Plant Derived Compound- Luteolin Promising Role against SARS-CoV-2 Protein

Hezinglila Grace, V. Mathivanan, Kevizano Jacinta Zashumo and D. Leelavathi

Research Journal of Agricultural Sciences
An International Journal

P- ISSN: 0976-1675
E- ISSN: 2249-4538

Volume: 13
Issue: 05

Res. Jr. of Agril. Sci. (2022) 13: 1449–1453

CARAS

Res. Jr. of Agril. Sci. (Sep-Oct 2022)
13(5): 1449–1453

ISSN: 0976-1675 (P)
ISSN: 2249-4538 (E)

www.rjas.org

Full Length Research Article

Plant Derived Compound- *Luteolin* Promising Role against SARS-CoV-2 Protein

Hezinglila Grace*[1], V. Mathivanan[2], Kevizano Jacinta Zashumo[3] and D. Leelavathi[4]

Received: 28 Jun 2022 | Revised accepted: 30 Aug 2022 | Published online: 21 Sep 2022

A B S T R A C T

The present study incorporated plant derived compound to intervene the effect caused by SARS-CoV-2 protein using *in silico* techniques. *Luteolin* (Lut) is a significant flavonoid generated from plants that is found in a variety of edible herbs and vegetables possessing anti-inflammatory, anti-cancer, anti-oxidant, anti-apoptotic, and neurotrophic activities. In this study, the bioactivity of *Luteolin* derived from vegetable is studied using advanced Cheminformatics tools. Next, the SARS-CoV-2 protein sequence is retrieved and applied to an automated docking server in order to identify the molecular interaction between SARS-CoV-2 protein sequence and *Luteolin*. The results obtained from docking showed good affinity between *Luteolin* and SARS-CoV-2 protein sequence. All the results obtained were analyzed in 3D form using 3D visualization tools. In conclusion, the molecular dynamic studies clearly revealed that the identified compound *Luteolin* is a potential inhibitor for the selected target protein sequence of SARS-CoV-2.

***Key words*:** *Luteolin*, SARS-CoV-2, Swiss Similarity, HDOCK, Discovery studio

The World Health Organization (WHO) declared an unexpected pandemic outbreak of newly identified diseases, severe acute respiratory disease syndrome corona virus 2(SARS-CoV-2) in December 2019. SARSCoV-2 can cause serious side effects, such as septic shock and multiple organ failure, which can be fatal, especially in high-risk individuals, such as those that are immunocompromised and have underlying illnesses such malignancies, diabetes, cardiovascular disease, and chronic respiratory disorders [1]. The current COVID-19 outbreak was caused by the highly contagious SARS-CoV-2 bacterium, which has been linked to an unusually high number of infections and fatalities worldwide. The major problem confronting our global healthcare system is the paucity of therapeutic interventions for COVID-19 [2]. The SARS-CoV-2 spike (S) protein is made up of two subunits, S1 and S2, and is essential for receptor identification and cell membrane fusion. The host receptor Angiotensin-converting enzyme 2 (ACE2) is recognized and bound by the receptor-binding domain of the S1 subunit, while the two-heptad repeat domain of the S2 subunit facilitates the fusing of the viral cell membrane [3]. For viral entrance and subsequent replication, interactions between the SARS-CoV-2 receptor binding domain and the Angiotensin-converting enzyme 2 (ACE2) are essential. Finding a suitable small-molecule drug that can bind and disrupt regulatory processes has remained challenging due to the broad and featureless contact surfaces of both proteins [4]. Researchers have frequently concentrated on ways to interfere with the functional proteins on the virus's active binding site, the spike that binds to human cells, in the quest to develop viable treatments for SARS-CoV-2, the virus that causes COVID-19 [5].

The development of novel drug delivery technologies for the encapsulation of plant active metabolites, including organic, inorganic, and hybrid nanoparticles, has made remarkable progress over the past few decades [6]. There is always a need for new and innovative medicines. Despite improvements in synthetic chemistry, nature continues to be a valuable source for the development of new drugs [7]. *Luteolin* (Lut) is a significant flavonoid generated from plants that is found in a variety of edible herbs and vegetables. Studies using both human and animal models have demonstrated that *Lut* possesses a variety of pharmacological effects, including anti-inflammatory, anti-cancer, anti-oxidant, anti-apoptotic, and neurotrophic activities [8-9]. According to several studies, *Luteolin*'s protective properties are explained by its ability to prevent 2003-emerging SARS-CoV from entering human receptors and fusing with them. Therefore, regular consumption of foods that have a suitable quantity of *Lut* in our diets may be beneficial in preventing both the SARS-CoV-2 infection and the ensuing symptoms in COVID-19 patients [10]. Flavonoids and their derivatives may represent potential compounds to be investigated in upcoming clinical trials to bolster the

* **Hezinglila Grace**
✉ hezinglilaanar@gmail.com

[1, 3-4] P. G. and Research Department of Zoology, Ethiraj College for women, Chennai - 600 008, Tamil Nadu, India

[2] P. G. and Research Department of Zoology, Dr. Ambedkar Government Arts College, Vysarpadi, Chennai - 600 039, Tamil Nadu, India

pharmacological library against corona virus infections owing to their pleiotropic effects and lack of systemic toxicity [11].

Our rate and possibility of discovering therapeutic metabolites have increased as a result of recent developments in bioinformatics and *in silico* screening [7]. Drug development can be conducted more efficient and low expense by using computational methods to discover compounds early on that exhibit both favourable and unwanted features. To better understand the molecular mechanisms of small compounds, computational techniques like molecular docking, molecular dynamics (MD), and enhanced sampling methodologies are frequently utilized in drug design, discovery, and development [12]. A complete understanding of drug release processes, material qualities, formulation/device factors, and their interactions with drug release profiles are necessary for designing improved drug delivery systems. Quantitatively achieving the objective goals is challenging without the proper computational tools. As a result, computational techniques for dosage form design have been created [13]. The present study included a range of computational tools owing to the benefits of computational methods in drug design.

MATERIALS AND METHODS

Ligand-based virtual screening

Virtual screening is one of the most used computer methods in pharmacological research. These web tools and databases enable computational professionals as well as wet-lab researchers to effectively incorporate a wide variety of data sources and cutting-edge drug design techniques into the routine research operations [14]. Using the Swiss Similarity web tool [15] the canonical SMILES of *Luteolin* molecule that were retrieved from NCBI PubChem (https://pubchem.ncbi.nlm.nih.gov/) were run for virtual similarity screening.

Molecular drug docking studies

HDOCK (http://hdock.phys.hust.edu.cn/) server was employed for docking *Luteolin* bioactive compound and Spike glycoprotein of SARS-CoV-2. The HDOCK server is a highly integrated set of tools for robust and quick protein-protein docking that includes homology search, template-based modelling, structure prediction, macromolecular docking, biological information incorporation, and task administration [16]. Several biological processes depend critically on interactions between proteins-proteins and DNA/RNA. It is useful to determine the intricate structures of these interactions, and molecular docking has been crucial in this process [17].

Visualization of the docked compound

After molecular drug docking studies of *Luteolin* bioactive compound and Spike glycoprotein of SARS-CoV-2, visualization of their 3D structure was done using Discovery Studio.

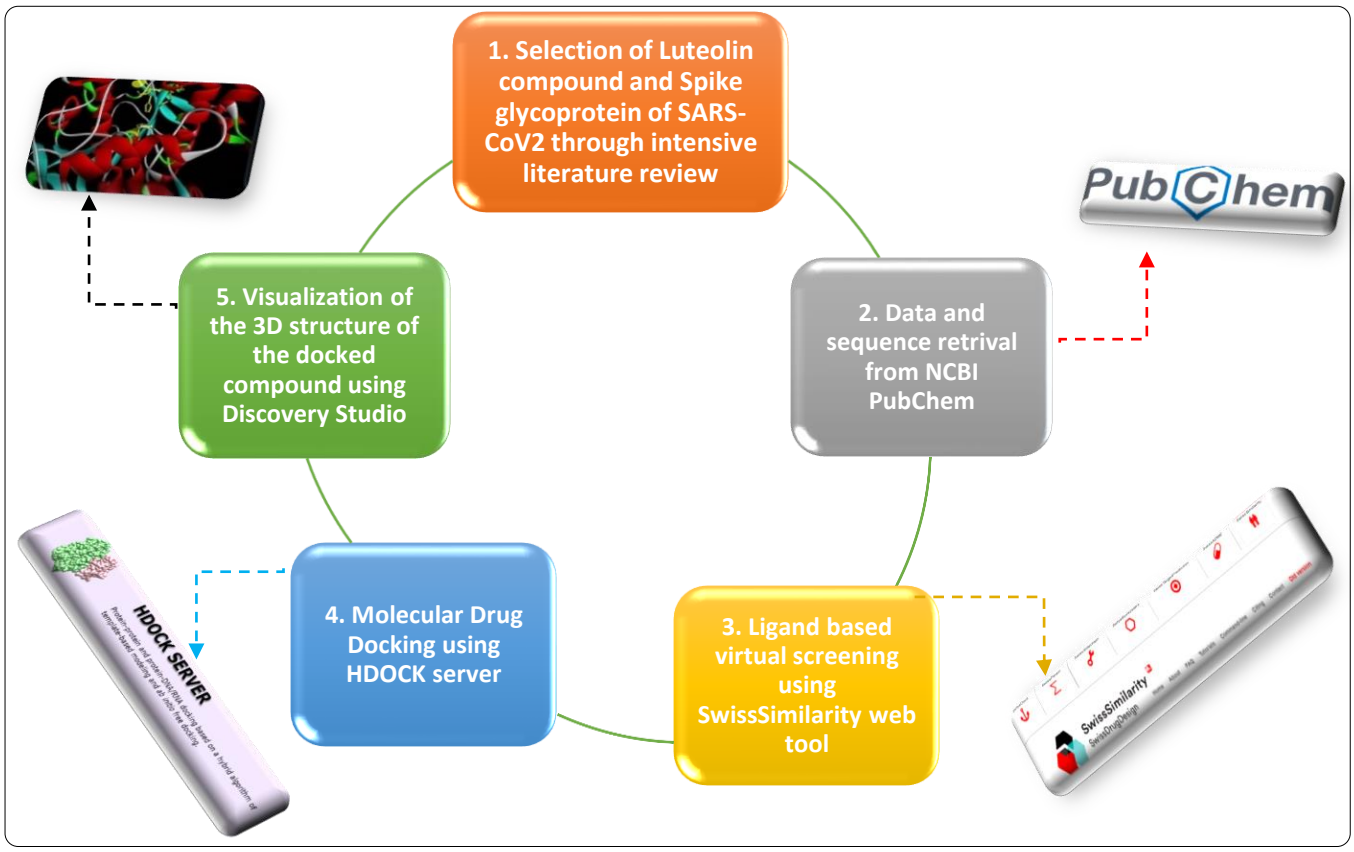

Fig1 Work sequence of the present study

RESULTS AND DISCUSSION

An interface for ligand-based virtual screening of chemical libraries is provided by the online programme Swiss Similarity (http://www.swisssimilarity.ch), which enables users to look for compounds that are similar to a query molecule [18]. The fingerprinting technique chosen for the molecular representation, however, might have a substantial impact on the similarity values for a given set of compounds [18-19]. As seen in (Fig 4-6), the output of the query compound is shown with calculated similarity and scores. All similarity scores, which were determined using various methods, ranged from 0 for completely different compounds to 1 for identical ones. According to the similarity principle, the Swiss Similarity output list of molecules should be enriched in compounds that are anticipated to have comparable protein targets to the query molecule and can, as a result, be procured and experimentally examined first [19]. For simple visualization, output

compounds are displayed in the web browser along with their calculated similarity to the query compound [17]. Swiss Similarity provides many compound libraries for screening, including licensed drugs, identified bioactive molecules, readily available commercial compounds, and compounds that can be produced synthetically. Swiss Similarity offers a variety of 2D and 3D molecular fingerprints that encode compounds in various digital forms that may be used to calculate molecular similarity [20]. Molecular Drug docking studies for *Luteolin* bioactive compound and Spike glycoprotein of SARS-CoV-2 employing HDOCK server illustrating drug binding affinities of Ligand and Receptor as seen in (Fig 7) and the docked compound is viewed using Discovery Studio as seen in (Fig 8-10). Docking is a sampling and scoring process when two distinct structures are given, docking seeks to sample every potential binding mode between them. The sampled binding modes are then ranked during and/or after sampling using a scoring algorithm [17]. The results obtained clearly showed that the intramolecular electrostatic force is based on the binding affinity between the ligand-receptor complexes. (Table 1) clearly demonstrates the ligand and receptor interface amino acid residues which shows that the selected drug compound can act as an efficient inhibitor for the target corona virus protein.

Table 1 Receptor- Ligand interface residue

Receptor interface residue(s)	Ligand interface residue(s)	Receptor- Ligand interface residue pair (s)
PHE 338A 2.995	0 2.499	338A - 0 2.995
PHE 342A 3.128		342A - 0 3.128
TYR 365A 2.499		365A - 0 2.499
LEU 368A 2.999		368A - 0 2.999
TYR 369A 3.154		369A - 0 3.154
ASN 370A 3.539		370A - 0 3.539
SER 371A 3.490		371A - 0 3.490
ALA 372A 2.910		372A - 0 2.910
SER 373A 4.948		373A - 0 4.948
PHE 374A 2.839		374A - 0 2.839
PHE 377A 2.918		377A - 0 2.918
PHE 392A 3.530		392A - 0 3.530
ILE 434A 3.044		434A - 0 3.044
LEU 513A 3.168		513A - 0 3.168

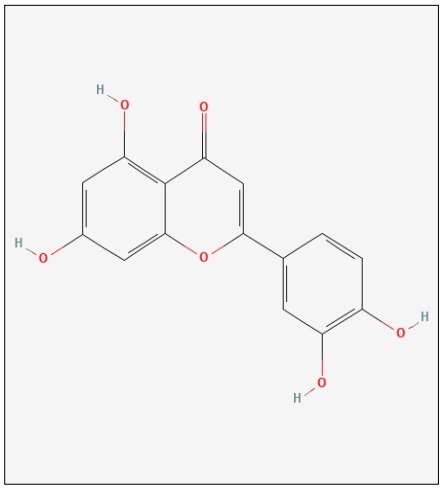

Fig 2 Basic skeleton structure of *Luteolin* compound

>pdb|7TF5|A Chain A, Spike glycoprotein
MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHV
SGTNGTKRFDNPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPF
LGVYYHKNNKSWMKSEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPI
NLVRDLPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYN
ENGTITDAVDCALDPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRFASV
YAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVRQIAPGQTGKIAD
YNYKLPDDFTGCVIAWNSNNLDSKVGGNYNYRYRLFRKSNLKPFERDISTEIYQAGSTPCNGVQGFNCYF
PLQSYGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFL
PFQQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSNQVAVLYQGVNCTEVPVAIHADQLT
PTWRVYSTGSNVFQTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSRGSASSVASQSIIAYTMSLG
AENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECSNLLLQYGSFCTQLNRALTGI
AVEQDKNTQEVFAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSPIEDLLFNKVTLADAGFIKQYGDC
LGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGPALQIPFPMQMAYRFNGIG
VTQNVLYENQKLIANQFNSAIGKIQDSLSSTPSALGKLQDVVNQNAQALNTLVKQLSSNFGAISSVLNDI
LSRLDPPEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLM
SFPQSAPHGVVFLHVTYVPAHEKNFTTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNT
FVSGNCDVVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVA
KNLNESLIDLQELGKYEQGSGYIPEAPRDGQAYVRKDGEWVLLSTFLGRSLEVLFQGPGHHHHHHHHSAW
SHPQFEKGGGSGGGGSGGSAWSHPQFEK

Fig 3 FASTA sequence of Spike glycoprotein of SARS-CoV2

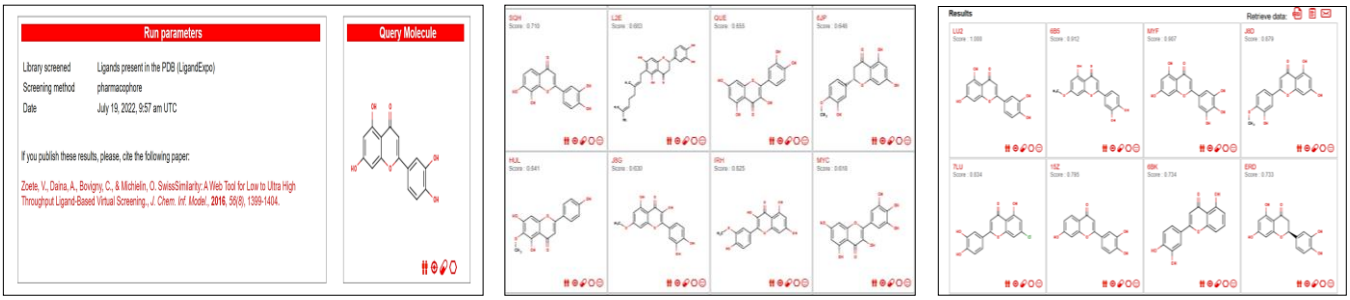

Fig 4 Bioactive compound- *Luteolin* screened for similarity using Pharmacophore (2D) sscreening method

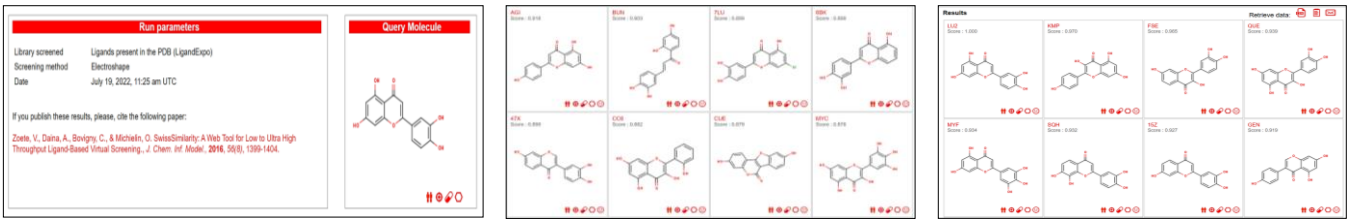

Fig 5 Bioactive compound –*Luteolin* screened for similarity using Electroshape (3D) screening method

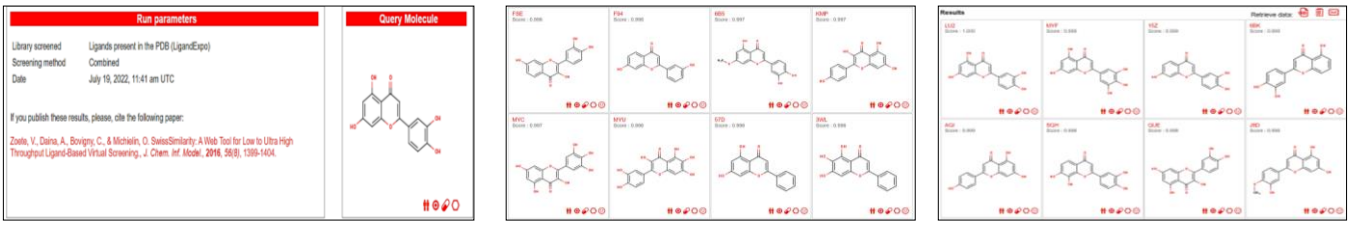

Fig 6 Bioactive compound - *Luteolin* screened for similarity using Combined (2D&3D) screening method

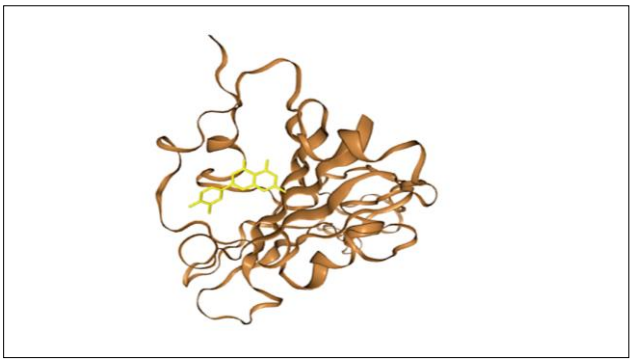

Fig 7 Molecular docking studies of *Luteolin* compound and Spike glycoprotein of SARS-CoV-2 employing HDOCK server illustrating drug binding affinities of Ligand and Receptor. Ligand (*Luteolin* compound) indicated in yellow colour and Receptor (Spike glycoprotein) of sars-cov-2 indicated in brown colour

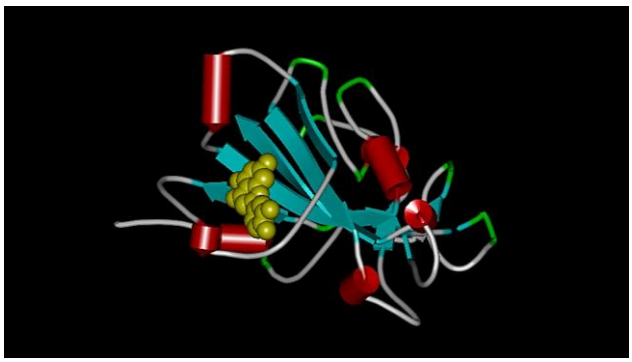

Fig 8 Schematic model view of *Luteolin* compound and spike glycoprotein of SARS-CoV-2 viewed under visualization tool-Discovery studio. Red cylinder like represents Alpha helix, white thread like represents coiled region, Blue arrow like represents Beta sheet, and Green represent turns

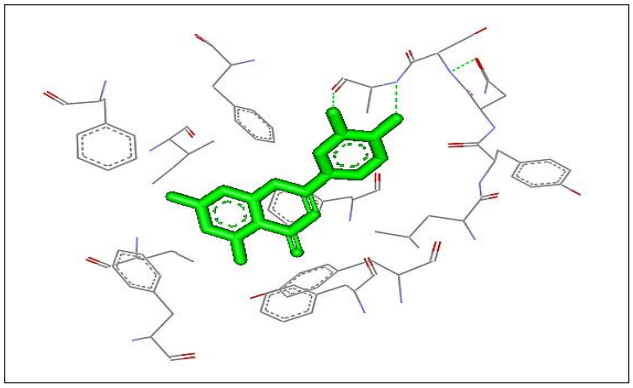

Fig 9 3D structure of *Luteolin* compound and spike glycoprotein of SARS-CoV-2 illustrating the Ligand interaction viewed with Discovery studio

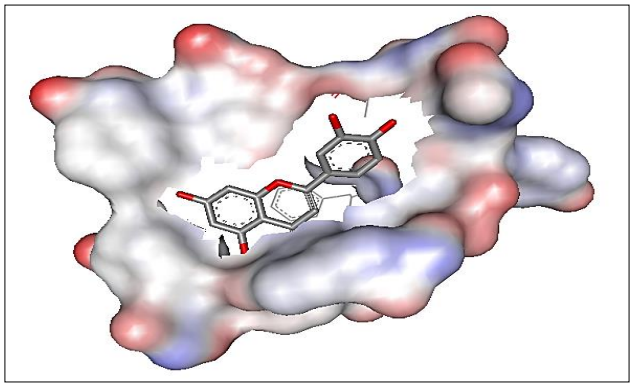

Fig 10 3D structure of *Luteolin* compound and spike glycoprotein of SARS-CoV-2 illustrating Surface around Ligand viewed with Discovery studio

CONCLUSION

A fatal corona virus (CoV) entered human society for the third time since the turn of the millennium, causing a global healthcare catastrophe that overwhelmed the system and had an impact on the globe economy. From this research investigation, we conclude that *Luteolin* efficiently inhibits SARS-CoV-2 protein. The results obtained from this study play a major role in the field of current viral informatics studies.

LITERATURE CITED

1. Alzaabi MM, Hamdy R, Ashmawy NS, Hamoda AM, Alkhayat F, Khademi NN, Al Joud SMA, El-Keblawy AA, Soliman SSM. 2022. Flavonoids are promising safe therapy against COVID-19. *Phytochemistry Reviews* 21(1): 291-312.
2. Shawan MMAK, Halder SK, Hasan MA. 2021. Luteolin and abyssinone II as potential inhibitors of SARS-CoV-2: an in silico molecular modeling approach in battling the COVID-19 outbreak. *Bull. Natl. Res. Cent.* 45(1): 27.

3. Huang Y, Yang C, Xu XF. 2020. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. *Acta Pharmacol. Sin*. 41: 1141-1149.
4. Alvarado W, Perez-Lemus GR, Menéndez CA, Byléhn F, de Pablo JJ. 2022. Molecular characterization of COVID-19 therapeutics : luteolin as an allosteric modulator of the spike protein of SARS-CoV-2 Check for updates. *Mol. Syst. Des. Eng.* 7: 58-66.
5. Alvarado W, Perez-Lemus GR, Menendez CA, Bylehn F, de-Pablo JJ. 2022. Molecular characterization of COVID-19 therapeutics: luteolin as an allosteric modulator of the spike protein of SARS-CoV-2. *Molecular Systems and Design Engineering* 7: 123-131.
6. Rahman HS, Othman HH, Hammadi NI. 2020. Novel drug delivery systems for loading of natural plant extracts and their biomedical applications. *Int. Jr. Nanomedicine* 15: 2439-2483.
7. Anwar N, Teo YK, Tan JBL. 2019. The role of plant metabolites in drug discovery: Current challenges and future perspectives. *In*: (Eds) Swamy M., Akhtar M. Natural Bio-active Compounds. *Springer*, Singapore. https://doi.org/10.1007/978-981-13-7205-6_2
8. Miean KH, Mohamed S. 2001. Flavonoid (myricetin, quercetin, kaempferol, luteolin, and apigenin) content of edible tropical plants. *Jr. Agric. Food Chemistry* 49(6): 3106-3112.
9. Ansari WA, Ahamad T, Khan MA. 2020. Luteolin: A dietary molecule as potential anti-COVID-19 Agent, 16 June, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-35368/v1]
10. Russo M, Moccia S, Spagnuolo C, Tedesco I, Russo GL. 2020. Roles of flavonoids against coronavirus infection. *Chem. Biol. Interact* 328: 109211. doi:10.1016/j.cbi.2020.109211
11. Shadrack DM, Deogratias G, Kiruri LW, Onoka I, Vianney JM, Swai H, Nyandoro SS. 2021. Luteolin: a blocker of SARS-CoV-2 cell entry based on relaxed complex scheme, molecular dynamics simulation, and metadynamics. *Jr. Mol. Model*. 8: 27(8): 221.
12. Zhou Y, Wu XY. 2013. Application of computational tools in the design of controlled drug delivery systems. 10.13140/RG.2.1.2932.6564.
13. Singh N, Chaput L, Villoutreix BO. 2021. Virtual screening web servers: designing chemical probes and drug candidates in the cyberspace. *Briefings in Bioinformatics* 22(2): 1790-1818. https://doi.org/10.1093/bib/bbaa034
14. Zoete V, Daina A, Bovigny C, Michielin O. 2016. SwissSimilarity: A web tool for low to ultra-high throughput ligand-based virtual screening. *Jr. Chem. Inf. Model*. 56(8): 1399-1404.
15. Kim S, Thiessen PA, Bolton EE, Chen J, Fu Gindulyte A, Han L, He J, He S,Shoemaker BA, Wang J, Yu B, Zhang J, Bryant SH. 2016. PubChem substance and compound databases. *Nucleic Acids Res.* 4: 44(D1): D1202-13. doi: 10.1093/nar/gkv951
16. Yan Y, Tao H, He J. 2020. The HDOCK server for integrated protein–protein docking. *Nat. Protoc*. 15: 1829-1852. https://doi.org/10.1038/s41596-020-0312-x
17. Yan Y, Zhang D, Zhou P, Li B, Huang SY. 2017. HDOCK: A web server for protein-protein and protein-DNA/RNA docking based on a hybrid strategy. *Nucleic Acids Res*. 45(W1): W365-W373. doi:10.1093/nar/gkx407
18. Bragina ME, Daina A, Perez MAS, Michielin O, Zoete V. 2022. The SwissSimilarity 2021 Web Tool: Novel chemical libraries and additional methods for an enhanced ligand-based virtual screening experience. *Int. Jr. Mol. Science* 23(2): 811.
19. Daina A, Zoete V. 2019. Application of the SwissDrugDesign Online Resources in Virtual Screening. *Int. Jr. Mol. Science* 20(18): 4612
20. Cereto-Massagué A, Ojeda MJ, Valls C, Mulero M, Garcia-Vallvé S, Pujadas G. 2015. Molecular fingerprint similarity search in virtual screening. *Methods* 71: 58-63.