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Potential of Luteolin Against the SARS CoV2 Main Protease (M^{Pro}): A Molecular Docking

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ABSTRACT

COVID-19 or SARS CoV2 have caused a devastation situation in the world. People are dying at a rapid rate while scientists and researchers are facing problems in designing a virus against this disease. Many FDA approved drugs have been prescribed but they are not that effective. There is an urgent need for a vaccine with no side effects to cure this disease permanently. Nature had a hidden treasure of medicinal plants that can help the humans in eradicating this disease, one of them is Luteolin. It has shown anti-inflammatory, anti-cancer properties and have been previously used against other homologous strains of the virus existing previously. It is our hope to design a proper vaccine or drug against to overcome this pandemic situation. The current research is based on the in-silico studies of Luteolin and SARS CoV2 main protease to display potential of Luteolin as potential therapy against COVID-19. The results of present study form a basis of further experiments to examine Luteolin as antiviral compound.

KEY WORDS: ATOMIC CONTACT ENERGY (ACE), COVID-19, GLOBAL ENERGY, FLAVANOID, LUTEOLIN, SARS COV2 M^{PRO}.

INTRODUCTION

In 2020 world is facing a pandemic named as COVID-19 or Corona Virus Disease 2019. This disease has already killed a million of people and is still on loose to kill more. Coronavirus strain identified as Severe Acute Respiratory Disorder Corona Virus 2 (SARS CoV2) is help responsible for this pandemic. Today, 21 October 2020, there are total 41.5M cases worldwide and increasing every day (Figure 1). Many researches are still trying to find the compound that can inhibit this virus(Worldometer (2020), WHO (2020)).

As shown in Figure 2, Main target is to stop the interaction of viral protein and human receptors, it was found out that SARS CoV2 Spike protein binds to the ACE-2 receptors present on human cell. This suggests that blocking the ACE-2 receptors in humans can reduce the chances of infecting a healthy person. But problem arises in the patients who are already infected, for them SARS CoV2 Main protease (MPro) is the target. MProor 3CLPro is best characterized as the target to discover a drug or vaccine against SARS CoV2. Main protease with the papain-like proteases is responsible for handling out the polyproteins that are translated by Viral RNA(L. Zhang (2020), U. Umesh (2020).

Figure 1: Total Cases World Wide (Worldometer et. al. (2020).

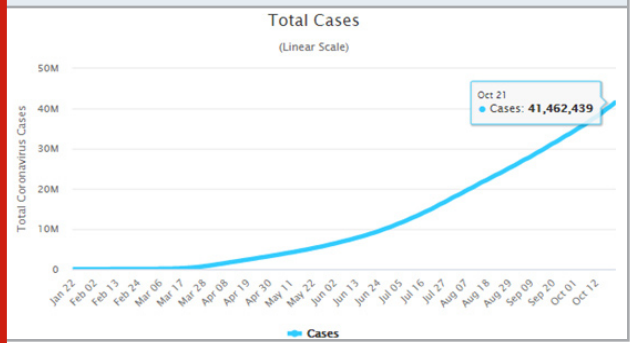

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Figure 2: Overview of Practice to inhibit SARS CoV2(Setiyawan et. al. (2020)

Our nature if full of medicinal plants and herbs, one of them is Luteolin (Lut). It occurs naturally in many herbs, vegetables and fruits which can be consumed. Besides it is found n many natural products but its bioavailability is very low calculated to 4.10% in 50mg/kg. Luteolin or Lut is well known for its various properties like anti-inflammatory, anticancer, antioxidant and many other pharmacological properties. Based on the literature survey it was found out that Lut can be a bioactive compound that can inhibit the COVID-19. Few studies showed that Lut inhibited the entry of virus and further inhibiting the fusion of virus with human receptor in previous SARS CoV which emerged in China, 2003. Having a daily diet full of Lut can help us to inhibit or decrease the chances of having us infected with COVID-19. Present study will be about discussing the molecular docking studies of Lut with SARS CoV2 Main Protease(W A. Ansari (2020), P. Shree (2020).

Literature Review: Pandey, Preeti, et al. stated in a research about the binding energy of different phytochemicals with the SARS CoV2 spike protein. They found that Luteolin had a binding energy of -8.2kcal/mol on the S2 domain of Spike protein. They concluded in their research that Lipinski's Rule is satisfied and the compounds they selected can be the new anti-viral drug against the COVID-19. They didn't showed the binding energy of Luteolin on Main protease of SARS CoV2. In present study researcher will be discussing the in-silico studies of Luteolin on SARS CoV2 MPro.(P. Pandey et. al. (2020). Yu, Ran, et al. discussed about the computational studies done on the structural proteins of SARS CoV2 and phytochemicals. They used AutoDockVina to calculate the binding energies.

They concluded in their research that Luteolin have low binding energy with the corona virus which suggests that it might have strong anti-viral activity. They didn't discussed about the bonds formed, and the distance between the bonds. In present study, researcher will be discussing about the Binding energy, Bonds formed, distance between bonds and Atomic Contact Energy (ACE)(R. Yu et. al. (2020). Ansari, Waseem Ahmad, et al. in a research article discussed that Luteolin was interacting at the active sites of Spike protein and was forming hydrogen and hydrophobic bonds. They also calculated that Lut has a strong binding energy of -9.37kcal/mol. They concluded Luteolin as the most stable docked structure. They didn't discussed about the Distance between the bonds and ACE. Present research will be discussing the bond distance and other parameters(W. A. Ansari et. al. (2020).

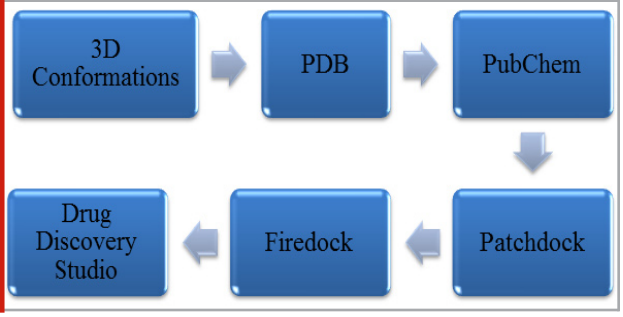
COVID-19 is increasing at a rapid rate yet no medicine or vaccine has been discovered to cure or to stop the spread of this disease. Many Food and Drug Administration (FDA) approved drugs are being used to treat the patients that are having the infection but these medicines are not that much effective and there is a need for the better treatment for the welfare of the world. Natural products have always helped the world to counter the major problems and nature hides many secrets to overcome many life threatening disease. This research is a step to find out of the nature's gift to humans, Luteolin is a flavanoid that is found in many edible vegetable, herbs and even in fruits. This phyto-compound have previously helped in China to inhibit the other strain of corona virus that is SARS CoV This current research is about the in-silico studies done to study the interaction between Lut and SARS CoV2. This research will help researchers in their in-vitro studies.

Research Questions: What is the effect of naturally occuring Luteolin on SARS CoV2 Main protease?

METHODOLOGY

Design: Three dimensional files of ligand and receptor were downloaded from the web servers. Protein Data Bank (PDB) was accessed for Main protease and PubChem was accessed for luteolin. After downloading and formatting the files in .pdb format with the help of Open Babel they were subject to docking with the help of a online docking tool PatchDock. PatchDock provides the 3D conformations regarding the docked complex. Top 10 docked complex were further analysed using firedock, which provides the Gibbs free energy or ΔG. This energy is same as the binding energy. Top 3 docked models with least ΔG were then visualised using the BOVIA drug discovery studio and bonds formed and distance between the bonds were calculated (Figure 3).

Figure 3: Flow Chart representing the protocol



Sample: 3D structure files were downloaded from the RCSB PDB for Main Protease and PubChem for Luteolin. In Figure 4, Quaternary structure of protein is shown where red spirals are representing the α-helices and the cyan coloured ribbons are the β-plated sheets of the SARS Cov2 Main Protease. In Figure 5, a 3D ball in stick model of the ligand which is Luteolin is represented, the big black balls are representing the carbons, the red balls are for oxygen and

the small white balls are hydrogen. A single stick between the balls represents the single bond while the double sticks represent the double bonds.

Figure 4: Quaternary Structure of SARS CoV2 Main Protease

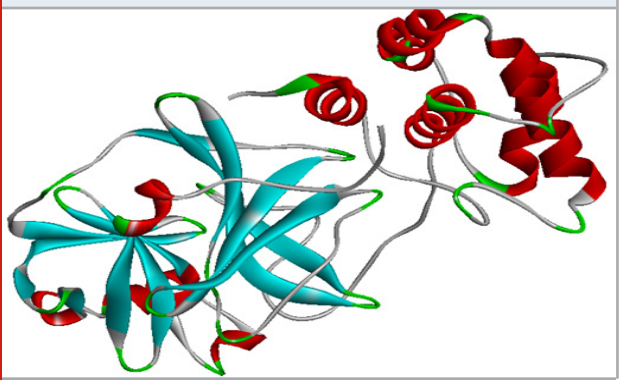
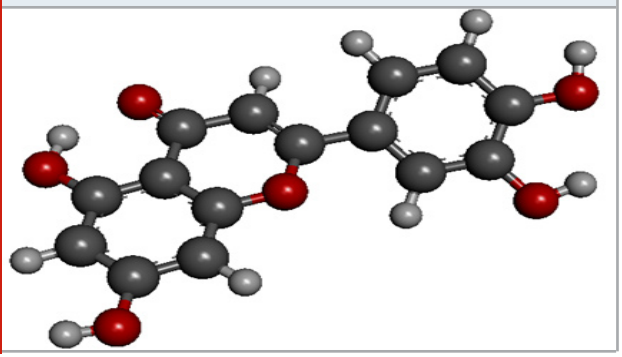


Figure 5: 3D Ball and Stick Structure of Luteolin

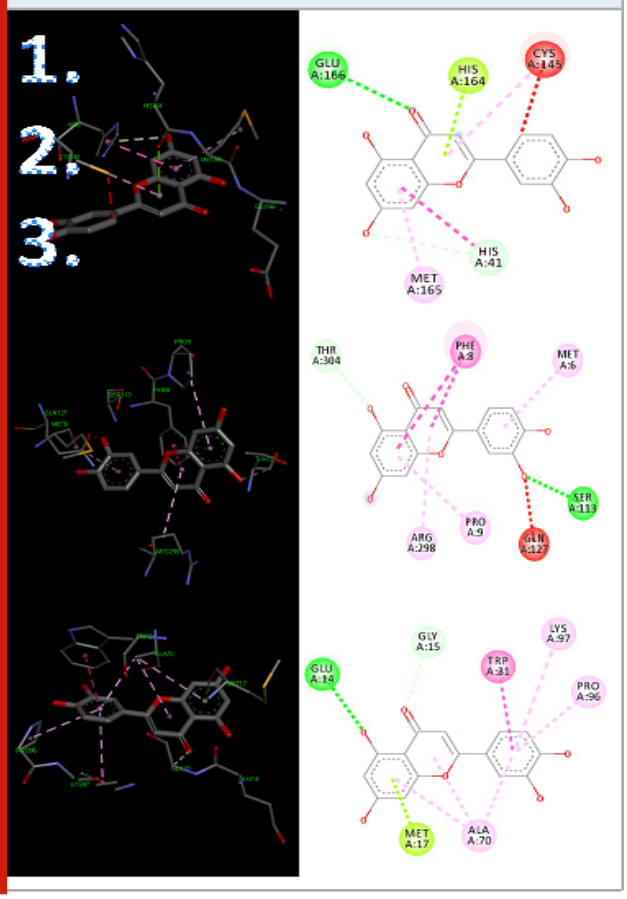


Instrument: Public Chemistry (PubChem) is accessed to download the 3D structure of Luteolin in SDF format. PubChem is a server which is launched by National institute of Health (NIH) in 2004. This is a freely accessible database of chemical information. Anyone can access this information by the means of a computer and an internet, you can upload the chemical information and it can be accessed by anyone worldwide. It consists of chemical information like Molecular structure, patents, and toxicity information and chemical properties. This chemical information is very useful to many researches in finding out many important drugs.

3D structure of SARS CoV2 has been downloaded from Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) in PDB format. It is an open database led by Helen M. Berman. Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB), here all the information about the different viral, bacterial and any other protein information can be found and can be downloaded. This information is used by many researchers to complete their research and further help the world.

OPEN BABEL is an easily accessible tool that coverts the different chemical molecules file formats to another format. It is used to convert the SDF format of luteolin to PDB format. After downloading and formatting the files in PDB format they were subject to docking with the help of PatchDock. PatchDock only accepts files that are in PDB format. In the receptor box we need to put the protein that we are targeting which is SARS Cov2 Main Protease and in the Ligand box we need to put the compound that is used to target a protein which is Luteolin. Patchdock is a free available web server that is used for molecular docking. It is a docking algorithm that performs docking on the basics of geometry. It finds the docking transformations that give the best complementarity. It is highly efficient because of its fast transformational search.

Figure 6: 1- Three dimensional and two dimensional docked Complex of Model 1; 2- Three dimensional and two dimensional docked Complex of Model 2; 3- Three dimensional and two dimensional docked Complex of Model 3



After obtaining the 3D docked complex from PatchDock, they are forwarded to FireDock by just clicking on the 'GO' button in front of the FireDock on the PatchDock web server page. FireDock is an easily accessible server that is used for protein -protein docking and it generates results by calculating the ΔG. BOVIA Drug Discovery Studio was used to visualise the bonds and distance between the formed bonds. It is a molecular modelling suite that has various features that helps in molecular modelling and simulation.

Figure 7: 3D Structure of Model 1 showing Hydrophobicity

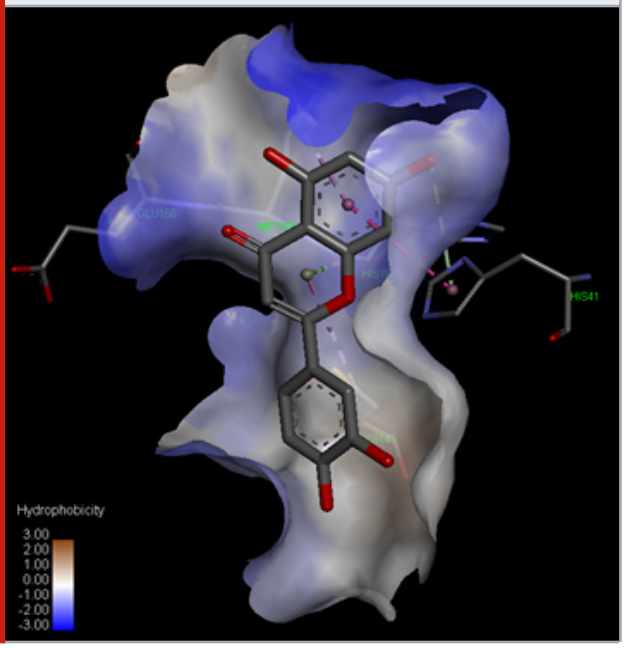
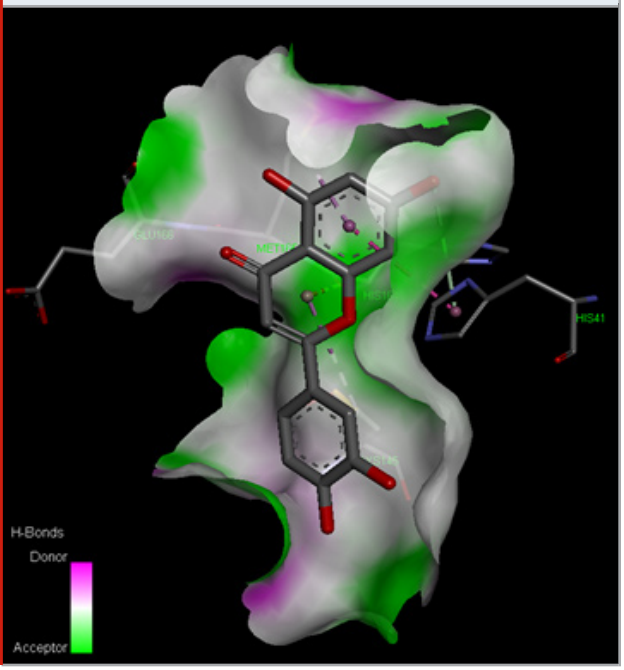


Figure 8: 3D structure of Model 1 showing H-bonds



Data Collection: Top 3 Docked Complexes were downloaded from FireDock and they were visualized using drug discovery studio (Figure 6). Their 2D structure were constructed and bonds formed and distance between the formed bonds was calculated. In Figure 7, Hydrophobicity cloud was formed, dark blue region represents the negative hydrophobicity, and white region represents the nutral region while the reddish brown region represents the positive hydrophobicity region. In Figure 8, H-bonds cloud was formed. Green region represents the acceptor molecule region while the purple region represents the donor molecule region.

Table 1. Score, ΔG and ACE of top 3 docked model

S.No.	Score	ΔG (kcal/mol)	ACE (kcal/mol)
1	3796	-36.04	-10.88
2	3770	-35.63	-8.75
3	3702	-34.62	-9.27

Table 2. Ligand Protein interaction, Distance and types of bonds formed in Docked model 1.

S.No.	Ligand : Protein	Distance	Bond Type
1	UNL1 : GLU166	3.07734	Hydrogen Bond
2	UNL1 : HIS41	4.0504	Hydrogen Bond
3	UNL1 : HIS41	4.07812	Hydrophobic
4	UNL1 : CYS145	4.8768	Hydrophobic
5	UNL1 : MET165	4.37297	Hydrophobic

Data Analysis: Top 3 docked model are compared top each other and it was found that the model 1 has the least ΔG of -36.04 kcal/mol and an Atomic Contact Energy of -10.88 Kcal/mol as shown in Table 1. Model 1 was further analysed and it was recorded in Table 2 that Luteolin (UNL1) was forming 2 hydrogen bonds with GLU116 and HIS41 and 3 hydrophobic bonds with HIS41, CYS145 and MET165 of the main protease. The distance between the bonds was ranging from 3 - 4 in hydrogen and 4 - 48 in hydrophobic bonds.

RESULT AND DISCUSSION

Docking studies helps the researchers and scientists to find out perfect candidates that can help the human society. In this present study interaction between Lut and SARS CoV2 Main protease was studied and found out that Lut was forming H-bonds with GLU166 and HIS41 and Hydrophobic bonds with HIS41, CYC145 and MET165. The bond distance was ranging from 3-5. The ΔG of best docked model was found out to be -36.04 kcal/mol and ACE was -10.88kcal/mol. ΔG is same as the binding energy and ACE is the energy of replacing the atom/molecule with another atom/molecule. These energies represents that Lut have an efficient binding with the SARS Cov2 Main protease.

CONCLUSION

COVID-19 has emerged as a pandemic in 2020 and huge loss to human life is faced. Researches are under trial but still no vaccine or drug against this disease has been found. Computation studies are the best platform to find out the potential of any compound against a disease. This study revealed the binding energy of naturally occurring Luteolin against SARS CoV2 main protease. Docking

results revealed that the Lut have a higher dock score and a sufficient amount of ACE and global energy to say that Lut have some pharmacological properties that be used against COVID-19. Lut is already known to cure many type of disease may it be anticancer or anti-inflammatory. Therefore, based on the results achieved it can be concluded that Lut have a potential and can be a promising phyto-compound against SARS CoV2 Main protease. Moreover, further in-vitro research is needed to estimate the compound's efficiency in targeting COVID-19.

REFERENCES

Ansari, W.A., Ahamad, T., Khan, M.A., Khan, Z.A. and Khan, M.F., 2020. Luteolin: a dietary molecule as potential anti-COVID-19 agent.

COVID, W., 19. Coronavirus Pandemic: Coronavirus Cases.

Pandey, P., Rane, J.S., Chatterjee, A., Kumar, A., Khan, R., Prakash, A. and Ray, S., 2020. Targeting SARS-CoV-2 spike protein of COVID-19 with naturally occurring phytochemicals: an in silico study for drug development. Journal of biomolecular Structure and Dynamics, pp.1-11.

Shree, P., Mishra, P., Selvaraj, C., Singh, S.K., Chaube, R., Garg, N. and Tripathi, Y.B., 2020. Targeting COVID-19 (SARS-CoV-2) main protease through active phytochemicals of ayurvedic medicinal plants–Withania somnifera (Ashwagandha), Tinospora cordifolia (Giloy) and Ocimum sanctum (Tulsi)–a molecular docking study. Journal of Biomolecular Structure and Dynamics, pp.1-14.

Singh, P., Hariprasad, V.R., Babu, U.V., Rafiq, M. and Rao, R.P., 2020. Potential phytochemical inhibitors of the coronavirus RNA dependent RNA polymerase: a molecular docking study.

Umesh, Kundu, D., Selvaraj, C., Singh, S.K. and Dubey, V.K., 2021. Identification of new anti-nCoV drug chemical compounds from Indian spices exploiting SARS-CoV-2 main protease as target. Journal of Biomolecular Structure and Dynamics, 39(9), pp.3428-3434.

Yu, R., Chen, L., Lan, R., Shen, R. and Li, P., 2020. Computational screening of antagonists against the SARS-CoV-2 (COVID-19) coronavirus by molecular docking. International Journal of Antimicrobial Agents, 56(2), p.106012.

Zhang, L., Lin, D., Sun, X., Curth, U., Drosten, C. and Sauerhering, L., & Hilgenfeld, R.(2020). Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. Science, 368(6489), pp.409-412.