discussion

On 19 December, the outbreak of a respiratory disease spread in Wuhan, city of China. The spread of this disease occurred by a virus known as *SARS-nCov2* and within a month this disease was spread all over the world and on 11th march it was considered as Pandemic. A team of researchers and scientists strongly upheld that a new vaccine or a drug was crucial to fight against the

infection. Some of the herbs were also considered as potential drug agents. One of the herb *Cassia angustifolia* was chosen to study the inhibitory effect against *SARS-nCoV2*. Diverse compounds of *Cassia angustifolia* (*Sennoside B, 6-Hydroxymusicin, Tinnevellin Glucoside, Aloe-Emodin, and Kaempferol*) were selected according to their Lipinski's physiochemical parameter and their docking results were compared with different commercially used drugs such as *Hydroxychloroquine*, *Ribavirin*, *Favipiravir*, *and Remdesivir*. Docking results show that the compounds of *Cassia angustifolia*, *Sennoside B* - and *Aloe-emodin,* have the lowest binding energies as compared to the commercially used drugs *Ribavirin* and *Favipiravir*.

High throughput drug screening through molecular docking has been recognized as a key technique for in-silico therapeutic design. Our work is important because it can be compared to more comprehensive studies such as the Supercomputer based docking of SARS COV-2 viral spike protein with human ACE2 receptor carried out by the US department of energy. Having screened more than 8000 ligands, the top scoring Vina ligand had a score of -7.4 kcal/mol while Sennoside B in our study had a score of -9.05 kcal/mol. The results therefore show that high throughput screening of natural compounds could lead to more potent therapeutic options, validating the purpose and design of our study.

We conclude our discussion by making instance that the compounds of *Cassia angustifolia* are more compatible drug agents against the *SARS-nCov2* as compared to the scores obtained from the clinically used drugs. This hypothesis still needs more research to validate.

The main purpose of the current study is to use natural herbs as a potential drug agent against the main protease of the novel coronavirus (SARS-COV2) infection. Results obtained by molecular docking showed that Cassia angustifolia and its compounds Sennoside B and Aloe-emodin have the lowest binding energies when compared to the commercial drugs of Hydroxychloroquine and Favipiravir. Hence, we can consider that Cassia angustifolia having Sennoside B and Aloe-emodin may have the potential to act as an antiviral drug against this pandemic. However, further *in-vitro* and *in-vivo* studies are still needed to validate this hypothesis, postulated through this initial computer aided prediction of the aforementioned compounds as potential drug agents.

Competing Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' Contribution

(RS) envisaged the idea, involved in critical thinking, analysis of data, editing, proofread and correspondence with journal. (KA), (GA) and (AI) helped in data analysis, initial write-up and composing, (SZ) helped in understanding the statistics behind the used software and comparing their algorithms for better hits, (MZY) helped in critical thinking and proof reading the manuscript.

References

1. Singhal T. A review of coronavirus disease-2019 (COVID-19). The Indian Journal of Pediatrics, (2020); 1-6.
2. Li Y, Liu X, Guo L, Li J, Zhong D, et al. Traditional Chinese herbal medicine for treating novel coronavirus (COVID-19) pneumonia: protocol for a systematic review and meta-analysis. Systematic reviews, (2020); 91-6.
3. Ahmed SI, Hayat MQ, Tahir M, Mansoor Q, Ismail M, et al. Pharmacologically active flavonoids from the anticancer, antioxidant and antimicrobial extracts of Cassia angustifolia Vahl. BMC complementary and alternative medicine, (2016); 16(1): 460.
4. Osman N, Jambi E, Aseri N. Assessment of antidiabetic and antioxidant activities of Cassia angustifolia and Feoniculum vulgare in diabetic rats. International Journal of Pharmaceutical Research & Allied Sciences, (2017); 6(2).
5. Yuniarto A, Sukandar EY, Fidrianny I, Setiawan F, Ketut I. Antiobesity, Antidiabetic and Antioxidant Activities of Senna (Senna alexandrina Mill.) and Pomegranate (Punica granatum L.) Leaves Extracts and Its Fractions. International Journal of Pharmaceutical and Phytopharmacological Research (eIJPPR), (2018); 8(3): 18-24.
6. Ferner RE, Aronson JK (2020) Chloroquine and hydroxychloroquine in covid-19. British Medical Journal Publishing Group.
7. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, et al. Compassionate use of remdesivir for patients with severe Covid-19. (2020); 382(24): 2327-2336.
8. Wu Q, Wang Z, Fu M, Tang L, He Y, et al. Chemical constituents from the leaves of Cassia angustifolia. Zhong yao cai= Zhongyaocai= Journal of Chinese medicinal materials, (2007); 30(10): 1250-1252.
9. Al-Marzoqi AH, Hadi MY, Hameed IH. Determination of metabolites products by Cassia angustifolia and evaluate antimicobial activity. Journal of Pharmacognosy and Phytotherapy, (2016); 8(2): 25-48.
10. Lipinski CAJDDTT. Lead-and drug-like compounds: the rule-of-five revolution. (2004); 1(4): 337-341.
11. Pollastri MPJCpip. Overview on the Rule of Five. (2010); 49(1): 9.12. 11-19.12. 18.
12. Seeliger D, de Groot BLJJoc-amd. Ligand docking and binding site analysis with PyMOL and Autodock/Vina. (2010); 24(5): 417-422.