Molecular docking analysis of SARS-CoV-2 linked RNA dependent RNA polymerase (RdRp) with compounds from *Plectranthus amboinicus*

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Abstract:
It is of interest to document the molecular docking analysis of SARS-CoV-2 linked RNA dependent RNA polymerase (RdRp) with compounds from Plectranthus amboinicus. Hence, we report the binding features of rutin, Luteolin, Salvianolic acid A, Rosmarinic acid and p-Coumaric acid with the target protein SARS-CoV-2 linked RNA dependent RNA polymerase (RdRp) for further consideration.

Key words: SARS-CoV-2, RdRp, Plectranthus amboinicus, molecular docking

Background:
The new strain of coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome) is the infectious disease COVID-19 [1]. The structures of different SARS-CoV-2 protein / enzymes were solved. The structure data of RNA-dependent RNA polymerase (RdRp) and papain protease and key protease is relevant in drug discovery [2,3]. RdRp is the main enzyme that replicates the viral RNA genome and is it a promising drug target [3-4]. RdRp of the SARS-CoV-2 shares 96 per cent of the sequence identity with SARS-CoV and hence the compounds or medications that are efficient towards RdRp of SARS-CoV are considered to be effective against the novel CoV. Molecular docking analysis of known RdRp-inhibiting antivirals, other FDA-approved medications, and phytochemicals to repurpose SARS-CoV-2 is documented [5]. The use of conventional medicines as an adjuvant for the treatment of COVID-19 is known [6,7,8]. Therefore, it is of interest to document the molecular docking analysis of SARS-CoV-2 linked RNA dependent RNA polymerase (RdRp) with compounds from Plectranthus amboinicus.

Table 1: List of Selected compounds from Plectranthus amboinicus

| S.No | Compound Name                                      |
|------|----------------------------------------------------|
| 1    | 1,2-Benzenediol-4-(1,1 dimethylethyl)_CID_12290195 |
| 2    | 1-Epi-cubenol_CID_519857                          |
| 3    | 2-Phenyl ethyl tetrahydrofuran_519964912          |
| 4    | 3,7,11,15-Tetramethyl-2-hexadecan-1-ol_CID_5366244 |
| 5    | 5,7,8,9-Trihydroxyflavone (apigenin)_CID_5280443   |
| 6    | 5,6-Dihydroxy-3,7-dimethoxy flavone_CID_5318869    |
| 7    | Aromadendrene_CID_91354                           |
| 8    | Carvacrol_CID_10364                               |
| 9    | Chavicol_CID_68148                                |
| 10   | Chrysoeriol_CID_5280666                            |
| 11   | Cirsimaritin_CID_188323                            |
| 12   | Durohydroquinine_CID_136346                        |
| 13   | Eriodictyol_CID_440735                             |
| 14   | Eugenol_CID_3314                                  |
| 15   | Geraniol_CID_637566                               |
| 16   | Germacrene D_CID_521569                           |
| 17   | Luteolin_CID_5280445                              |
| 18   | p-Coumaric acid_CID_637542                        |
| 19   | Rosmarinic acid_CID_5281792                       |
| 20   | Rutin_CID_5280805                                 |
| 21   | Salvianolic acid A_CID_5281793                     |
| 22   | Salvigenin_CID_161271                             |
| 23   | Spathulenol_CID_92231                              |
| 24   | Thymoquinone_CID_10281                            |

Table 2: Molecular docking results obtained from PyRx

| S.No | Compound Name          | Binding Energy Kcal/mol | Hydrogen bond interaction | Length |
|------|------------------------|-------------------------|---------------------------|--------|
| 1    | Rutin_CID_5280805      | -8.1                    | THR-556                   | 2.3    |
| 2    | Luteolin_CID_5280445   | -7.5                    | THR-594                   | 2.6    |
| 3    | Salvianolic acid A_CID_5281793 | -7.2         | ARG-555                   | 2.1    |
| 4    | Rosmarinic acid_CID_5281792 | -6.8       | ARG-533                   | 2.2    |
| 5    | P-Coumaric acid_CID_637542 | -6.7       | THR-545                   | 2.1    |

Materials and Methods:
Protein Preparation:
The three-dimensional structure of the protein RdRp of SARS-CoV-2 (PDB ID: 6M7I) was downloaded from the Protein Data Bank (www.rcsb.org/pdb). This structure is solved [10] with 2.9 Å resolution using electron microscopy. Three non-structured proteins (NSPs) such as one NSP7 and two NSP8 are involved in the structure as cofactors. NSP12, which is RdRp, is chain A and consists 851 amino acids. All water molecules, ions, and ligands were separated from the protein molecule using the PyMOL software. The hydrogen atoms were applied to the receptor molecule using the AutoDock Vina software’s MG Tools [11] and saved in the Pdbqt format.
Compound preparation:
Thirty compounds from the *Plectranthus amboinicus* plant were gleaned from literature. The compound structures were downloaded in .sdf format from the database of PubChem compounds (www.pubchem.ncbi.nlm.nih.gov/). All the compounds were translated to .Pdb format by using the online smiles converter. The energy of all ligands was minimized and translated to the PDBQT file format.

Molecular docking and interaction analysis:
The grid box around the binding pocket is positioned using a standard protocol [12]. PyRx has been used to screen the ligand files against the protein [13]. The interactions between the targeted protein and the ligands were analysed using the Pymol Molecular Visualization Tools [14].

Drug-likeness prediction:
The Lipinski filters (http://www.scfbio-iitd.res.in / software / drugdesign / lipinski.jsp) were used to measure the drug likeness of the compounds from the docking calculation. Four of the five parameters defined for drug likeness are molecular mass, cLogP, hydrogen donor and acceptor and molar refractive index [14].

Results and Discussion:
It is of interest to document the molecular docking analysis of SARS-CoV-2 linked RNA dependent RNA polymerase (RdRp) with compounds (Table 1) from *Plectranthus amboinicus*. Hence, we report the binding features of rutin, Luteolin, Salvianolic acid A, Rosmarinic acid and p-Coumaric acid with the target protein SARS-CoV-2 linked RNA dependent RNA polymerase (RdRp) for further consideration (Table 2). The interactions between the targeted protein and the ligands were analysed using the Pymol Molecular Visualization Tools as shown in Figure 1.

**Figure 1:** Molecular docking data of SARS-CoV-2 RdRp with (a) Rutin; (b) Luteolin; (c) Salvianolic acid A; (d) Rosmarinic acid and (e) p-Coumaric acid. Proteins are shown in ribbon and compounds are shown with stick representations.
Table 3: The drug likeness properties of selected compounds

| Compound name         | Molecular Mass | Hydrogen bond donor | Hydrogen bond donor | LogP | Molar Refractivity |
|-----------------------|----------------|---------------------|---------------------|------|-------------------|
| Rutin                 | 610            | 10                  | 16                  | -1.8788 | 137.495483       |
| Luteolin              | 280            | 4                   | 6                   | -1.66883 | 61.04194          |
| Salvianolic acid      | 494            | 7                   | 10                  | 3.3429 | 128.466552       |
| Rosmarinic acid       | 360            | 5                   | 8                   | 1.7633 | 89.796974        |
| p-Coumaric acid       | 164            | 2                   | 4                   | 1.49   | 44.776596        |

- *Molecular mass less than 500 Dalton; - *Less than 5 hydrogen bond donors; - *Less than 10 hydrogen bond acceptors; - *High lipophilicity (expressed as LogP less than 5)

- *Molar refractivity should be between 40-130

Conclusion:
We report the binding features of rutin, Luteolin, Salvianolic acid A, Rosmarinic acid and p-Coumaric acid with the target protein SARS-CoV-2 linked RNA dependent RNA polymerase (RdRp) for further consideration.

References:
[1] Aanouz I et al. J Biomol Struct Dyn. 2020 6:1. [PMID: 32306860].
[2] Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. Life Sci. 2020 248:117477. [PMID: 32119961].
[3] Li G and De Clercq E Nat Rev Drug Discov. 2020 19:149. [PMID: 32176666].
[4] Morse JS et al. ChemBioChem. 2020 2:730. [PMID: 32022370].
[5] Wu C et al. Acta Pharm Sin B. 2020 10:766. [PMID: 32292689].
[6] Yang Y et al. Int J Biol Sci. 2020 16:1708. [PMID: 32226288].
[7] Liu M et al. Pharmacol Res. 2020 158:104896. [PMID: 32438037].
[8] Singh RH et al. Biogerontology. 2008 9:369. [PMID: 18931935].
[9] Alasbahi RH and Melzig MF. Planta Med. 2010 76:653. [PMID: 20178070].
[10] Gao Y et al. Biometrical. 2020.
[11] Trott O et al. J Comput Chem. 2010 31:455. [PMID: 19499576].
[12] Lim SV et al. BMC Bioinformatics. 2011 12:524. [PMID: 22373153].
[13] Dallakyan S and Olson AJ, Methods Mol Biol. 2015 1263:243. [PMID: 25618350].
[14] Lipskis CA. Drug Discov Today Technol. 2004 1:337. [PMID: 24981612].