In Silico Identification of Active Phytochemicals against COVID-19 by Targeting the SARS-CoV-2 Spike Glycoprotein Through Molecular Docking: A Drug Repurposing Approach

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ABSTRACT

The spread of coronavirus disease (COVID-19) has become one of the most significant pandemics in modern human history, affecting more than 70 million people worldwide. Currently, only a few fda-approved drugs have suggested fighting the infection, in the absence of a specific antiviral treatment. Thus, repurposing the presently available drugs or using plant-based bioactive compounds can be the fastest possible solution. In this study, the computational methodology of molecular docking techniques was performed to screen and identify the viable potent inhibitors against the SARS-CoV-2 spike protein from a library of 200 active phytochemicals, based on their highest binding affinity towards the target protein. Later, the binding affinities of these phytochemicals were compared with that of the fda-approved drug fluvoxamine, which is currently in use against the mild COVID-19 patients. Out of these, 86 phytochemicals that exhibited better binding energy of value ≤7.00kcal/mol, is selected for adme (absorption, distribution, metabolism, and excretion) analysis and drug likeliness studies to check the feasibility of these compounds. Whereas, 79 out of 86 phytochemicals showed a better theoretical affinity with sufficiently bearable adme properties. Thus, they can be the lead molecule for further investigation and validation processes towards developing natural inhibitors against the SARS-CoV-2 virus.

Keywords: Novel Coronavirus, Phytochemicals, SARS-CoV-2, ADME, Drug likeliness, Molecular docking.

I. INTRODUCTION

Currently, the whole world is fighting against the novel Coronavirus, which has been declared as a global pandemic by the World Health Organization on 11th March 2020 [1]. It was first emerged in Wuhan (China) in December 2019, with a series of pneumonia cases of unknown etiology [2]. Later, it was isolated, identified, and named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses on 11th February 2020 [3]. As per the latest situation report released by WHO, globally, over 70 million confirmed cases and 1.6 million deaths have been reported so far due to COVID-19 as of 13th December 2020 [4]. An increase in the spread of the disease and its inability to control, in the absence of specific antiviral drugs or treatment, has resulted in high mortality and morbidity rates.

SARS-CoV-2 is a positive-sense single stranded RNA virus belonging to the family Coronaviridae and genera β-Coronaviruses [5][6]. This virus is known to be zoonotic, meaning it is transmitted between humans and animals. It has a higher transmissibility rate and spreads through droplets of saliva or discharge from the nose, when an infected person coughs or sneezes, or by touching contaminated surfaces and possibly through oral faecal route [7]. Clinical symptoms include fever, dry cough, sore throat, fatigue, nasal congestion, and in severe conditions, it may cause hypoxia, respiratory distress, and dyspnea [8].

The size of viral genome varies between 26-32 kb in length [9] with 76% identical to SARS-CoV and 93% similar to that of RaTG12 virus (found in Bats) [10], with a variable number of Open reading frames (around 6-11) [11]. The viral RNA located in the ORF1 translates two polyproteins, namely, pp1a and pp1ab, and encodes for 16 non-structural proteins (NSP), whereas remaining ORF’s codes for the structural proteins [12]. Structurally, SARS-CoV-2 contains four structural proteins, namely Spike (S), Envelope (E), Membrane (M), and Nucleocapsid (N) proteins [13]. Among these, Spike glycoprotein (S) found on the surface of SARS-CoV-2 helps in binding and its entry into the target cells via membrane fusion with Human Angiotensin converting enzyme (ACE 2) receptors of host cells [8]. The S1 subunit of the protein mediates the binding of the virus to the receptor membrane. Simultaneously, membrane fusion and internalization of the virus are brought about by the S2 domain of the spike glycoprotein [14][15]. Since this protein plays an essential role in virus entry, designing a new drug or inhibitor that can bind to this spike protein and inhibiting its access can be a solution against COVID-19. Despite WHO declared a pandemic, only a few specific antiviral drug or vaccine has been approved for Coronavirus treatment. Thus, creating an intense need to develop effective antiviral agent against SARS-CoV-2. The discovery and development of the new drug or vaccine are challenging and time-consuming processes that may vary from few months to years.
Therefore, repurposing the existing drugs or using phytochemicals from various medicinal plants can be an alternative to fight the infection.

In this regard, scientists worldwide are desperately searching for effective compounds that can be used to fight the infection by targeting various viral protein sites.

Humans have been exploring nature, mostly medicinal plants, since ancient times, looking for new compounds with curative properties to treat various diseases. India is a rich source of biodiversity, and most of the traditional systems of medicines, including Unani, Homeopathy, Ayurveda, and Siddha, are mainly plant-based compounds [16]. Plants are known to produce Primary and Secondary metabolites with diverse functions. Among them, secondary metabolites are chemically active compounds which include flavonoids, polyphenols, alkaloids, terpenoids, glycosides, diterpenoid lactones, steroids, etc. with their esteemed pharmacological activities such as antioxidant, antibacterial, anti-inflammatory, anticancer, antifungal, anti-allergic, and antiviral properties [17][18][19]. Since these compounds are comparatively more economical, readily available, and harboring fewer side effects and toxicity, they make it the best candidate to fight the pandemic.

In this regard, Insilico studies were made, which is an initial step in the drug discovery and development process, to identify the most potent compound by targeting the novel sites of the spike glycoprotein of SARS-CoV-2, a viral protein required for binding and its entry into the host cells. Currently, only a few FDA-approved drugs like Chloroquine, Hydroxychloroquine, Remdesivir, Bevacizumab, Fluvoxamine, etc., either alone or in combination with other drugs, are being used to treat the infection [20]. Randomized clinical trials carried on COVID-19 patients showed that Fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), class of anti-depressants, mostly prescribed for people suffering from an obsessive-compulsive disorder, was found to be effective by preventing clinical deterioration by stimulating the σ-1 receptor, which regulates cytokine production in patients with mild COVID-19 [21]. By considering this, Molecular docking was performed on various phytochemicals, and their binding energy was compared with Fluvoxamine.

I found that out of 200 phytochemicals, 86 showed a better binding affinity than Fluvoxamine towards the S1 or S2 domain of the glycoprotein, thus preventing the virus from binding or entering the host cells. Whereas 79 of them out of 86 phytochemicals showed satisfactorily allowable ADME and drug likeness properties.

Therefore, these studies intimate that most of these compounds can play the role of the antiviral drug against SARS-CoV-2, thus requiring further scientific investigations.

II. MATERIALS & METHODOLOGY

2.1 Preparation of Receptor

The cryo-electron microscopic 3-Dimensional structure of SARS-CoV-2 protein (PDB ID: 6VYB) was downloaded from RCSB Protein Data Bank [14] and was visualized by using Chimera 1.14 software [37]. The target chosen for this study was spike glycoprotein of SARS-CoV-2, which plays a crucial role in its attachment and internalization into the host cells. SARS-CoV-2 is a heterodimer protein consisting of Chain A, B, and C, as shown in Fig. 1. Out of these chains, Chain A of spike protein (represented in Fig. 2) was selected for docking, followed by protein optimization and energy minimization by using Swiss PDB Viewer [38].

![Figure 1: 3-Dimensional structure of SARS CoV-2 spike protein (PDB ID: 6VYB), Chain A (blue colored), Chain B (orange colored), and Chain C (green colored)](image1)

![Figure 2: 3-Dimensional structure of Chain A SARS CoV-2 spike protein](image2)

2.1.1 Protein Optimization & Energy minimization

Protein optimization is carried out in order to remove the additional molecules from protein files (.pdb), since their structure will interfere or alter the docking process by participating in it, thus causing the variation in the result.
Later, Energy minimization is carried out by SPDB viewer for the sake of removing the extra spaces and arranging the protein coordinates into the proper order. The result file is now reduced in the sizes. The swiss coordinates that were added are removed before docking.

| ATOM | 7388 | N  | SER A1147 | 210.015 216.184 117.768 1.00 |
|------|------|----|-----------|-----------------------------|
| 43.96|      |    |           |                             |
| ATOM | 7389 | N  | SER A1147 | 210.673 217.407 117.318 1.00 |
| 44.40|      |    |           |                             |
| ATOM | 7390 | C  | SER A1147 | 212.065 217.080 116.767 1.00 |
| 44.84|      |    |           |                             |
| ATOM | 7391 | O  | SER A1147 | 212.478 217.600 115.726 1.00 |
| 44.74|      |    |           |                             |
| ATOM | 7392 | CB | SER A1147 | 210.765 218.408 118.473 1.00 |
| 44.75|      |    |           |                             |
| ATOM | 7393 | OG | SER A1147 | 211.456 219.568 118.096 1.00 |
| 44.86|      |    |           |                             |
| TER  | 7394 | N  | SER A1147 |                             |
| 57.41|      |    |           |                             |
| ATOM | 7395 | N  | ALA B 27  | 192.129 155.190 221.632 1.00 |
| 56.36|      |    |           |                             |
| ATOM | 7396 | C  | ALA B 27  | 191.413 155.543 220.415 1.00 |
| 55.35|      |    |           |                             |
| ATOM | 7397 | C  | ALA B 27  | 191.360 157.064 220.268 1.00 |
| 57.55|      |    |           |                             |
| ATOM | 7398 | O  | ALA B 27  | 191.123 157.772 221.253 1.00 |
| 44.85|      |    |           |                             |
| ATOM | 7399 | CB | ALA B 27  | 189.993 154.965 220.434 1.00 |

**Figure 3: Protein Optimization using WordPad**

### 2.2 Preparation of Ligand

A library of 200 active phytochemicals from well known medicinal plants was created and was selected as ligands for docking. The 3-Dimensional structure of all these phytochemicals including Fluvoxamine was downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov) in structure-data file (sdf) format and was optimized by using Marvin sketch 20.13 (http://www.chemaxon.com). Later, the sdf file of all these ligands was converted into the pdb format by using Open Babel software 2.4.1 and was visualized in Chimera software 1.14. The 3-Dimensional structure of one of the phytochemicals (Withaferin A) is represented in Fig. 4.

**Figure 4: 3-Dimensional structure of Withaferin**
2.3 Prediction of Active Binding site

The active binding sites for spike glycoprotein were predicted by using the CASTp web server [39].

2.4 Molecular Docking of Receptor and Ligand

The molecular docking of SARS-CoV-2 spike protein with the selected compounds was performed by using AutoDock software 1.5.6 [40]. Initially, both the protein and ligands were converted into pdbqt format by removing water molecules and adding polar hydrogen and Gasteiger charges. During docking, the protein was considered to be rigid and the ligand as flexible. The genetic algorithm (GA) was kept at 100. Based on the CASTp results, 3 different grid regions were selected for docking with the grid value, as mentioned in Table 1.

Table 1: The docking parameters used for all the ligands

| Region no. | X - Coordinate | Y - Coordinate | Z - Coordinate | Dimensions (Å) | Grid space (Å) |
|------------|----------------|----------------|----------------|----------------|----------------|
| 1          | 187.738        | 226.379        | 221.810        | 86 x 70 x 94   | 0.500          |
| 2          | 185.710        | 211.633        | 234.217        | 76 x 62 x 84   | 0.500          |
| 3          | 211.705        | 222.835        | 214.334        | 46 x 42 x 88   | 0.500          |

The grid center for docking was set on the active sites of the spike protein. Each ligand was docked, with these grid parameters separately. Furthermore, the best binding affinity (highest negative) obtained from all the three regions was analyzed using MGL tools 1.5.6 [41] and were chosen for further analysis. Molecular interactions between the protein-ligand complexes, including hydrogen bonds, were studied and outlined using Ligplot+ 2.2 software [42]. Similarly, docking for all the selected ligands was performed on SARS CoV-2, and their results were depicted.

2.5 ADME analysis & Drug likeliness

ADME (absorption, distribution, metabolism, and excretion) properties of the ligands were calculated using the online SwissADME web tool [43], based on the selected compounds’ Canonical SMILES obtained from the PubChem database. The critical parameters for ADME properties include Lipinski’s rule of five, the solubility of the drug, pharmacokinetic properties, and drug likeliness was deliberated [44]. All the calculated values of the observed properties are provided in Table 5.

III. RESULTS & DISCUSSIONS

This study focused on the drug repurposing against the spike glycoprotein of Chain A (S1 & S2) domain of SARS-CoV-2 (PDB ID: 6VYB) as a potential therapeutic target for the treatment of COVID-19. Since it plays a crucial role in its attachment and internalization into the host cells, blocking the active sites of this protein can inhibit its entry into the host cells. Therefore, identifying a potential drug or inhibitor against this spike glycoprotein can be a solution for the treatment of COVID-19.

In this way, a library of ligands consisting of 200 phytochemicals extracted from various medicinal plants was created, including Fluvoxamine, which is currently being used to treat the patients with mild COVID-19.

3.1 Virtual screening & Visualization

Molecular docking is a crucial tool to understand drug biomolecular interactions in the field of Computer assisted drug design [22]. The main objective of ligand-receptor docking is to predict the predominant binding mode of a ligand with a receptor (protein) of a known 3-Dimensional structure [23]. Binding energy (B.E) is the capability of a specific ligand (small molecule) and the strength by which a compound interacts and binds to a target molecule's active sites. This data is used to study and compare the binding affinity of different ligands with their corresponding receptor molecule. Lower the binding energy, greater the affinity of a ligand towards the receptor molecule. Thus, a compound with a higher negative value can be chosen as a viable drug candidate.

The effect of 200 phytochemicals, including FDA-approved Fluvoxamine, a class of anti-depressants drug, were studied by selecting them as ligands and were docked individually with the receptor spike glycoprotein (6VYB) Chain A of SARS CoV-2.

Docking protein and ligand (phytochemical) results with the B.E. of value ≤ -7.00 Kcal/mol are represented in the below tables, along with their interacting residues.

Table 2: Molecular docking analysis to find out the presumed binding sites of few inhibitors on SARS CoV-2 spike protein with the grid parameter of X = 187.738, Y = 226.379, Z = 221.81 with the dimensions of 86 x 70 x 94 (Å).

| Name of the medicinal plant | Compound | PubChem ID | Binding Affinity (kcal/mol) | Interacting Domain of Spike Protein | Interacting Amino acid Residues |
|----------------------------|----------|------------|-----------------------------|-----------------------------------|--------------------------------|
| Fluvoxamine                | 5324346  | -5.38      | N-terminal of S1 domain     | Hydrogen bond (H-bond): ILE 235, ASP 198, GLY 232. Hydrophobic interactions (H-I): ASN 87, PHE 86, ILE 233, ASN 234, ASN 196. |
From Table 2, Fluvoxamine showed the binding energy of value -5.38Kcal/mol towards the N-terminal of the S1 domain. Withaferin A extracted from *Withania somnifera* plant showed the lowest B.E. of value -9.15 Kcal/mol, towards the N-terminal of S1 domain, which is known to exhibit anti-inflammatory, anticancer, anti-angiogenic, anti-metastatic, pro-apoptotic, and radiosensitizing properties [24][25]. Whereas, Homoplantagin in extracted from *Salvia plebeia* showed the highest B.E. of -7.01 Kcal/mol, towards N-terminal of S1 domain, which is known to exhibit anti-inflammatory [26], antioxidative [27], antiviral property against influenza virus [28] and is also known to serve as a protective therapeutic agent against the development of atherosclerosis [29].
Table 3: Molecular docking analysis to find out the presumed binding sites of few inhibitors on SARS CoV-2 spike protein with the grid parameter of X = 185.71, Y = 211.633, Z = 234.217 with a dimensions of 76 x 62 x 84 (Å).

| Name of the medicinal plant | Compound | PubChem ID | Binding Affinity (kcal/mol) | Interacting Domain of Spike Protein | Interacting Amino acid Residues |
|-----------------------------|----------|------------|----------------------------|-----------------------------------|--------------------------------|
| Prunus cerasoides            | Kaempferol | 5280863    | -7.27                      | C-terminal of S1 domain            | H-bond: GLN 564, ARG 567, H-I: ARG 577, PHE 543, LEU 546, PHE 565, ASN 544, VAL 576, HIS 519, LEU 517. |
|                             | Pinostrobin | 4101463    | -7.18                      | C-terminal of S1 domain            | H-I: VAL 576, PHE 565, PHE 543, GLN 564, ARG 577, ASN 544, LEU 546, HIS 519, PHE 392, CYS 391, THR 393, GLU 516, LEU 518, LEU 517. |
|                             | Dihydrotector ochrysin | 73201 | -7.12                      | C-terminal of S1 domain            | H-I: ARG 577, VAL 576, GLN 564, PHE 565, PHE 543, ASN 544, LEU 546, HIS 519, CYS 391, GLU 516, THR 393, LEU 518, LEU 517, PHE 392. |
|                             | Pinocembrin | 68071      | -7.04                      | C-terminal of S1 domain            | H-I: ARG 577, VAL 576, GLN 564, PHE 565, PHE 543, ASN 544, HIS 519, CYS 391, LEU 517, PHE 392. |
|                             | Delta- Selinene | 520383 | -7.57                      | C-terminal of S1 domain            | H-I: THR 333, VAL 362, LYS 528, LYS 529, PRO 527, ILE 332, PHE 329, PRO 330, ASN 331, GLY 526, CYS 525. |
| Bidens tripartita           | Copaene | 12303902   | -7.14                      | C-terminal of S1 domain            | H-I: SER 530, ILE 332, PRO 330, CYS 525, VAL 362, ASN 531, LYS 528, PHE 329, PRO 527, GLY 526. |
|                             | Guaiene | 6949       | -7.01                      | C-terminal of S1 domain            | H-bond: CYS 391. H-I: VAL 576, ASN 544, PHE 565, ARG 577, HIS 519, GLN 564, PHE 543, LEU 546, LEU 517, GLY 545, LEU 390. |
| Curcuma longa               | Bisdemethoxycurcumin | 5315472 | -7.16                      | C-terminal of S1 domain            | H-bond: GLN 564. H-I: HIS 519, ARG 577, ASN 544, PHE 565, VAL 576, GLY 545, LEU 546, PHE 543, THR 547. |
|                             | Demethoxycurcumin | 5469424 | -7.05                      | C-terminal of S1 domain            | H-bond: ASN 544, CYS 391. H-I: HIS 519, PHE 565, LEU 517, PHE 543, LEU 546, GLY 545, THR 547, LEU 390. |
| Glycyrrhiza glabra          | Glycyrrhetinic acid | 10114   | -9.31                      | C-terminal of S1 domain            | H-bond: ARG 567, HIS 519, H-I: LEU 518, PHE 565, LEU 517, GLY 381, LEU 546, GLY 545, LEU 390. |
|                             | Isoliquiritigenin | 638278  | -8.44                      | C-terminal of S1 domain            | H-bond: ARG 577. H-I: PHE 543, LEU 546, GLY 545, VAL 576, PHE 565, ASN 544, ALA 522, GLN 564, THR 393, HIS 519, CYS 391, LEU 517, LEU 518, GLU 516. |
|                             | Liquiritigenin | 114829   | -8.01                      | C-terminal of S1 domain            | H-bond: ARG 577, GLN 564. H-I: PHE 543, VAL 576, PHE 565, HIS 519, LEU 546, ASN 544, CYS 391, PHE 392, LEU 517. |
|                             | Chavicine | 1548912   | -8.77                      | C-terminal of S1 domain            | H-bond: ASN 544, GLN 564, CYS 391. H-I: VAL 576, PHE 543, ARG 577, LEU 546, PHE 565, ALA 522, GLY 545, THR 393, HIS 519, PHE 392, LEU 517. |
|                             | Cis-      | 1018788   | -7.8                       | C-terminal of S1 domain            | H-bond: ASN 544, ARG 577. |
| Plant Name                      | Compound          | Purity (mm) | Domain | C-Terminal of S1 | H-Bond             |
|--------------------------------|-------------------|------------|--------|------------------|--------------------|
| *Desmodium gangeticum*         | Imperatorin       | 78         | 5      |                   |                    |
|                                | Resveratrol       | 445154     | 4      |                   |                    |
|                                | Pterostilbene     | 5281727    | 3      |                   |                    |
| *Echinops albicatus*            | Apigenin          | 1333892    | 1      |                   |                    |
| *Fritillaria thunbergii*        | Verticine         | 131900     | 7      |                   |                    |
| *Fritillaria thunbergii*        | Peiminine         | 167691     | 3      |                   |                    |
| *Glycine max*                  | Genistein         | 1231900    | 1      |                   |                    |
|                                | Ononin            | 5280961    | 2      |                   |                    |
|                                | Psoralea corylifolia | 5280907 | 2      |                   |                    |
| *Tinospora cordifolia*          | Magnoflorin       | 2353       | 5      |                   |                    |
|                                | Berberine         | 1333892    | 1      |                   |                    |
| *Vaccinium vitis-idaea*         | Pterostilbene     | 10212      | 1      |                   |                    |
|                                | Resveratrol       | 5281727    | 3      |                   |                    |
| *Angelica dahuirica*            | Imperatorin       | 317611     | 5      |                   |                    |

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| Plant Name                  | Alpha           | C-terminal of S1 domain | H-bond                        |
|----------------------------|-----------------|-------------------------|-------------------------------|
| Annona glabra              | Cadinol         | -7.61                   | H-bond: SER 530.             |
|                            | 6431302         |                         | H-I: ASN 331, PRO 330, CYS 525, ILE 332, PHE 329, LYS 528, LYS 529, VAL 362, PRO 527, GLY 526. |
| Azadirachta indica         | Gedunin         | -7.55                   | H-bond: THR 547, HIS 519.    |
|                            | 12004512        |                         | H-I: LEU 546, ASN 544, CYS 391, GLY 545, LEU 390, PHE 565, LEU 517. |
| Betula alba                | Betulinic acid  | -8.59                   | H-bond: SER 530.             |
|                            | 64971           |                         | H-I: LYS 528, LYS 529, ASN 331, PHE 329, VAL 362, GLY 526, CYS 525, PRO 330, THR 333, ILE 332. |
| Bletilla striata           | Bulbocol        | -7.00                   | H-bond: ASN 544.             |
|                            | 102316540       |                         | H-I: THR 547, LEU 546, LEU 390, GLY 545, PHE 543, CYS 391, GLN 564, HIS 519, PHE 565, LEU 517. |
| Camellia sinensis          | Theaflavin      | -7.55                   | H-bond: CYS 379, PHE 377.    |
|                            | 135403798       |                         | H-I: LYS 378, PRO 384, SER 383, VAL 382, TYR 369, SER 371, THR 376, SER 375, PHE 374, ALA 372. |
| Catharanthus roseus        | Vindolinine     | -7.75                   | H-bond: CYS 391.             |
|                            | 24148538        |                         | H-I: ASN 544, PHE 565, LEU 546, PHE 543, LEU 517, HIS 519, LEU 390, GLY 545. |
| Cunninghamia konishii      | Cedrol          | -7.2                    | H-bond: GLY 526.             |
|                            | 65575           |                         | H-I: SER 530, GLN 580, ASN 331, PHE 329, ILE 332, PRO 330, LYS 528, CYS 525, PRO 527, VAL 362. |
| Curcuma heyneana           | Germacrone      | -7.09                   | H-bond: LYS 528.             |
|                            | 6436348         |                         | H-I: SER 530, PRO 330, PHE 329, VAL 362, CYS 525, ASN 331, PRO 527, GLY 526, CYS 361, ILE 332. |
| Curcuma wenyuan           | Furanodiene     | -7.06                   | H-bond: HIS 519, ASN 544.    |
|                            | 636458          |                         | H-I: ARG 567, LEU 517, ALA 522, THR 393, CYS 391, PHE 392, GLU 516, PHE 543, LEU 546. |
| Ferula pseuddalliacea a    | Kamolonol       | -9.07                   | H-bond: ASN 544, ARG 567, GLN 564. |
|                            | 46883037        |                         | H-I: PHE 565, HIS 519, LEU 517, GLY 545, LUE 390, VAL 576, ARG 577, PHE 543, PRO 579, LEU 546. |
| Hopea malibato             | Balanocarpo 1   | -8.12                   | H-bond: CYS 391, ARG 567, THR 393. |
|                            | 478626          |                         | H-I: THR 547, LEU 546, HIS 519, GLU 516, ASN 544, PHE 565, GLY 545, LEU 390, PHE 529, LEU 517, LEU 518 |
| Litchi chinensis           | Procyanidin A2  | -7.47                   | H-bond: THR 393, THR 547.    |
|                            | 124025          |                         | H-I: ARG 567, ASP 571, GLU 516, LEU 517, LEU 518, HIS 519, LEU 546, GLY 545, PHE 392, ALA 522, CYS 391, ASN 544 |
| Marrubium vulgare          | Marrubiin       | -8.44                   | H-bond: GLN 564.             |
|                            | 73401           |                         | H-I: PHE 543, VAL 576, LEU 546, GLY 545, CYS 391, PHE 565, ASN 544, HIS 519, LEU 517. |
| Melaleuca quinquenervia    | Viridiflorol    | -7.6                    | H-bond: PRO 530, ILE 332.    |
|                            | 11996452        |                         | H-I: ASN 331, SER 530, CYS 525, GLY 526, LYS 529, LYS 528, PHE 329, PRO 527, VAL 362. |
| Momordica charantia        | Momordicin e I  | -8.43                   | H-bond: ARG 567.             |
|                            | 14807332        |                         | H-I: VAL 576, ARG 577, GLN 564, HIS 519, PHE 543, LEU 546, CYS 391, GLY 545, ASN 544, LEU 517, PHE 565. |
| Momordica                 | Foetidin        | -8.40                   | H-bond: SER 530.             |
|                            | 1594506         |                         |                                |
from hepatoprotective properties of S1 domain, which is known to exhibit anti-B.E. of value 9.31Kcal/mol, towards the C-terminal of S1 domain 

Nicotiana tabacum Bergamotene 521569 -7.68 C-terminal of S1 domain H-I: LEU 517, HIS 519, GLN 564, ASN 544, CYS 391, ARG 577, LEU 546, PHE 565, VAL 576, PHE 543.

Oryza sativa Sakuranetin 73571 -7.64 C-terminal of S1 domain H-bond: GLN 564. H-I: LEU 546, VAL 576, PHE 565, ASN 544, ARG 577, PHE 543, PHE 392, HIS 519, CYS 391, THR 393, LEU 517, LEU 518, GLU 516.

Piper cubeba Bisabolene 3033866 -8.07 C-terminal of S1 domain H-I: GLN 564, ARG 577, PHE 565, LEU 546, PHE 543, ASN 544, GLU 516, HIS 519, LEU 517, THR 393, PHE 392, CYS 391, LEU 518.

Polygonatum odoratum Diosgenin 99474 -8.09 C-terminal of S1 domain H-I: VAL 382, SER 383, CYS 379, PRO 384, TYR 369, PHE 377, ALA 372, PHE 374, THR 376, SER 371, SER 375.

Putranjiva roxburghii Wall Amentoflavone 5281600 -7.44 C-terminal of S1 domain H-bond: THR 549. H-I: LEU 517, HIS 519, LEU 390, PHE 565, ARG 567, LEU 546, GLY 545, PHE 541, THR 573, ILE 587, THR 547, GLY 548.

Withania somnifera Withanolide 5347776 5 -8.61 C-terminal of S1 domain H-bond: SER 530, LEU 335. H-I: ASN 331, PRO 330, ILE 332, PRO 527, GLY 526, THR 333, ASN 334, VAL 362, LYS 528, LYS 529.

Similarly, from Table 3, Glycyrrhetinic acid extracted from Glycyrrhiza glabra showed the lowest B.E. of value -9.31Kcal/mol, towards the C-terminal of S1 domain, which is known to exhibit anti-inflammatory, antiparasitic, anticancer, antibacterial, and hepatoprotective properties [30]. Bulbocodin extracted from Bleitilla striata showed the highest B.E. of -7.00 Kcal/mol, towards the C-terminal of S1 domain, which is known to possess good antibacterial properties against various bacterial strains including Methicillin-resistant Staphylococcus aureus ATCC 43300 (MRSA), Bacillus subtilis ATCC 6051, S. aureus ATCC 6538 and this plant is also known to exhibit antioxidant, anticancer, antibacterial and antiviral activities [31][32].

| Name of the medicinal plant | Compound | PubChem ID | Binding Affinity (kcal/mol) | Interacting Domain of Spike Protein | Interacting Amino acid Residues |
|----------------------------|----------|------------|-----------------------------|-----------------------------------|-------------------------------|
| Beta Eudesmol              | 91457    | -7.47      | S2 domain                   | H-bond: SER 975, LEU 977. H-I: ASN 856, PHE 855, MET 740, TYR 741, GLY 744, ARG 1000, LEU 966, VAL 976. |
| Pterocarpol                | 12314741 | -7.21      | S2 domain                   | H-bond: LEU 977, SER 975, PHE 855. H-I: TYR 741, ASN 856, MET 740, GLY 744, LEU 966, ARG 1000, VAL 976. |
| Cryptomeriol               | 165258   | -7.01      | S2 domain                   | H-bond: LEU 977, SER 975. H-I: VAL 976, GLY 744, ARG 1000, TYR 741, LEU 966, MET 740, ASN 856, PHE 855. |
| Adiantum                   | 15558363 | -8.2       | S2 domain                   | H-I: VAL 963, SER 967, LEU 966, SER 975, ASN 856, ASN 978, LEU 977, ARG 1000, GLY 744. |

Table 4: Molecular docking analysis to find out the presumed binding sites of few inhibitors on SARS CoV-2 spike protein with the grid parameter of X = 211.705, Y = 222.835, Z = 214.334 with the dimensions of 46 x 42 x 88 (Å).
| Plant Species                | Chemical Compound       | IC50 Value | Binding Site          | H-bonded Residues                                                                 | H-bound Residues                                                                 |
|-----------------------------|-------------------------|------------|-----------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Lunulatum                   | Filicenol-B             | 10111424   | -8.14 S2 domain       | LEU 977, SER 975, H-I: LEU 966, SER 967, VAL 976, TYR 741, ARG 1000, ASN 856, GLY 744, MET 740, PHE 855. |                                                                                   |
| Glycyrrhiza glabra          | Glabridin               | 124052     | -7.5 S2 domain        | H-bond: LEU 977, GLY 744, ARG 1000.                                               | H-bound: LEU 966, SER 967, SER 975, VAL 976, CONT 743, ASN 856.                  |
| Tinospora cordifolia        | Licochalcone A          | 5318998    | -7.49 S2 domain       | H-bond: ARG 1000, GLY 744, H-I: LEU 963, LYS 964, SER 967, SER 975, VAL 976, PHE 855, ASN 856, LEU 977, ILE 742, MET 740, TYR 741. |                                                                                   |
| Amaranthus viridis          | Betasitosterol          | 222284     | -8.2 S2 domain        | H-bond: LEU 977, VAL 963, SER 967, ARG 1000, ASN 856, MET 740, SER 975, SER 976, GLY 744, MET 740, VAL 976, H-I: LEU 977, VAL 976, ARG 1000. |                                                                                   |
| Alpinia officinarum         | Galangin                | 5281616    | -7.1 S2 domain        | H-bond: ARG 1000, GLY 744, H-I: LEU 966, SER 967, SER 975, VAL 976, ASN 856, MET 740, GLY 744, LEU 977. |                                                                                   |
| Catharanthus roseus         | Vindolidine             | 12932039   | -8.45 S2 domain       | H-bond: LEU 977, ARG 1000, APR 995, ASP 994.                                       | H-bound: LEU 966, SER 975, SER 967, SER 975, VAL 976, LYS 964, VAL 963, ASN 856, MET 740, GLY 744. |
| Cryptomeria japonica        | Isopimaric acid         | 442048     | -7.46 S2 domain       | H-bond: LEU 977, ARG 1000, APR 995, ASP 994.                                       | H-bound: LEU 966, SER 975, SER 967, SER 975, VAL 976, LYS 964, VAL 963, ASN 856, MET 740, GLY 744. |
| Daucus carota               | Betacarotene            | 5280489    | -9.52 S2 domain       | H-bond: ARG 1014, GLN 1010, ALA 958, TYR 1007, THR 961, THR 1006, GLN 965, SER 1003, GLN 602, GLY 999, PHE 970, THR 998, ARG 995, ASP 994. | H-bound: LEU 977, ARG 1000, APR 995, ASP 994.                                     |
| Laburnum anagyroides        | Luteone                 | 5281797    | -7.5 S2 domain        | H-bond: LEU 977, ARG 1000, APR 995, ASP 994.                                       | H-bound: LEU 977, ARG 1000, APR 995, ASP 994.                                     |
| Linum usitatissimum         | Matairesinol            | 119205     | -7.06 S2 domain       | H-bond: ARG 1000, H-I: LEU 977, ASN 856, VAL 976, SER 975, GLY 744, MET 740, PHE 855. | H-bound: ARG 1000, ASN 856, VAL 976, SER 975, GLY 744, MET 740, PHE 855.          |
| Piper nigrum                | Piperine                | 638024     | -7.16 S2 domain       | H-bond: GLN 956, ARG 1014, H-I: THR 961, GLN 1010, TYR 1007, ALA 958, THR 1006, SER 1003, GLN 1002, GLY 999, PHE 970, THR 998, ARG 995, ASP 994. | H-bound: GLN 956, ARG 1014, H-I: THR 961, GLN 1010, TYR 1007, ALA 958, THR 1006, SER 1003, GLN 1002, GLY 999, PHE 970, THR 998, ARG 995, ASP 994. |
| Prunus cerasoides           | Chrysine                | 5281607    | -7.03 S2 domain       | H-bond: GLY 744, LEU 977, ARG 1000.                                               | H-bound: GLY 744, LEU 977, ARG 1000.                                             |
| Salvia officinalis          | Safficinolide           | 85152699   | -8.01 S2 domain       | H-bond: ARG 1000, LEU 977, SER 975, VAL 976, SER 967, LEU 966, MET 740, TYR 741, ASN 856. | H-bound: ARG 1000, LEU 977, SER 975, VAL 976, SER 967, LEU 966, MET 740, TYR 741, ASN 856. |
And from Table 4, Beta-carotene extracted from *Daucus carota* plant showed the lowest B.E. of -9.52 Kcal/mol, towards the S2 domain, which is found to possess antioxidative [33], anticancer properties and is also known to enhance the immune system [34]. Whereas, Cryptomeridicol extracted from *Pterocarpus santalinus* showed the highest B.E. of -7.01 Kcal/mol, towards the S2 domain. In silico docking studies on this phytochemical reveals it as a potent drug candidate against the Hepatitis B virus [35].

In total, out of 200 screened phytochemicals, 86 of them exhibited binding energies of value ≤ -7.00Kcal/mol upon docking, which is significant in comparison to Fluvoxamine. And the range of binding energy varies from -9.52 to -7.00 Kcal/mol wherein 4 phytochemicals showed binding energies of < -9.00 Kcal/mol, 29 phytochemicals showed -9.00 < x ≤ -8.00 Kcal/mol (x = Binding energy) and 53 phytochemicals showed -8.00 < x ≤ -7.00 Kcal/mol. The docking values of all those phytochemicals, including Fluvoxamine, showed binding affinity towards all three regions, namely S1-N terminal, S1-C terminal, and S2 domain of the spike glycoprotein. Molecular interactions between the ligand-receptor, including Hydrogen bonds, are listed in Table 2, 3 and 4. Docking results were confirmed through H-bond and visualization. The putative binding site of Withaferin A on receptor spike protein SARS-CoV-2 is represented in Fig. 5 and Fig. 6 represents the interacting amino acid residues of SARS CoV-2 spike protein with Withaferin A.

**Table 5: ADME properties of few selected inhibitors against SARS-CoV-2 (spike protein)**

| Name of The Phytochemical | Molecular Weight (<500 Da) | MlogP (<4.15) | H – Bond Donor (5) | H – Bond Acceptor (<10) | Violations | Drug Likeliness |
|---------------------------|---------------------------|---------------|-------------------|------------------------|------------|-----------------|
| Fluvoxamine               | 318.33                    | 2.56          | 1                 | 7                      | 0          | Yes             |
| Betacyanin                | 550.47                    | -4.72         | 8                 | 13                     | 3          | No              |
| Gangetinin                | 418.48                    | 3.37          | 0                 | 5                      | 0          | Yes             |
| Naringin                  | 580.53                    | -2.77         | 8                 | 14                     | 3          | No              |
| Oleanane                  | 412.73                    | 9.05          | 0                 | 0                      | 1          | Yes             |

4.2 ADME studies & Drug likeliness prediction

Best molecular interactions between the ligand and receptor were selected through visualization. The interactions with the lowest binding energies, i.e., ≤ -7.00Kcal/mol, were chosen for ADME analysis to check the ligand's drug-likeness that follows Lipinski's Rule of Five.

Lipinski's rule of five is a rule of thumb to measure drug likeliness (or) to find whether the compound with specific therapeutic properties is likely to have chemical and physical properties that would make it an orally active drug. This rule outlines the molecular properties necessary for a drug's pharmacokinetics in the human body, such as Absorption, distribution, metabolism, and excretion. The guideline prioritized that the compound should have the following criteria,

1. Molecular mass less than 500 Daltons,
2. A logarithm octanol-water partition coefficient (MlogP) should not exceed 4.15,
3. No more than 5 hydrogen bond donor,
4. No more than 10 hydrogen bond acceptor.

The violation of more than 1 of these conditions predicts that a compound is not an orally active drug [36].

Thus, the selected phytochemicals (< B.E. ≤ -7.00Kcal/mol) were screened virtually using the Swiss ADME web tool. And their molecular weight, MlogP, Hydrogen donor, and Hydrogen acceptor were analyzed and are enlisted in Table 5.
| Compound                | Mass   | Retention Time | Peak Area | Width | Detection | Status |
|-------------------------|--------|----------------|-----------|-------|-----------|--------|
| Morusin                 | 420.45 | 2.09           | 3         | 6     | 0         | Yes    |
| Ursolic acid            | 456.70 | 5.82           | 2         | 3     | 1         | Yes    |
| Maslinic acid           | 472.70 | 4.97           | 3         | 4     | 1         | Yes    |
| Ginsenosides            | 444.73 | 6.00           | 2         | 2     | 1         | Yes    |
| Piperlongumunine        | 273.33 | 2.14           | 1         | 3     | 0         | Yes    |
| Eusacphic Acid          | 488.70 | 4.14           | 4         | 5     | 0         | Yes    |
| Homoplantaginin         | 462.4  | -1.89          | 6         | 11    | 2         | No     |
| Withaferin A            | 470.60 | 2.75           | 2         | 6     | 0         | Yes    |
| Kaempferol              | 286.24 | -0.03          | 4         | 6     | 0         | Yes    |
| Pinostrobin             | 270.28 | 1.52           | 1         | 4     | 0         | Yes    |
| Dihydrotectochrysin     | 270.28 | 1.52           | 1         | 4     | 0         | Yes    |
| Pinocembrin             | 256.25 | 1.27           | 2         | 4     | 0         | Yes    |
| Delta-Selinene          | 204.35 | 4.63           | 0         | 0     | 1         | Yes    |
| Copaene                 | 204.35 | 5.65           | 0         | 0     | 1         | Yes    |
| Guaiene                 | 204.35 | 4.63           | 0         | 0     | 1         | Yes    |
| Bisacurone              | 252.35 | 1.66           | 2         | 3     | 0         | Yes    |
| Bisdemethoxycurcumin    | 308.33 | 2.13           | 2         | 4     | 0         | Yes    |
| Demethoxycurcumin       | 338.35 | 1.80           | 2         | 5     | 0         | Yes    |
| Glycyrrhetic acid       | 470.68 | 4.87           | 2         | 4     | 1         | Yes    |
| Isoliquiritigenin       | 256.25 | 1.58           | 3         | 4     | 0         | Yes    |
| Liquiritigenin          | 256.25 | 1.27           | 2         | 4     | 0         | Yes    |
| Chavicine               | 285.34 | 2.39           | 0         | 3     | 0         | Yes    |
| Cis-Piperettine         | 311.37 | 2.78           | 0         | 3     | 0         | Yes    |
| Caryophyllene           | 204.35 | 4.63           | 0         | 0     | 1         | Yes    |
| Desmodin                | 382.41 | 2.06           | 1         | 6     | 0         | Yes    |
| Gaetelin                | 420.50 | 3.37           | 1         | 5     | 0         | Yes    |
| Genkwanin               | 284.26 | 0.77           | 2         | 5     | 0         | Yes    |
| Apigenin                | 270.24 | 0.52           | 3         | 5     | 0         | Yes    |
| Verticene               | 431.65 | 3.83           | 3         | 4     | 0         | Yes    |
| Peimnine                | 429.64 | 3.68           | 2         | 4     | 0         | Yes    |
| Genistein               | 270.24 | 0.52           | 3         | 5     | 0         | Yes    |
| Ononin                  | 430.40 | -0.89          | 4         | 9     | 0         | Yes    |
| Corylin                 | 320.34 | 2.20           | 1         | 4     | 0         | Yes    |
| Psoralen                | 186.16 | 1.48           | 0         | 3     | 0         | Yes    |
| Magnoflorine            | 342.41 | -1.71          | 2         | 4     | 0         | Yes    |
| Berberine               | 336.36 | 2.19           | 0         | 4     | 0         | Yes    |
| Pterostilbene           | 256.30 | 2.76           | 1         | 3     | 0         | Yes    |
| Resveratol              | 228.24 | 2.26           | 3         | 3     | 0         | Yes    |
| Imperatorin             | 270.28 | 2.14           | 0         | 4     | 0         | Yes    |
| Alpha Cadinol           | 222.37 | 3.67           | 1         | 1     | 0         | Yes    |
| Gedunin                 | 482.57 | 2.56           | 0         | 7     | 0         | Yes    |
| Compound            | MW     | SD    | Rf   | M     | Status |
|---------------------|--------|-------|------|------|--------|
| Betulinic acid      | 456.70 | 5.82  | 2    | 3    | Yes    |
| Bulbocol            | 364.43 | 3.62  | 2    | 4    | Yes    |
| Theaflavin          | 564.49 | -0.79 | 9    | 12   | No     |
| Vindolinine         | 336.43 | 3.12  | 1    | 3    | Yes    |
| Cedrol              | 222.37 | 3.81  | 1    | 1    | Yes    |
| Germacrone          | 218.33 | 3.37  | 0    | 1    | Yes    |
| Furanodiene         | 216.32 | 3.33  | 0    | 1    | Yes    |
| Kamolonol           | 398.49 | 3.00  | 1    | 5    | Yes    |
| Balanocarpol        | 470.47 | 2.13  | 6    | 7    | Yes    |
| Procyanidin A2      | 576.5  | 0.14  | 9    | 12   | No     |
| Marrubiin           | 332.43 | 4.06  | 3    | 4    | Yes    |
| Viridiflorol        | 222.37 | 3.18  | 1    | 1    | Yes    |
| Momordicine I       | 472.7  | 4.06  | 3    | 4    | Yes    |
| Foetidin            | 382.49 | 3.83  | 1    | 4    | Yes    |
| Bulbocodin          | 456.53 | 4.06  | 4    | 5    | Yes    |
| Bergamotene         | 204.35 | 4.63  | 0    | 0    | Yes    |
| Sakuranetin         | 286.28 | 0.96  | 2    | 5    | Yes    |
| Bisabolene          | 204.35 | 4.53  | 0    | 0    | Yes    |
| Diosgenin           | 414.62 | 4.94  | 1    | 3    | Yes    |
| Amentoflavone       | 538.46 | 0.25  | 6    | 10   | No     |
| Withanolide         | 470.60 | 2.75  | 2    | 6    | Yes    |
| Beta Eudesmol       | 222.37 | 3.67  | 1    | 1    | Yes    |
| Pterocarpol         | 238.37 | 2.74  | 2    | 2    | Yes    |
| Cryptomeridiol      | 240.38 | 2.88  | 2    | 2    | Yes    |
| Adiantone           | 412.69 | 6.73  | 0    | 1    | Yes    |
| Filicenol-B         | 426.72 | 6.92  | 1    | 1    | Yes    |
| Piperine            | 285.34 | 2.39  | 0    | 3    | Yes    |
| Glabrirdin          | 324.37 | 2.73  | 2    | 4    | Yes    |
| Licochalcone A      | 338.40 | 2.92  | 2    | 4    | Yes    |
| Beta sitosterol     | 414.71 | 6.73  | 1    | 1    | Yes    |
| Tinocordiside       | 396.47 | 0.28  | 4    | 7    | Yes    |
| Zeylanone           | 374.34 | 0.69  | 2    | 6    | Yes    |
| Vindoloidine        | 369.48 | -1.17 | 2    | 3    | Yes    |
| Alpha spinasterol   | 412.69 | 6.62  | 1    | 1    | Yes    |
| Safficinolide       | 344.40 | 2.25  | 1    | 5    | Yes    |
| Luteone             | 354.35 | 1.09  | 4    | 6    | Yes    |
| Beta carotene       | 536.87 | 8.96  | 0    | 0    | Yes    |
| Isopimaric acid     | 302.45 | 4.54  | 1    | 2    | Yes    |
| Galangin            | 270.24 | 0.52  | 3    | 5    | Yes    |
| Matairesinol        | 358.39 | 1.9   | 2    | 6    | Yes    |
| Chrysin             | 254.24 | 1.08  | 2    | 4    | Yes    |
It was observed that most of the compounds, including Fluvoxamine, followed the Lipinski rule of 5, however out of 86 phytochemicals, 60 of them showed zero violations, 19 showed 1 violation, 3 phytochemicals showed 2 violations, and 4 of them showed 3 violations. Hence, ADME analysis and drug likeliness studies of all the 86 phytochemicals were conducted. Out of which, only 79 of them exhibited satisfactorily acceptable properties, thus intimating that these phytochemicals have the potential to form an antiviral drug or inhibitor against SARS-CoV-2. The ADME properties of Withaferin A against SARS CoV-2 spike protein is represented in Fig. 7.

Figure 7: ADME properties of Withaferin A against SARS CoV-2 spike protein.

IV. CONCLUSIONS

Currently, the outbreak of the COVID-19 has become the biggest threat to human health, and the non-availability of any specific antiviral drug has created a global challenge for developing an effective drug or inhibitor against SARS-CoV-2 that can be quickly produced and easily distributed at an affordable cost. In this situation, the Insilico approach can be a handy tool to identify the bioactive compound that can inhibit its entry into the host cells, which can be the possible therapeutic solution against the disease. The drug repurposing approach has been effectively used to identify the most appropriate potent drugs or inhibitors. The present study is based on identifying potential inhibitors against the spike glycoprotein of SARS CoV-2 by employing various bioinformatic tools.

In this study, 79 phytochemicals extracted from various medicinal plants capable of binding to either S1 or S2 domain of SARS-CoV-2 protein with better binding energies than that of repurposed Fluvoxamine drug that is currently in use for treating the patients with mild COVID-19 were identified. This finding suggests that all of these 79 phytochemicals can serve as effective alternative therapeutics against the COVID-19 infection. However, most of the current research is theoretically based and does not present any analytical validation. Therefore, further optimization and validation processes, including preclinical and clinical studies, are required to form a viable drug candidate. Apart from that, many more such bioactive compounds from other medicinal plants existing in the biodiversity need to be further explored.

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