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Molecular Docking studies of Apigenin, Kaempferol, and Quercetin as potential target against spike receptor protein of SARS COV

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ABSTRACT

COVID-19 has been categorized as a pandemic in early 2020 and is known to cause by Severe Acute Respiratory Syndrome Coronavirus (SARS–CoV2). Numerous investigators and people in the scientific community are trying to find a superlative way to avert and cure the ailment by using phytochemicals. Abundant studies have revealed that flavonoids can be very operative in averting virus-mediated infection. The purpose of this study was to accomplish molecular docking studies among plant-derived flavonoids (Apigenin, Kaempferol, and Quercetin) and spike receptor (PDB ID: 2AJF) protein of coronavirus. Pyrx virtual screening tool and biovia discovery studio visualizer were utilized in the current molecular docking investigations. Outcomes of docking studies exposed that selected phytochemicals have interacted with targeted spike receptor protein with binding energies in the range of -6.3 to -7.3 kcal. In conclusion among the various selected ligands, quercetin may be a better inhibitor for the deactivation of SARS-Coronavirus.

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1 Introduction

In December 2019, the breakout of Corona-virus or COVID-19 in Wuhan was an awful disease that caused millions of deaths worldwide (Sood et al. 2020). Throughout history, this coronavirus has killed more human beings than any other infectious disease. In the early month of January 2020, COVID-19 had been characterized as a pandemic by the World Health Organization (WHO). According to the Report of WHO to date, there are 398,785,192 confirmed cases and 5,771,443 deaths in 206 Nations (WHO 2020). Corona-viruses are a diverse group of viruses that belongs to the family *coronaviridae*. They are composed of a long RNA strand. Their genome is the largest among all RNA viruses. They are named after the crown-like spikes present on their surface. The main infection is caused by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) (Sood et al. 2021; Vashishth and Tehri 2020). SARS-CoV-2 Ibeta coronavirus belongs to the *coronaviridae* family, similar to Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). It is one among the 36 coronaviruses in the family of *coronaviridae* within the order Nidovirals. Members of this family are mainly known to cause respiratory or intestinal diseases in various creatures including humans (Tuli et al. 2021a). Recent research suggests that natural plant-based compounds such as phytochemicals including flavonoids, alkaloids, and others may be useful in the development of safe SARS-CoV treatments (Talwar et al. 2020; Vardhan and Sahoo 2020; Silveira et al., 2020; Tuli et al. 2021a; Tuli et al. 2021b;). In the year 2020, Vardhan and Sahoo (2020) pursued in silico computational analysis of phytochemicals including glycyrrhizic acid, limonin, 7-deacetyl-7-benzoylgedunin, maslinic acid, corosolic acid, obacunone, and ursolic acid and suggested their utility as promising drugs to target proteins of SARS-CoV-2. Similarly, Hall and Ji (2020) explored the in-silico potential of Zanamivir, Indinavir, Saquinavir, and Remdesiviras proteinase inhibitors. In the present study, three molecules from the flavonoid class were chosen to investigate the binding affinity with spike protein of coronavirus.

2 Materials and methods

In this present study of in silico docking, we have used different online bioinformatics servers, databases, and tools that help us to study the docking interaction of flavonoids such as Apigenin, Kaempferol, and Quercetin against spike protein of SARS-CoV.

2.1 Software's Used in Docking interaction

We have used Pyrx virtual screening tool and Biovia discovery studio visualizer. PyRx is a free and open-source virtual screening tool. It is a mixture of numerous software like AutoDockVina, AutoDock 4.2, Mayavi, Open Babel, and others. PyRx includes a docking wizard with an easy-to-use user interface which makes it a valuable tool for Computer-Aided Drug Design. Biovia discovery studio is a software suite that enables life science researchers to analyze and model molecular structures, sequences, and other data. Vina and AutoDock 4.2 are the docking software used by PyRx. The software provides tools for displaying and editing data as well as performing simple data analysis. Discovery studio offers many tools for working with and visualizing data.

2.2 Retrieval of Three-Dimensional Structure

The Three-dimensional Structure of the SARS coronavirus spike receptor-binding domain with PDB ID:2AJF (Figure 1) was retrieved from the online database RCSB protein data bank and which was later on viewed in PyMol software. The energy minimization and optimization of the target molecule were studied in the Swiss Protein Databank Viewer. In the 3-D structure of PDB ID:2AJF, all the water molecules were removed which were not involved in ligand interaction, and all the missing atoms and valences were corrected (Rivas 2019).

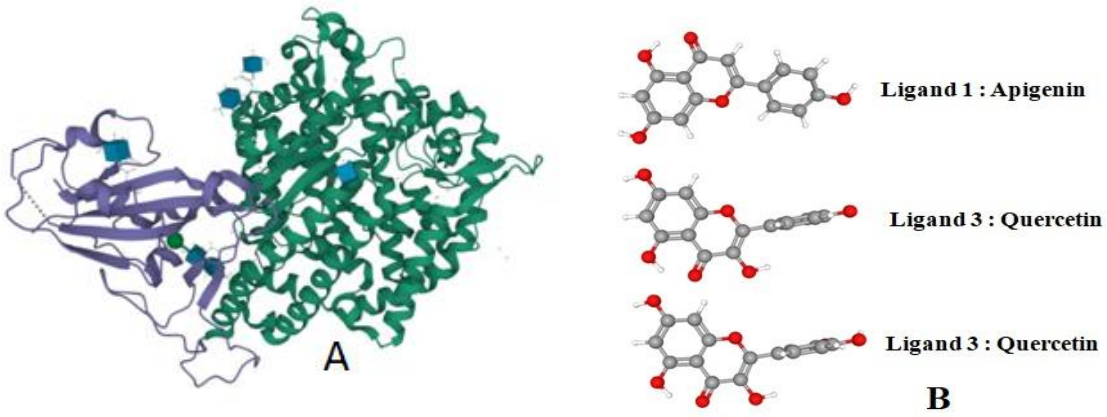


Figure 1 (A) Three-dimensional structure of SARS coronavirus spike receptor-binding domain with PDB ID:2AJF; (B) Ligands used in the study derived from PubChem Apigenin, Kaempferol and Quercetin

Table 1 Prediction of Molecular properties of Apigenin, Kaempferol and Quercetin by Molinspiration and 'Lipinski's rule of five

Properties	Ligands		
	Apigenin	Kaempferol	Quercetin
Molecular Weight	270.24	286.24 g/mol	302.23
XLogP3	1.7	2.46	1.5
Hydrogen Bond Donor Count	3	4	5
Hydrogen Bond Acceptor Count	5	6	7
Rotatable Bond Count	1	1	1
GPCR ligand	0.07	-0.10	-0.06
Ion channel modulator	-0.09	-0.21	-0.19
Kinase inhibitor	0.18	0.21	0.28
Enzyme Inhibitor	0.26	0.26	0.36
Protease inhibitor	-0.25	-0.27	-0.25
Nuclear receptor ligand	0.34	0.32	0.36
Topological Molecular polar surface area	90.89	111.13	131.35
Molar Refractivity	73.99	76.01	78.03

2.3 Selection and Preparation of Ligands and Prediction of Molecular Properties

The Ligands used in the study Apigenin, Kaempferol, and Quercetin are chosen from plants and herbs sources. All the three ligands were retrieved by PubChem (Figure 1) and saved in MOL SDF format and energy minimization, hydrogen bonds, and geometrical confirmations were done and modified in Marvin-Bean Package. The online tool Lipinski rule of 5 (Lipinski et al. 2001) and Molinspiration [www.molinspiration.com] were used for screening of identified ligands and it was found that all the three ligands were found to obey the Lipinski rule of 5. All the three ligands were used for the study that is shown in Table 1 with their physiochemical characteristics and Lipinski rule of 5 criteria.

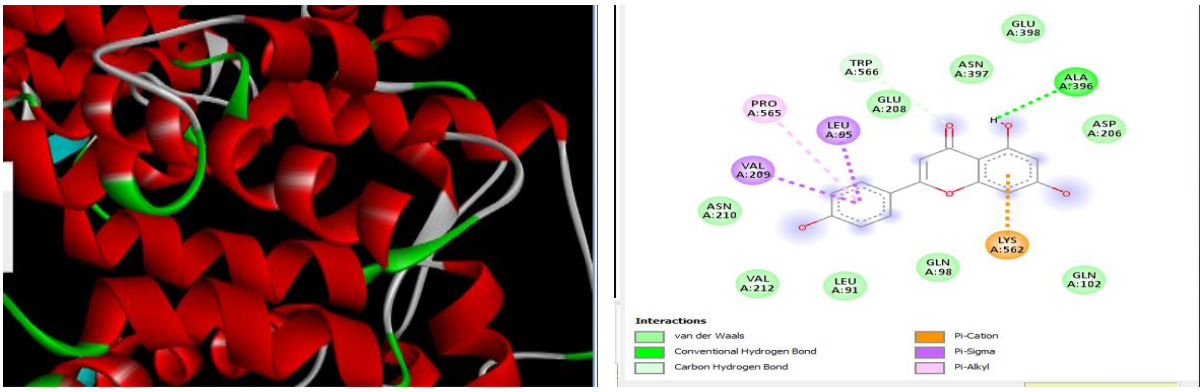
2.4 Molecular docking

The virtual screening is used to study the Ligand and Protein binding affinity along with the binding of the drug targets, protein receptors /or enzymes for interactions. We have used a free version of PyRx software to study molecular docking. All the default docking algorithms were used, and all the coordinates X, Y, and Z were set in the grids which were placed in the active site pocket center, and the lowest binding energies were the best suitable for interactions (Trott and Olson 2010)

3 Results and discussion

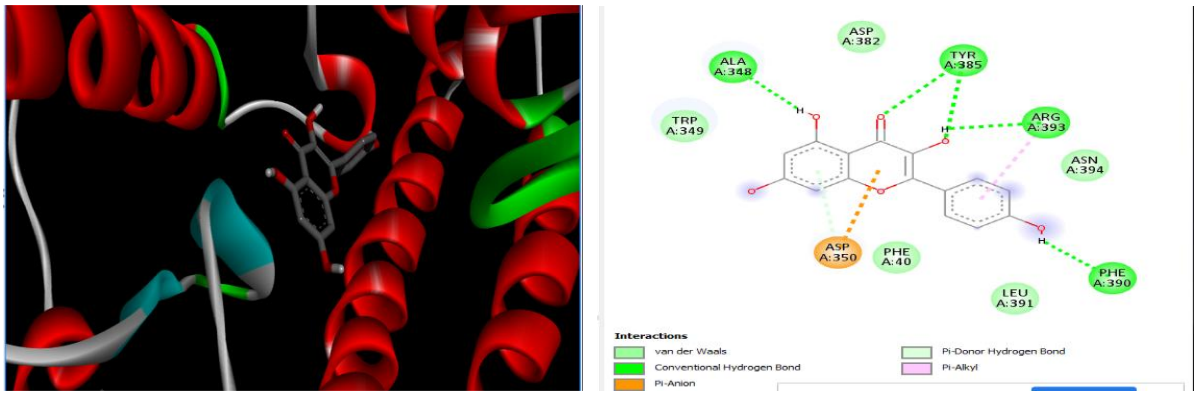
Previously, constructing and designing a drug was a lengthy, costly, and time-consuming process that took more than ten years and millions of dollars to complete. Computer aided drug design, also known as molecular docking, has become popular in recent years as a way to study protein-ligand interactions and properties such as hydrophobicity, binding energy, hydrogen bond donor-acceptor, geometry complementarily, and electron distribution. These interactions between ligands and receptors aid in the development of new medicines or therapies to treat deadly diseases (Tuli et al. 2020; Tuli et al. 2021c). The scientific community and pharmaceutical companies are concentrating on novel compounds with the aid of molecular docking techniques to speed up the drug development process. The root mean square deviation values (RMSD) were used to evaluate the docking results for the tested ligands with the receptor protein in this analysis. These RMSD values were based on the coordinates between the atoms and their conformational changes. The binding energy (kcal/mol) data enables us to investigate and compare the binding affinity of various ligands/compounds with their respective target receptor molecules. Binding energy represents the sum of total internal energy minus the energy which is linked to the unbound system. The lower binding energy indicates a higher affinity of the ligand for the receptor. In other words, Lower the binding energy the most favorable is docking results. The ligand with the highest affinity can be selected as a possible drug candidate for further research. The result of docking studies revealed that the ligands had good binding energy with the target molecule (Figure 2, 3, and 4) 2AJF, spike receptor protein of SARS-CoV, ranging from -6.3 to -7.3 kcal (Table 2, 3 and 4). Recently, Hagar et al. (2020) investigated the anti-covid activities of N-Heterocycles by using computational tools (Hagar et al. 2020). Similarly, several phytochemicals including nelfinavir, lopinavir,

kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, epicatechin-gallate, zingerol, gingerol, and allicin were investigated as anti-covid therapeutics by using in silico tools (Khaerunnisa et al. 2020). Terpenoids based molecules have also been utilized to study in silico molecular interactions against covid associated proteins. The results are acknowledged to have inhibitory actions of Ginkgolide A against novel COVID-19 protease.



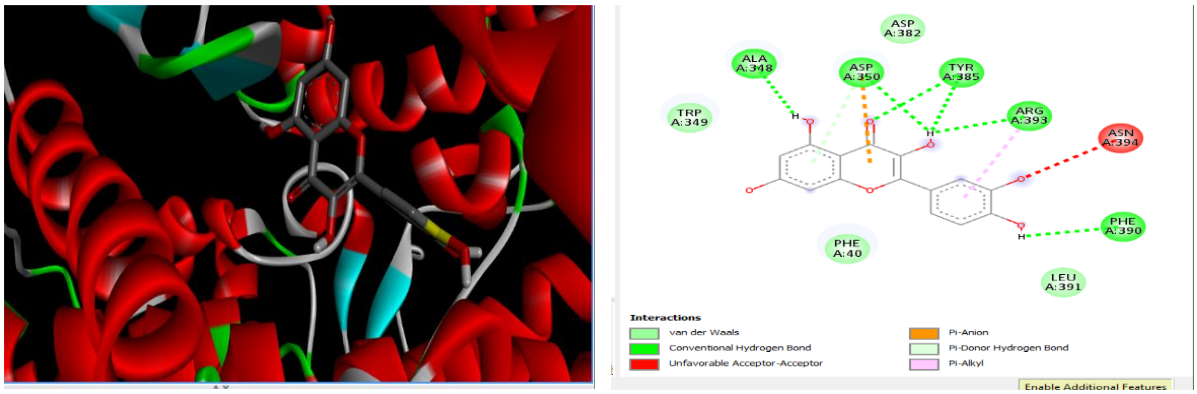
(A) (B)

Figure 2 Conformational changes observed due to the binding of Apigenin with PDB ID:2AJF (A) shows surface area interactions of Apigenin with receptor binding domain of SARS-CoV (B) is 2D interactions of Apigenin and receptor protein



(A) (B)

Figure 3 Confirmational changes observed due to the binding of Kaepmferol with PDB ID:2AJF (A) shows surface area interactions of Kaempferol with receptor binding domain of SARS-CoV (B) is 2D interactions of Kaempferol and receptor protein.



(A) (B)

Figure 4 Confirmational changes observed due to the binding of Quercetin with PDB ID:2AJF (A) shows surface area interactions of Quercetin with receptor binding domain of SARS-CoV (B) is 2D interactions of Quercetin and receptor protein.

Table 2 Interactions of Apigenin with receptor protein and values of binding energy and RMSD

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
2ajf_5280443_uff_E=233.26	-7.3	0	0
2ajf_5280443_uff_E=233.26	-7.2	6.891	3.559
2ajf_5280443_uff_E=233.26	-6.9	13.973	12.242
2ajf_5280443_uff_E=233.26	-6.8	20.256	17.001
2ajf_5280443_uff_E=233.26	-6.8	16.906	14.701
2ajf_5280443_uff_E=233.26	-6.8	15.177	14.141
2ajf_5280443_uff_E=233.26	-6.7	16.785	14.446
2ajf_5280443_uff_E=233.26	-6.7	14.581	12.753
2ajf_5280443_uff_E=233.26	-6.6	32.537	29.924

Table 3 Interactions of kaempferol with receptor protein and values of binding energy and RMSD

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
2ajf_5280863_uff_E=362.50	-7	0	0
2ajf_5280863_uff_E=362.50	-6.9	6.928	4.355
2ajf_5280863_uff_E=362.50	-6.8	6.472	5.494
2ajf_5280863_uff_E=362.50	-6.7	6.376	3.474
2ajf_5280863_uff_E=362.50	-6.7	7.519	6.346
2ajf_5280863_uff_E=362.50	-6.6	15.16	14.177
2ajf_5280863_uff_E=362.50	-6.6	6.56	2.158
2ajf_5280863_uff_E=362.50	-6.5	39.152	37.253
2ajf_5280863_uff_E=362.50	-6.5	7.298	5.063

Table 4 Interactions of quercetin with receptor protein and values of binding energy and RMSD

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
2ajf_5280343_uff_E=380.43	-7.1	0	0
2ajf_5280343_uff_E=380.43	-7	7.378	3.781
2ajf_5280343_uff_E=380.43	-6.9	26.609	22.918
2ajf_5280343_uff_E=380.43	-6.9	14.91	14.03
2ajf_5280343_uff_E=380.43	-6.8	44.95	44.112
2ajf_5280343_uff_E=380.43	-6.7	6.041	3.612
2ajf_5280343_uff_E=380.43	-6.7	7.4	3.615
2ajf_5280343_uff_E=380.43	-6.7	35.398	32.864
2ajf_5280343_uff_E=380.43	-6.6	6.445	3.707

Conclusions

Natural flavonoids were verified *in silico* for their possible interactions with spike receptor protein of COVID by using molecular docking tools to validate their drug-like candidature. The study revealed that quercetin was a better inhibitor for the inactivation of SARS-Coronavirus and should be pursued as a promising drug candidate for this virus. Further in vitro and clinical studies are needed to design effective COVID-19 drugs if the high efficacy function of quercetin is taken into account.

Conflict of interest

The authors declare no potential conflict of interest.

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