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Insilico Analysis of Quercetin Derivatives Against Covid Nonstructural Protein

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Abstract: **-** Covid 19 emerged in Wuhan, China in 2019 and spread across the world causing severe problem for animals including human. It is important to develop a potent drug for covid from natural source because variants emerge every day. The present work aims to develop an inhibiter for Covid spike protein ID 6W4H from the derivatives of natural flavonoid Quercetin. as ligand molecules. Towards this insilico docking analysis was performed using Auto Dock 1.5.6 on spike protein downloaded from RCS PDB with quercetin ligands taken from PubChem database. Best docking pose for ligand protein interaction and docking affinity values were calculated. Binding affinity ranging from -9.6 Kcal/mol and -13.5 K cal/mol was obtained for the libands studied. The highest binding affinity was shown by ligand 3-rhamnosyl-glucosyl quercetin and can be further developed as inhibitor for the protein. Other ligand also can act as potent inhibitor for targeted protein.The toxicitystudy of ligand molecules were carried out by protox II and all ligands except quercetin dihydrate and methyl quercetin were found to fall under less toxicity class 5. The study demonstrated the potential of quercetin as an inhibitor against against Covid spike protein.
Keywords*: Quercetin, Docking, Binding Affinity*

1.Introduction

Natural flavonoids are bioactive phytochemicals for treating various diseases. Flavonoids are a class of polyphenolic compounds from plant origin having pharmacological effects. Quercetin is one of such important flavonoids with immense potential for curing diseases. Pharmacological effects of flavonoids for treating viral diseases gained attention in developing as drug for Covid 19. First incidence of SARS CoV-2 occurred in Wuhan city of China in December 2019 and has migrated globally and emerged as a major threat to mankind [3]. Covid viruses are enveloped single-stranded RNA viruses that have been reported to infect both humans and animals with a high recombination rate [4]. Covid spike (S) glycoprotein has gained greater attention as a key target for the development of drugs, vaccines, diagnostics, and therapeutic antibodies [5]. The entry of coronavirus into host cells is mediated by the glycoprotein (transmembrane spike S) that consists of two functional subunits: S1 subunit for its binding to host cell receptor and S2 subunit for the fusion between cellular and viral membranes [6,9]. Thus, our main objective is to evaluate the binding interaction of Quercetin and its derivatives against Covid spike glycoprotein by using molecular docking approaches.

2.Objectives

The main objective of the present study is to determine ligand Quercetin derivative with highest binding affinity to the targeted protein ID 6W4H. Hence to determine potent inhibitor for Covid 19.

3.Methods

Docking Tools Docking is an automated computational programme for finding binding affinity of ligand molecules to the target protein. It explains how a ligand interact with a protein through various forces like hydrogen bonding, van der Waals forces etc. Conformational effects are also important.

3.1. Preparation of receptor (Target structure).

Structure of Target protein of COVID-19 spike glycoprotein (PDB-ID:6CS2) was downloaded from the protein data bank (RCSB PDB) database (Figure 1) and saved it in pdb format. The target structure was then optimized using Discovery studio and Auto dock tool for molecular docking. The protein needed to be docked should be prepared by removing the additional molecules attached to it like water molecule, i.e., the protein should contain only amino acids. It is done by using PyMol. Docking is performed using Auto Dock 1.5.6. The protein selected for docking was minimised using BIOVIA software. It gives the 3D diagram of protein - ligand interaction.

3.2. Ligand selection and Preparation.

All the Ligand molecules including flavonoid Quercetin (natural flavonoid) and its fifteen derivatives were selected for docking analysis, and their 3D structure was downloaded from the PubChem database and saved it in sdf format.

3.3. Manual Docking protocol using Auto Dock 1.5.6.

Auto Dock tool was used to identify the best ligand binding conformation (good pose) in the target protein. This tool utilizes the scoring function for analysing the binding conformations through free binding energy. Subsequent docking steps were followed.

3.4 Ligand toxicity Prediction

Protox II is used for predicting ligand toxicity.

3.5 Ribbon Structure of Protein ID 6W4H with Resolution

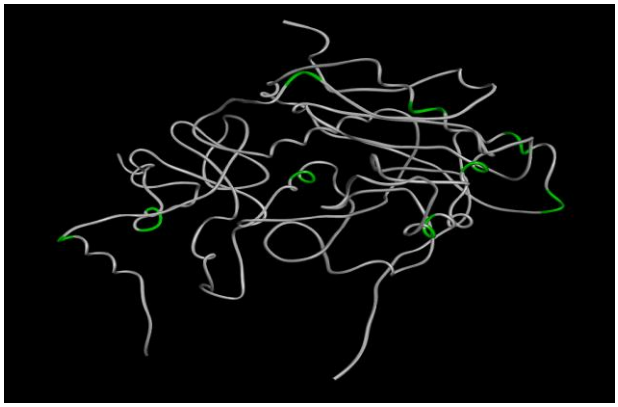


Figure 1 Structure of Protein ID 6W4H with Resolution: 1.80 A

4. Result

4.1 Selection of ligand molecule

All selected 16 ligand molecule structure downloaded from PubChem and docking performed using these.

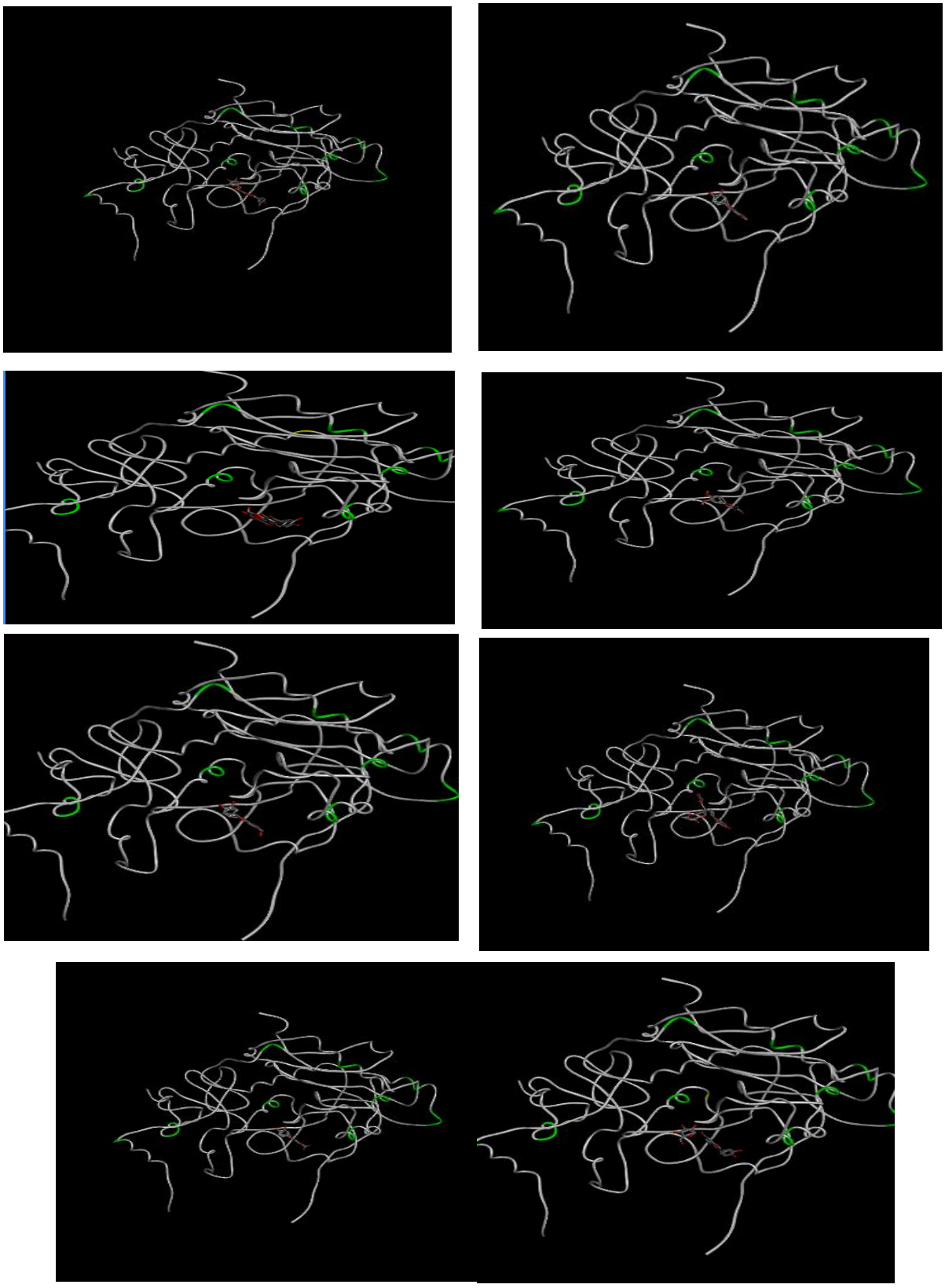
4.2 Toxicity of ligands

It is predicted by using Protox II. Result showed that flavonoid Quercetin is fall under less toxicity class 3 but all other ligands fall under lowest toxicity class 5. Hence these selected ligands can act as a potent drug.

4.3 Figure 2. Molecular docking analysis between 6W4H and Ligands. (A) 3D Protein-ligand Interaction. (B) 2D Interaction between the active site residues of ligand and protein

Fig 2A shows 3D structure for Docking of Non-structural protein PDB ID 6W4H with various Quercetin derivatives such as Quercetin-3-rutinoside, quercetin-3-o-rhamnoside, velloquercetin, Quercetin-3-o-glucoside,

3-rhamnosyl-glucosyl quercetin, quercetin-3,3',4'-triglucoside, quercetin-3-o-glucoronide, Quercetin7-o-glucoside, quercetin-3'-o-phosphate, quercetin-3-arabinofuranoside, methyl quercetin, 6-chloro quercetin, Quercetin hydrate, Quercetin 4 methyl ether, Quercetin 5-methyl ether, Quercetin 3,3' dimethyl ether respectively.



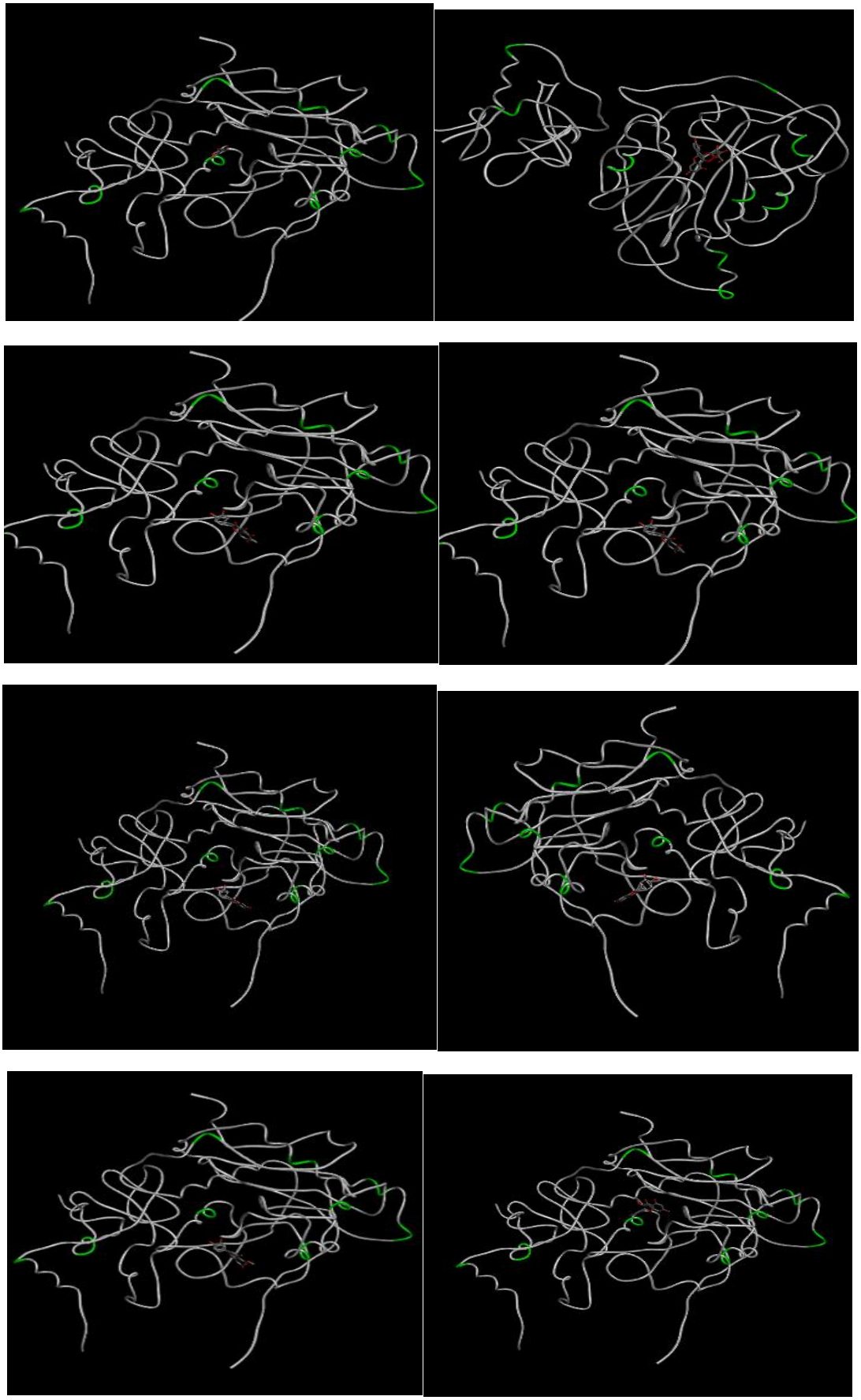
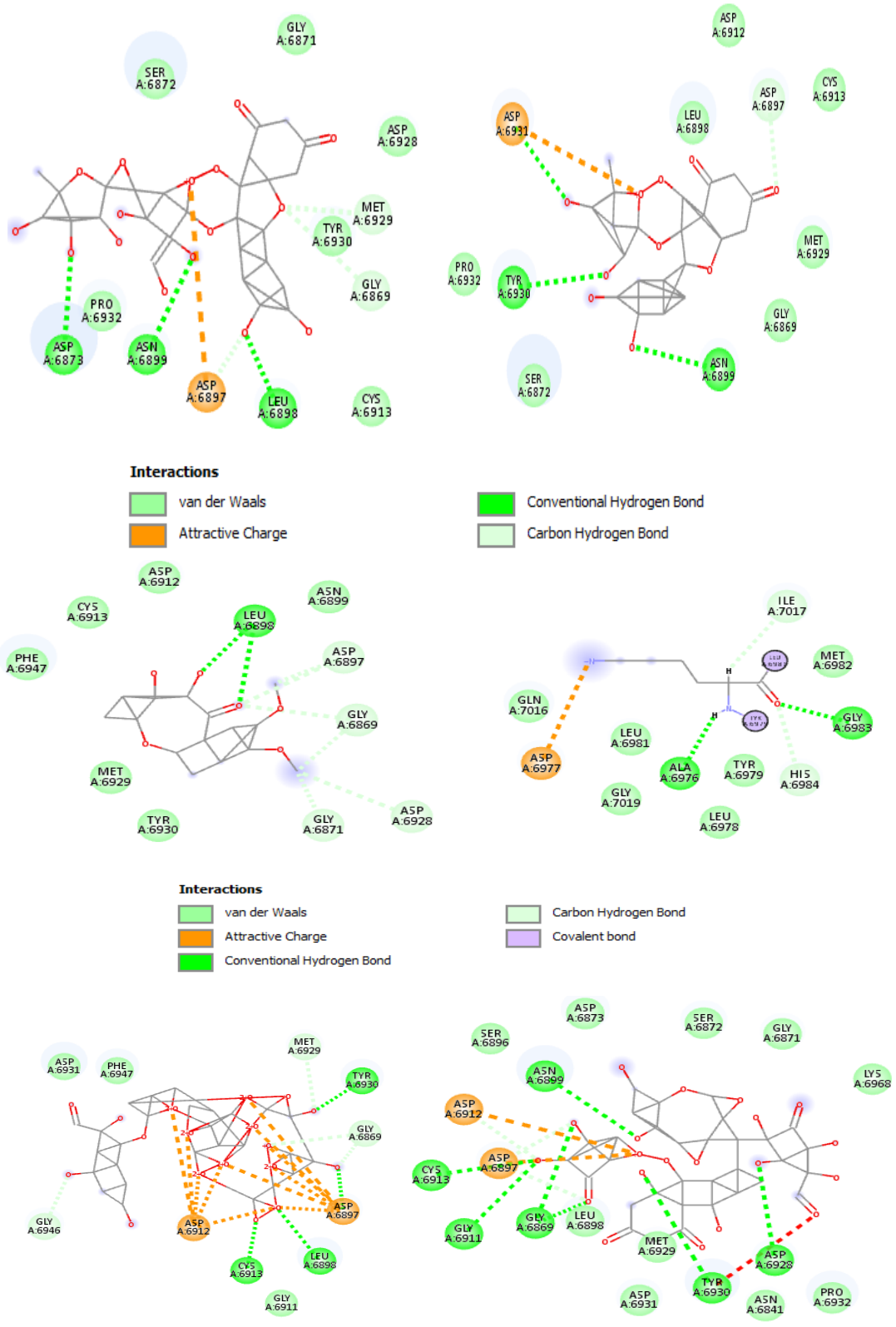
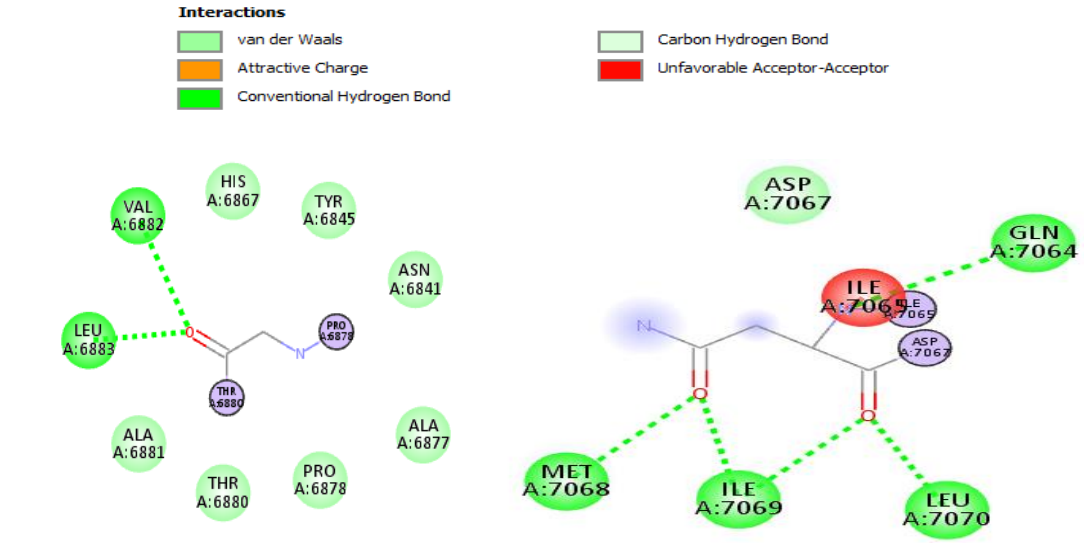


Fig 2A 3D structure for protein ligand interaction

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Attractive Charge
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Unfavorable Acceptor-Acceptor
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TYR A:6845
VAL A:6882
ASN A:6841
LEU A:6883
ALA A:6881
ALA A:6877
THR A:6880
PRO A:6878
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MET A:7068
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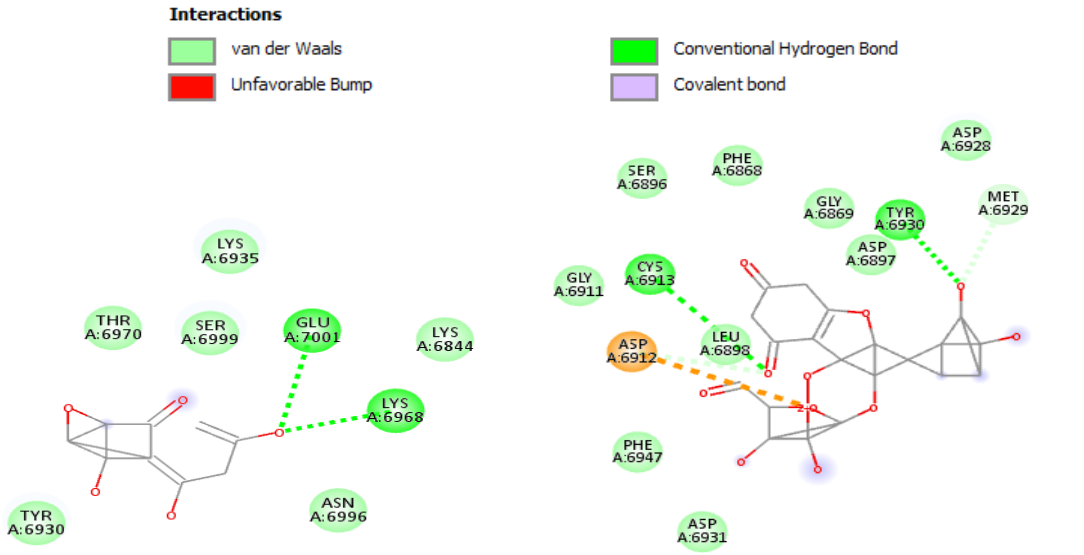
Interactions
van der Waals
Unfavorable Bump
Conventional Hydrogen Bond
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THR A:6970
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GLU A:7001
LYS A:6844
LYS A:6968
TYR A:6930
ASN A:6996
ASP A:6928
SER A:6896
PHE A:6868
GLY A:6869
TYR A:6930
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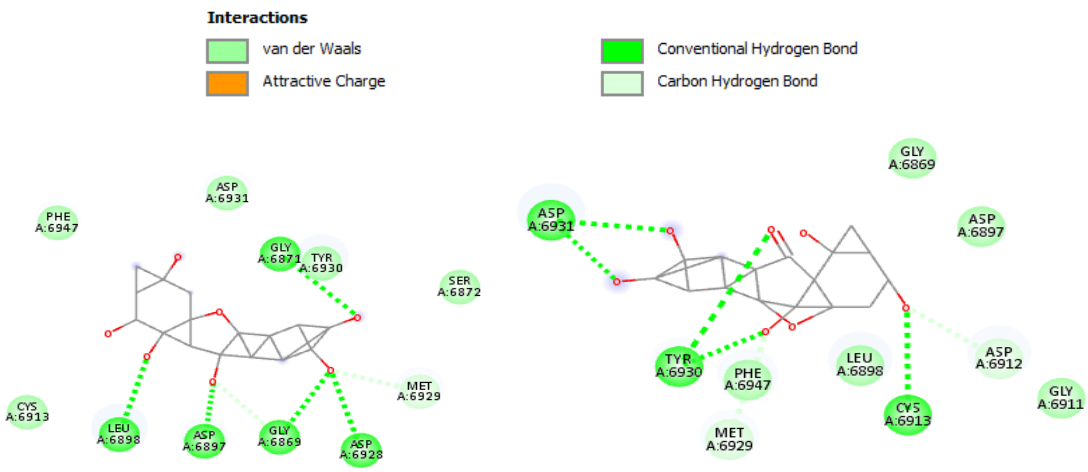
ASP A:6912
LEU A:6898
PHE A:6947
ASP A:6931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van der Waals
Attractive Charge
Conventional Hydrogen Bond
Carbon Hydrogen Bond
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GLY A:6871
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MET A:6929
CYS A:6913
LEU A:6898
ASP A:6897
GLY A:6869
ASP A:6928
GLY A:6869
ASP A:6931
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GLY A:6911
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MET A:6929

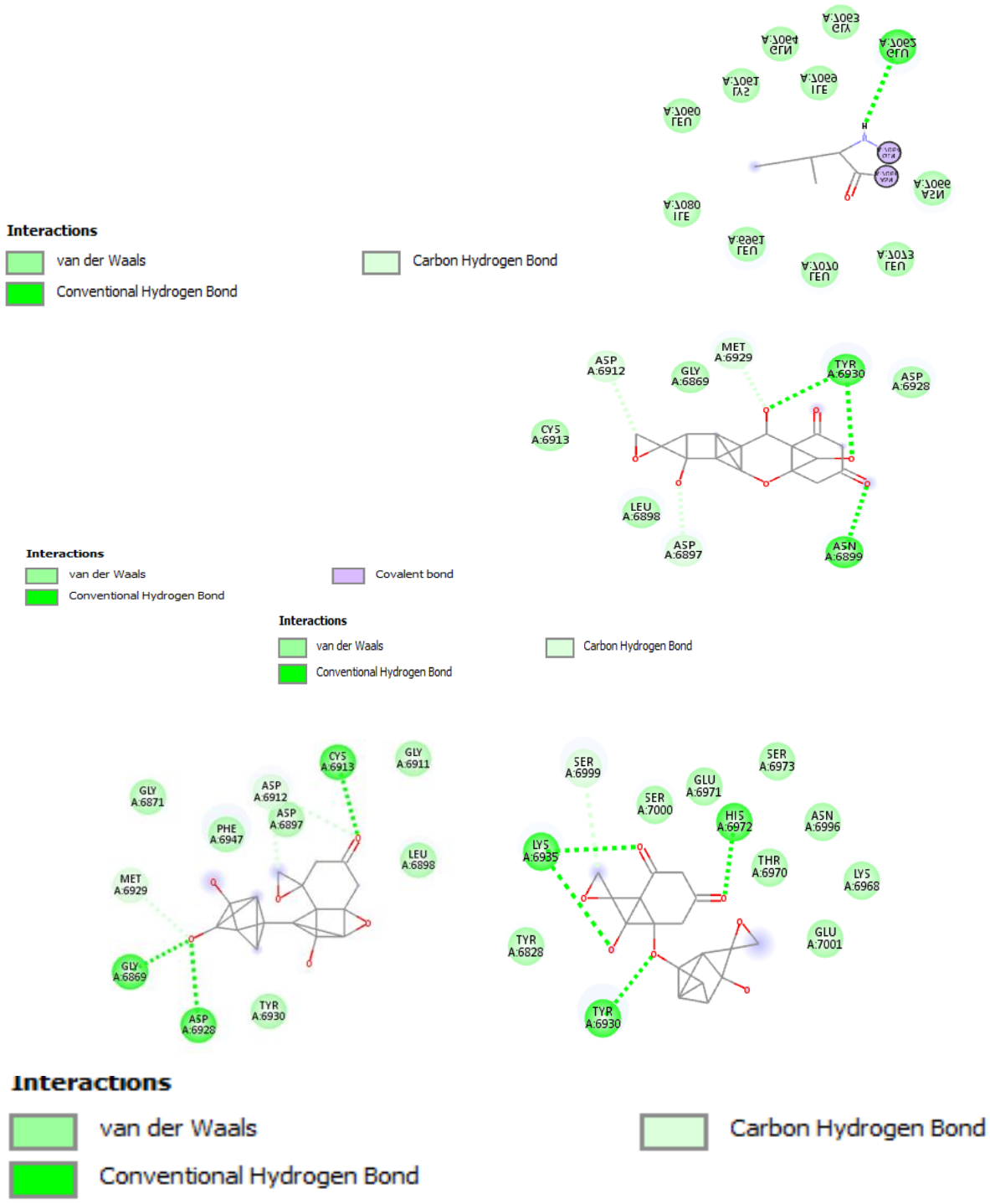
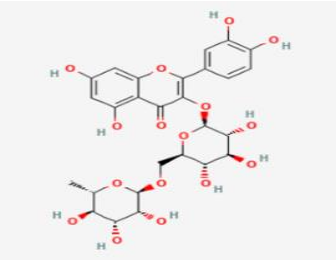
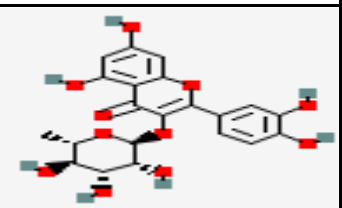
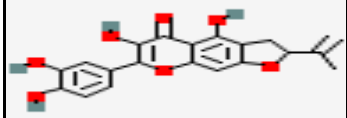
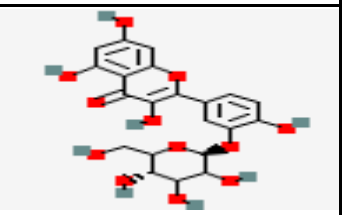
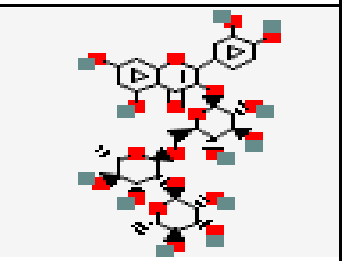
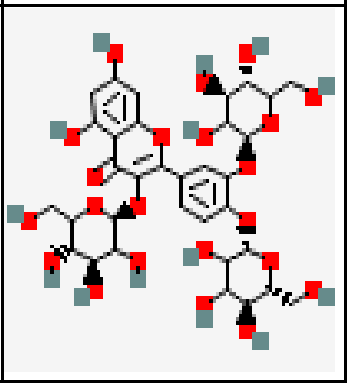
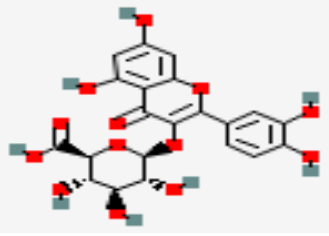
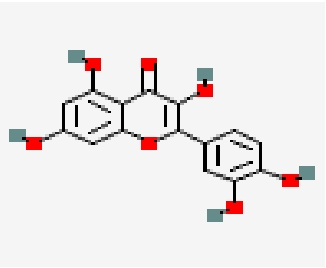
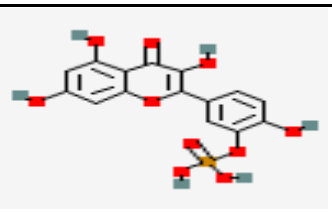
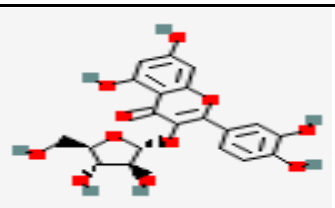
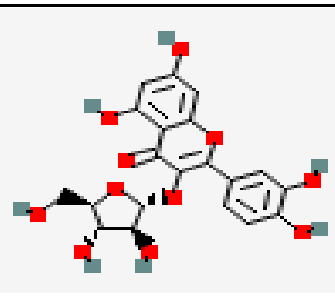
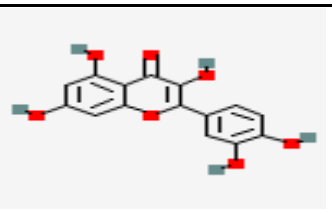
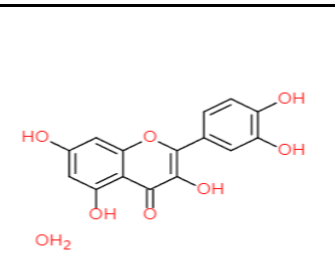


Fig.2B. 2D diagram of docking ligand with target protein ID 6W4H

Results obtained for docking all ligand with covid spike protein ID 6W4H in Table 1 below.

Sl.No.	Ligand	Structure	Docking Score/Affinity (kcal/mol)	No. of Hydrogen bonds	Amino acid residue involved	Oral Toxicity class
1	Quercetin-3-rutinoside		-11.3	3	ASP A:6873, ASN A:6899, LEU A:6898	5
2	quercetin-3-o-rhamnoside		-10.9	3	TYR A:6930, ASP A:6931. ASN A:6899	5
3	Velloquercetin		-9.9	2	LEU A:6898(2)	5
4	quercetin 3-o-glucoside		-10.5	2	ALA A:6976, GLY A:6983	5
5	3-rhamnosyl-glucosyl quercetin		-13.5	4	TYR A:6930, ASP A:6897, LEU A:6898, CYS A:6913	5
6	quercetin-3,3',4'-triglucoside		-12.2	7	ASN A:6899, CYS A:6913, GLY A:6911, GLYA:6869(2), TYR A:6930, ASP A6938	5

7	quercetin-3-o-glucoronide		-10.5	2	VAL A:6882, LEU A:6883	5
8	Quercetin7-o-glucoside		-10.9	5	GLN A:7064, LEU A:7070, ILE A:7069(2), MET A:7068	5
9	quercetin-3'-o-phosphate		-10.5	2	GLU A:7001, LYS A:6968	5
10	quercetin-3-arabinofuranoside		-10.5	2	CYS A:6913, TYR A:6930	5
11	methyl quercetin		-9.6	5	GLY A:6871, ASP A:6928, GLY A:6869, ASP A:6897, LEU A:6898	3
12	6-chloro quercetin		-9.6	5	ASP A:6931(2), TYR A:6930(2) , CYS A:6913	5
13	Quercetin hydrate		-9.7	1	GLU A:7062	3

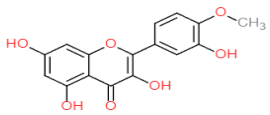
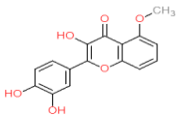
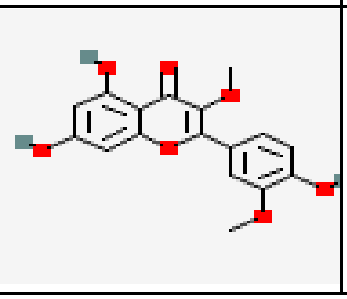
14	Quercetin 4-methyl ether		-9.7	3	TYR A:6930(2), ASN A:6899	5
15	Quercetin 5-methyl ether		-9.5	3	CYS A:6913, GLY A:6869, ASP A:6928	5
16	Quercetin 3,3' dimethyl ether		-9.3	4	LYS A:6935, TYR A:6930, HIS A:6972	5

Table 1: Structure of various quercetin derivatives and binding affinity, No. of amino acid residue Hydrogen bonds, am toxicity of the quercetin derivatives with covid spike protein (ID 6W4H)

5.Discussions

Computational pharmacology has gained greater attention toward improving clinical use and drug development [8]. Drug development from a natural source is important because of its nontoxic nature. Quercetin flavonoid is lipophilic in nature. So, preparation of its water-soluble derivative with lowest toxicity class is most important.

Flavonoids are one of the important types of phytocompound which belong to a specific secondary metabolite of a plant (polyphenolic structure). They have exhibited significant medicinal benefits against various diseases, including Alzheimer's, cancer, atherosclerosis [7]. Quercetin has a wide range of pharmacological activities that include anti-oxidant, antimicrobial, anti-inflammatory, antimutagenic, antitumour, antidiabetic, Vaso-relaxant, immunomodulatory and both oestrogenic and anti-oestrogenic activities. However, some flavonoids have also shown significant antiviral potential such as HIV, Herpes, etc. [9]. These phytocompounds not only inhibit the virus attachment but also helps in the improvement of the immune system. COVID-19 coronavirus utilizes this densely glycosylated spike (S) protein to get entry into the host cell. And because of their (S protein) indispensable role, it became a target for vaccine design and drug development [7,9]. We have selected 16 potent antiviral quercetin derivatives for Molecular docking against covid spike protein target of ID 6W4H. All ligand falls under lower toxicity class 5 except Methyl quercetin and quercetin hydrate (Toxicity class 3. Hence these do not cause any side effects.

As a conclusion, in the case of protein 6W4H, among these 16 compounds, compound 5, 3-rhamnosyl-glucosyl quercetin showed highest binding efficacy in terms of lower binding energy (-13.5kcal/mol) with the target protein. Among these 16 compounds, compound 11, quercetin-3,3',4'-triglucoside (-12.2kcal/mol), compound 1, Quercetin-3-rutinoside (-11.3kcal/mol), showed better binding efficacy in terms of lower binding energy with the target protein. All others showed binding affinity above -6.5kcal/mol. Toxicity studies showed that most of the compounds fall under toxicity class 5. Based on the results, compound 5, 3-rhamnosyl-glucosyl quercetin showed the best efficacy (-13.5kcal/mol) against selected target protein ID 6W4H of COVID-19 and thus could be used as the potential therapeutic agent for COVID-19 treatment.

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