



# Evaluation of some plant-derived natural ingredients against SARS-CoV-2: An *in-silico* approach

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## Abstract

**Background:** The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), infected by a new strain of human coronavirus, has engulfed the whole globe with its vicious potential to eradicate humankind. The pandemic has emerged from the Wuhan provinces of China with high transmissibility. Researchers are rushing to discover vaccines and drugs for the disease, which is not known yet. In this study, we have focused on the *in-silico* screening of phytochemicals occurring naturally in plant extracts that could possibly interact with receptor binding motif (RBM) of spike protein and thereby inhibit virus-cell interaction.

**Materials and Methods:** In this study, we have taken 100 phytochemicals that have been studied in various viral interactions and have shown antiviral properties. Initially, these compounds were analyzed on the basis of their physicochemical and pharmacokinetic properties, biological activities, possible target interactions, similar compounds in humans, and gene regulations using bioinformatic tools, namely Swiss-ADME, PASS (prediction of activity spectra for substances), SwissTargetPrediction, similar ensemble approach (SEA) search server, DIEGP-pred, respectively and were filtered out on the basis of immunobiological activities and expression of genes involved in cytokine storm regulation and immunostimulation. Further, they were docked with the receptor-binding domain (RBD) of spike protein in the SARS-CoV-2 using SwissDock and analyzed by UCSF Chimera.

**Results:** A hundred phytochemicals were analyzed on the basis of their physicochemical, pharmacokinetics, biological activities, and gene expression. Out of which 20 compounds were found to be fit all the criteria and were docked with the receptor binding domain (RBD) of the spike protein of SARS-CoV-2. Although almost every one of them showed binding with RBD, two phytochemicals, namely, orientin and apigenin, naturally found in *Ocimum sanctum* and chamomile, were found to bind with RBM and interacted with amino acid sequences that are mainly involved in RBM-ACE2 (angiotensin-converting enzyme 2) interaction.

**Conclusions:** We have got phytochemicals that interact directly in the receptor-binding motif of the spike protein. These phytochemicals were also screened for their pharmacokinetics and physiochemical activities, which make sure that the compound holds efficient drug-like properties. This could be a robust test of an iterative framework of inhibiting virus-receptor interaction with the help of phytochemicals.

**Keywords:** Phytochemicals, SARS-CoV-2, Pharmacokinetics, Molecular docking



## Background

The first epidemic of 2019 was burst out in December when novel coronavirus (SARS-CoV-2, severe acute respiratory syndrome coronavirus 2) took place in Wuhan city, China.<sup>1,2</sup> Since the outbreak, it has been rapidly infecting people around the world and turned into a pandemic. The virus conserves significant phylogenetic and structural familiarity (about 80% nucleotide identity and 89.10%

nucleotide similarity) with the SARS-CoV.<sup>3,4</sup> Therefore, it has been named SARS-CoV-2 and has been placed in the same lineage.<sup>5</sup> Vaccines are under development, and to date, there is no permanent solution to eradicate the pandemic from the world. The transmission rate of the virus is massive worldwide, and hence all researchers over the world are keenly looking forward to the effective compounds that could act as anti-CoV therapeutic agents.



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The trimeric S protein envelops the surface of coronavirus and plays a crucial role during viral entry.<sup>6</sup> During infection, the S protein is cleaved into the N-terminal S1 subunit and C-terminal S2 subunit by host proteases.<sup>7</sup> S1 sequences are relatively well conserved within each coronavirus group but differ markedly between different groups. S1 contains two independent domains, the N-terminal domain and C domain, that can both serve as viral receptor-binding domains (RBDs). C domain binds to aminopeptidase N or *angiotensin-converting enzyme 2 (ACE2)* in coronaviruses that use them as receptors.<sup>8</sup> Compared to the synthetic inhibitors plant based-drugs have less toxicity and much safer to use. Natural products such as traditional medicines and plant-derived compounds (phytochemicals) are the rich sources of promising antiviral drugs.<sup>9,10</sup> Around 44% of the approved antiviral drugs between 1981 and 2006 were derived from natural products. Phytochemicals have been identified by computational drug development approaches to be effective against SARS-CoV-2.<sup>11-15</sup>

In this context, in our study, we have taken 100 potential phytochemicals that have been studied extensively in various antiviral interactions with coronavirus and analyzed their interactions with spike protein by using *in silico* approaches.

## Materials and Methods

### Phytochemicals in the Study

A hundred phytochemicals with reported antiviral properties were selected from the literature. All these phytochemicals were subjected to various physicochemical and pharmacokinetic analyses, and possible targets were predicted.

### Analysis of Physiochemical and Pharmacokinetics Properties Using the SwissADME

The molecules to be estimated for physiochemical and pharmacokinetics studies were input as Canonical SMILES, and the programme was run. Physiochemical properties such as the number of heavy aromatic atoms, fraction Csp<sup>3</sup>, rotatable bonds, H-bond receptors and donors, molecular refractivity, lipophilicity, and water solubility were determined. Pharmacokinetics properties included GI absorption, blood-brain barrier permeation, permeability glycoprotein (P-GP), and drug metabolism.<sup>13</sup>

### Predicting Biological Activity Using PASS

Evaluation of the general biological potential for drug-like compounds based on their structural formula can be performed with a computer program, PASS (prediction of activity spectra for substances). Information of the phytochemicals was input in CANONICAL smiles format. PASS software estimates the predicted activity spectrum of a compound as a probable activity or active (Pa) and probable inactivity or inactive (Pi). The PASS user obtains

output information as a list of predicted types of activity with the estimated probability for each type of activity: 'to be active,' Pa and 'to be inactive,' Pi. The probabilities, Pa and Pi values vary from 0.000 to 1.000 and, in general, Pa  $\neq$  Pi = 1. In this study, we set to cut off the value of Pa 'to be active' is Pa > 0.7 and select the compound for the prediction that occurs above the cut-off.<sup>14</sup>

### Predicting Biological Targets Using SwissTargetPrediction and Similar Ensemble Approach

SwissTargetPrediction is based on the observation that similar biological active molecules are more similar to targets in three different species. Therefore, the targets of a molecule can be predicted by combination with a known compound that is highly similar to the query molecule. A significant prospect is the accuracy similarity between the query molecule and the known compound. Whenever a compound shows a high similarity under the predictions have shown strong bind interactions with similar targets. The target probability value lies between 0 to 1, with the largest possible value being reached if the query molecule is a known compound of the target. The name of the target, their classes, and their Uniprot ID are displayed. The probability score indicates the activity of the compound.<sup>15</sup> The similarity ensemble approach (SEA) search server can be used to predict specific molecular targets. The sequence of structural similarity among targets by the similarity of the compound that binds to them is expressed as significant values and maximum Tanimoto similarity. The values exhibited a stronger relationship between compounds.<sup>16</sup>

### Prediction of Changes in Gene Expression Pattern Based on Protein Using DIGEP-Pred

DIGEP-Pred, which is a web service for *in silico* prediction of drug-induced changes of gene expression profiles. The genes regulated by the phytochemicals -either up- or downregulated can be studied on the basis of protein prediction. Parameters set were Pa > Pi and Pa > 0.5.<sup>17</sup>

### Extraction of Compounds on the Basis of Immunobiological Activities Directly Involved During Viral Infection

After analyzing physiochemical and pharmacokinetic properties of 100 phytochemicals, some of them were filtered out as they showed immunobiological activities and expression of genes involved in cytokine storm regulation and immunostimulation. The genes considered mainly were PRDX2, CD14, CD86, CD83, and CCL2. All five of them have a potential role in immunoregulation and antigen presentation during viral entry. CCL2 gene is one of several cytokine genes clustered on the q-arm of chromosome.<sup>17-19</sup>

### Protein-Ligand Docking using SwissDock and UCSF

## Chimera

### *Protein Molecular Modeling of Receptor Binding Domain of Spike Protein*

The sequence of receptor binding domain (RBD) of the spike protein stretching from 333 to 527<sup>20</sup> complexed with ACE2 was retrieved from RCSB PDB (ID: 6zlg). Thereafter, both the structures were separated individually, and, in this study, the RBD of spike protein is used as the receptor for protein-ligand docking.

### *Ligand Preparation of the Phytochemicals for Docking*

The 3-D structure of filtered phytochemicals was retrieved from PubChem<sup>21</sup> in pdf format. It was then converted in Mol2 using UCSF Chimera.

### *Protein-Ligand Docking Using SwissDock*

Both spike protein and ligand were prepared in their respective format (Receptor in PDB and ligand in Mol2) and were subjected for docking. Many binding clusters are generated (blind docking) in the target cavities and their full fitness (Kcal/mol) and delta G (Kcal/mol).

### *Analysis of Docked Models*

The interaction of the phytochemicals with the RBD of spike protein was analyzed using UCSF Chimera. Hydrophobic and hydrogen bonding were considered in the region of receptor binding motif (RBM), which extends from 438-506 amino acid sequence.

## Results

### *Physicochemical and Pharmacokinetic Properties of Phytochemicals*

The physicochemical and pharmacokinetic properties of the compounds are represented in Table S1. Lipophilicity has correlated to the biological activity of any drug molecule. This is responsible for the stronger binding to the target protein. Lipophilicity affects several other pharmacokinetic parameters of drug molecules such as lower water solubility, higher permeability in the gastrointestinal tract across the blood-brain barrier and other tissue membranes, higher protein binding). As per RO5 (Lipinski's rule of five), a chemical compound to be orally active in human should follow a minimum of three criteria of the following: (a) molecular weight  $\leq 500$ , (b) XLOGP3  $< 3.5$ , (c) hydrogen bond acceptor  $\leq 10$  and hydrogen bond donor  $\leq 5$ . Therefore, compounds following the rules are noted, and others are knocked out. Also, the pharmacokinetics of the compounds are also analyzed (Table S1).

### *Biological Activity of the Compounds*

Possible biological activity of all the compounds retrieved was analyzed, and the properties that could involve in the disease regulation are taken into consideration. Properties such as anti-inflammatory, antioxidant, HIV-1 integrase,

antioxidant (Table 1) have been highlighted and taken into further analyses, and other compounds were knocked out. The SEA search server is also used to predicate structural similarity and biological target molecule in different species. We observed many compounds showing structural similarity and active biological target molecules in the human species in the current study. The higher probability compounds in the human species are highlighted in Table 2.

### *Gene Expression Studies Induced by the Phytochemical Compounds*

The gene expression of the compounds evaluated using DIGEP-Pred, showed a plethora of genes involved in the various kinds of biological activities that have been regulated either positively or negatively by the compounds. In our study, we have taken five genes, namely PRDX2, CD14, CD86, CD83, CCL3, and CCL2 are taken into account from the displayed genes as they could be directly involved in the immunogenicity of the virus and cytokine regulation during disease. PRDX2 plays an antioxidant protective role in cells, and it may contribute to the antiviral activity of CD8(+) T-cells. The protein encoded by the CD14 gene is a surface antigen that is preferentially expressed on monocytes/macrophages. It cooperates with other proteins to mediate the innate immune response. CD86 and CD83 are involved in the antigen presentation, and CCL2 is one of several cytokine genes clustered on the q-arm of chromosome 17. Compounds regulating these were filtered and was subjected to further analysis (Table 3).

### *Binding of Phytochemicals With Spike Protein*

Out of 100 phytochemicals analyzed, 20 of them were filtered out using various parameters of physical and biological activities. These 20 phytochemicals were subjected to protein docking using SwissDock. The extracted file contained the clusters of docks having various binding affinity and  $\Delta G$  energy. The analysis of the interaction of these 20 phytochemicals with RBD of spike protein was carried out using UCSF Chimera. Although almost every compound showed a binding affinity with RBD in its pocket, it was noted that only two compounds, namely orientin and apigenin, showed hydrogen interactions in the region of RBM, where the spike protein interacts with ACE2.

The phytochemical Orientin binds with RBM of the spike protein with a full fitness of -1482.80 kcal/mol and  $\Delta G$  of -6.61 kcal/mol (Figure 1). Apigenin showed binding with RBM with a full fitness score of -1559.63 kcal/mol and  $\Delta G$  of -6.39 Kcal/mol (Figure 2). We also find that the targeted docking of orientin with RBD interacted with S494, N440, S477, and T478 OF RBD, and apigenin showed interaction with S494 and G502 of RBD.

**Table 1.** Biological Activities of Phytochemical compounds.

| S.No. | Compound Name        | Biological activity (Pa>Pi. Pa>0.7) |       |   |
|-------|----------------------|-------------------------------------|-------|---|
|       |                      | Pa                                  | Pi    | Activity  |
| 1     | Apigenin             | 0.912                               | 0.001 | Quercetin 2,3-dioxygenase inhibitor                 |
|       |                      | 0.911                               | 0.005 | HIF1A expression inhibitor                          |
|       |                      | 0.826                               | 0.003 | APOA1 expression enhancer                           |
|       |                      | 0.798                               | 0.008 | JAK2 expression inhibitor                           |
|       |                      | 0.791                               | 0.003 | Histamine release inhibitor                         |
|       |                      | 0.732                               | 0.004 | Antioxidant   |
|       |                      | 0.732                               | 0.002 | NOS2 expression inhibitor                           |
|       |                      | 0.730                               | 0.005 | Insulysin inhibitor                                 |
| 2     | Beta-sitosterol      | 0.886                               | 0.003 | Oxidoreductase inhibitor                            |
|       |                      | 0.849                               | 0.006 | Respiratory analeptic                               |
|       |                      | 0.796                               | 0.010 | Protein-disulfide reductase (glutathione) inhibitor |
|       |                      | 0.762                               | 0.009 | Immunosuppressant                                   |
| 3     | Bisdemethoxycurcumin | 0.980                               | 0.002 | HIF1A expression inhibitor                          |
|       |                      | 0.962                               | 0.001 | JAK2 expression inhibitor                           |
|       |                      | 0.825                               | 0.003 | TNF expression inhibitor                            |
|       |                      | 0.798                               | 0.001 | HIV-1 integrase (Strand Transfer) inhibitor         |
|       |                      | 0.780                               | 0.002 | HIV-1 integrase (3'-Processing) inhibitor           |
|       |                      | 0.733                               | 0.003 | Choleretic  |
|       |                      | 0.723                               | 0.002 | HIV-1 integrase inhibitor                           |
|       |                      | 0.704                               | 0.015 | Anti-inflammatory                                   |
| 4     | Brachyamide B        | 0.858                               | 0.002 | MMP9 expression inhibitor                           |
|       |                      | 0.874                               | 0.018 | Membrane integrity agonist                          |
|       |                      | 0.789                               | 0.004 | Neurotransmitter uptake inhibitor                   |
|       |                      | 0.774                               | 0.004 | Carminative   |
|       |                      | 0.739                               | 0.005 | TNF expression inhibitor                            |
|       |                      | 0.716                               | 0.005 | Sigma receptor agonist                              |
| 5     | Caleb in-A           | 0.903                               | 0.003 | JAK2 expression inhibitor                           |
|       |                      | 0.812                               | 0.006 | Anti-inflammatory                                   |
|       |                      | 0.754                               | 0.004 | Insulysin inhibitor                                 |
| 6     | Campesterol          | 0.839                               | 0.006 | Respiratory analeptic                               |
|       |                      | 0.761                               | 0.010 | Immunosuppressant                                   |
| 7     | Cirsilineol          | 0.934                               | 0.004 | HIF1A expression inhibitor                          |
|       |                      | 0.816                               | 0.027 | Ubiquinol-cytochrome-c reductase inhibitor          |
|       |                      | 0.769                               | 0.004 | Insulysin inhibitor                                 |
|       |                      | 0.760                               | 0.002 | NOS2 expression inhibitor                           |
|       |                      | 0.726                               | 0.004 | Histamine release inhibitor                         |
| 8     | Cirsimaritin         | 0.932                               | 0.004 | HIF1A expression inhibitor                          |
|       |                      | 0.849                               | 0.005 | JAK2 expression inhibitor                           |
|       |                      | 0.754                               | 0.004 | Insulysin inhibitor                                 |
|       |                      | 0.730                               | 0.002 | NOS2 expression inhibitor                           |
|       |                      | 0.701                               | 0.005 | Histamine release inhibitor                         |
| 9     | Cordifolioside A     | 0.852                               | 0.006 | Immunostimulant                                     |
| 10    | Cordioside           | 0.845                               | 0.006 | Respiratory analeptic                               |
|       |                      | 0.749                               | 0.011 | Immunosuppressant                                   |
| 11    | Crategolic acid      | 0.975                               | 0.001 | Insulin promoter                                    |

**Table 1.** Continued

| S.No. | Compound Name                                     | Biological activity (Pa>Pi. Pa>0.7) |       |   |
|-------|---|-------------------------------------|-------|---|
|       |   | Pa                                  | Pi    | Activity                                    |
|       |   | 0.880                               | 0.005 | Anti-inflammatory                           |
|       |   | 0.744                               | 0.004 | Antiviral (Influenza)                       |
| 12    | Curcumin  | 0.706                               | 0.002 | HIV-1 integrase (Strand Transfer) inhibitor |
| 13    | Cyclocurcumin                                     | 0.837                               | 0.005 | JAK2 expression inhibitor                   |
|       |   | 0.774                               | 0.014 | HIF1A expression inhibitor                  |
| 14    | Demethoxycurcumin                                 | 0.723                               | 0.002 | NOS2 expression inhibitor                   |
|       |   | 0.978                               | 0.001 | JAK2 expression inhibitor                   |
| 15    | Eugenitin   | 0.974                               | 0.002 | HIF1A expression inhibitor                  |
|       |   | 0.806                               | 0.011 | HIF1A expression inhibitor                  |
| 16    | Flavonol glucoside                                | 0.754                               | 0.002 | NOS2 expression inhibitor                   |
|       |   | 0.735                               | 0.004 | Histamine release inhibitor                 |
| 17    | Hesperetin  | 0.877                               | 0.002 | Histamine release stimulant                 |
|       |   | 0.766                               | 0.014 | HIF1A expression inhibitor                  |
| 18    | Isothymonin                                       | 0.705                               | 0.006 | Antidiabetic                                |
|       |   | 0.713                               | 0.014 | Anti-inflammatory                           |
| 19    | Isothymusin                                       | 0.909                               | 0.001 | NOS2 expression inhibitor                   |
|       |   | 0.911                               | 0.005 | HIF1A expression inhibitor                  |
| 20    | Kaempferol  | 0.778                               | 0.010 | JAK2 expression inhibitor                   |
|       |   | 0.959                               | 0.003 | HIF1A expression inhibitor                  |
| 21    | Orientin  | 0.833                               | 0.002 | NOS2 expression inhibitor                   |
|       |   | 0.824                               | 0.006 | JAK2 expression inhibitor                   |
| 22    | Pentadienoylpiperidine (1-Pentadienoylpiperidine) | 0.960                               | 0.003 | HIF1A expression inhibitor                  |
|       |   | 0.783                               | 0.002 | NOS2 expression inhibitor                   |
| 23    | Quercetin   | 0.788                               | 0.009 | JAK2 expression inhibitor                   |
|       |   | 0.759                               | 0.002 | Quercetin 2.3-dioxygenase inhibitor         |
|       |   | 0.969                               | 0.002 | HIF1A expression inhibitor                  |
|       |   | 0.951                               | 0.001 | Quercetin 2.3-dioxygenase inhibitor         |
|       |   | 0.797                               | 0.002 | NOS2 expression inhibitor                   |
|       |   | 0.836                               | 0.002 | Antiviral (influenza)                       |
|       |   | 0.819                               | 0.005 | Anti-inflammatory                           |
|       |   | 0.940                               | 0.004 | HIF1A expression inhibitor                  |
|       |   | 0.774                               | 0.005 | Antidiabetic                                |
|       |   | 0.759                               | 0.004 | Histamine release inhibitor                 |
|       |   | 0.750                               | 0.002 | Antiviral (herpes)                          |
|       |   | 0.745                               | 0.004 | Antiviral (influenza)                       |
|       |   | 0.708                               | 0.004 | Histamine release stimulant                 |
|       |   | 0.740                               | 0.005 | Insulin promoter                            |
|       |   | 0.721                               | 0.004 | Histamine release stimulant                 |
|       |   | 0.969                               | 0.002 | HIF1A expression inhibitor                  |
|       |   | 0.934                               | 0.001 | Quercetin 2.3-dioxygenase inhibitor         |
|       |   | 0.850                               | 0.002 | NOS2 expression inhibitor                   |
|       |   | 0.787                               | 0.009 | JAK2 expression inhibitor                   |
|       |   | 0.751                               | 0.003 | Histamine release stimulant                 |
|       |   | 0.720                               | 0.004 | Histamine release inhibitor                 |
|       |   |                                     |       |   |

**Table 1.** Continued

| S.No. | Compound Name               | Biological activity (Pa>Pi. Pa>0.7) |       |  |
|-------|-----------------------------|-------------------------------------|-------|--|
|       |                             | Pa                                  | Pi    | Activity                                     |
| 24    | Rhamnetin                   | 0.960                               | 0.003 | HIF1A expression inhibitor                   |
|       |                             | 0.873                               | 0.001 | NOS2 expression inhibitor                    |
|       |                             | 0.836                               | 0.002 | Quercetin 2.3-dioxygenase inhibitor          |
|       |                             | 0.783                               | 0.010 | JAK2 expression inhibitor                    |
|       |                             | 0.736                               | 0.004 | Histamine release stimulant                  |
| 25    | Rosmarinic acid             | 0.799                               | 0.005 | Antidiabetic                                 |
| 26    | Somniferine A (Somniferine) | 0.832                               | 0.002 | Histamine release stimulant                  |
| 27    | Stigmasterol                | 0.782                               | 0.007 | Immunosuppressant                            |
| 28    | Tinocordifolioside          | 0.738                               | 0.012 | Immunosuppressant                            |
| 29    | Tinocordioside              | 0.735                               | 0.004 | Antiviral (Influenza)                        |
|       |                             | 0.737                               | 0.013 | Immunosuppressant                            |
|       |                             | 0.713                               | 0.014 | Anti-inflammatory                            |
| 30    | Tinosporide                 | 0.891                               | 0.004 | Anti-inflammatory                            |
| 31    | Ursolic acid                | 0.970                               | 0.001 | Insulin promoter                             |
|       |                             | 0.927                               | 0.001 | Transcription factor NF kappa B stimulant    |
|       |                             | 0.864                               | 0.005 | Anti-inflammatory                            |
|       |                             | 0.761                               | 0.004 | Antiviral (Influenza)                        |
| 32    | Vicenin (Vicenin-2)         | 0.915                               | 0.005 | HIF1A expression inhibitor                   |
|       |                             | 0.759                               | 0.002 | Antiviral (herpes)                           |
| 33    | Withaferin A                | 0.850                               | 0.002 | Immunosuppressant                            |
| 34    | Withanolide                 | 0.798                               | 0.005 | Immunosuppressant                            |
| 35    | Withanolide B               | 0.779                               | 0.008 | Immunosuppressant                            |
| 36    | Within one                  | 0.762                               | 0.009 | Immunosuppressant                            |
| 37    | Thymoquinone                | 0.724                               | 0.018 | HIF1A expression inhibitor                   |
| 38    | Eugenol                     | 0.873                               | 0.004 | JAK2 expression inhibitor                    |
|       |                             | 0.715                               | 0.014 | Respiratory analeptic                        |
| 39    | Glycyrrhizin                | 0.924                               | 0.001 | Antiviral (influenza)                        |
| 40    |                             | 0.902                               | 0.001 | Transcription factor NF kappa B stimulant    |
|       |                             | 0.849                               | 0.005 | Anti-inflammatory                            |
|       |                             | 0.837                               | 0.007 | Immunostimulant                              |
| 41    | Anthraquinone               | 0.816                               | 0.007 | JAK2 expression inhibitor                    |
|       |                             | 0.774                               | 0.005 | IgA-specific metalloendopeptidase inhibitor  |
|       |                             | 0.759                               | 0.007 | Macrophage colony-stimulating factor agonist |
|       |                             | 0.747                               | 0.003 | Quinoprotein glucose dehydrogenase inhibitor |
|       |                             | 0.812                               | 0.001 | Platelet adhesion inhibitor                  |
| 42    | Baicalin                    | 0.813                               | 0.003 | Histamine release inhibitor                  |
|       |                             | 0.810                               | 0.005 | Anti-infective                               |
|       |                             | 0.736                               | 0.004 | Histamine release stimulant                  |
|       |                             | 0.745                               | 0.016 | HIF1A expression inhibitor                   |
|       |                             | 0.741                               | 0.011 | Anti-inflammatory                            |
|       |                             | 0.727                               | 0.004 | Antiviral (influenza)                        |
| 43    | Myricetin                   | 0.969                               | 0.002 | HIF1A expression inhibitor                   |
|       |                             | 0.917                               | 0.001 | Quercetin 2.3-dioxygenase inhibitor          |
|       |                             | 0.808                               | 0.002 | NOS2 expression inhibitor                    |
|       |                             | 0.733                               | 0.014 | JAK2 expression inhibitor                    |

**Table 1.** Continued

| S.No. | Compound Name           | Biological activity (Pa>Pi. Pa>0.7) |       |   |
|-------|-------------------------|-------------------------------------|-------|---|
|       |                         | Pa                                  | Pi    | Activity                                  |
| 44    | Andrographolide         | 0.713                               | 0.004 | Histamine release stimulant               |
|       |                         | 0.710                               | 0.003 | Interleukin 4 antagonist                  |
|       |                         | 0.720                               | 0.013 | Anti-inflammatory                         |
|       |                         | 0.868                               | 0.004 | Antileukemic                              |
|       |                         | 0.845                               | 0.005 | Anti-inflammatory                         |
|       |                         | 0.751                               | 0.011 | Immunosuppressant                         |
| 45    | Naringenin              | 0.911                               | 0.005 | HIF1A expression inhibitor                |
|       |                         | 0.846                               | 0.002 | NOS2 expression inhibitor                 |
| 46    | Bavachinin              | 0.895                               | 0.001 | NOS2 expression inhibitor                 |
|       |                         | 0.728                               | 0.013 | Respiratory analeptic                     |
| 47    | Neobavaisoflavone       | 0.923                               | 0.002 | Histidine kinase inhibitor                |
|       |                         | 0.765                               | 0.014 | HIF1A expression inhibitor                |
| 48    | Isobavachalcone         | 0.881                               | 0.001 | NOS2 expression inhibitor                 |
|       |                         | 0.778                               | 0.008 | Anti-inflammatory                         |
| 49    | 4'-O-methylbavachalcone | 0.854                               | 0.002 | NOS2 expression inhibitor                 |
| 50    | Psoralidin              | 0.853                               | 0.009 | HIF1A expression inhibitor                |
|       |                         | 0.964                               | 0.003 | HIF1A expression inhibitor                |
|       |                         | 0.878                               | 0.001 | Quercetin 2.3-dioxygenase inhibitor       |
|       |                         | 0.830                               | 0.003 | Histamine release inhibitor               |
|       |                         | 0.833                               | 0.006 | JAK2 expression inhibitor                 |
|       |                         | 0.798                               | 0.002 | NOS2 expression inhibitor                 |
|       |                         | 0.754                               | 0.003 | Leukotriene-B4 20-monooxygenase inhibitor |
| 51    | Luteolin                | 0.745                               | 0.005 | Insulysin inhibitor                       |
|       |                         | 0.839                               | 0.009 | HIF1A expression inhibitor                |
|       |                         | 0.948                               | 0.003 | Anti-infective                            |
|       |                         | 0.911                               | 0.005 | HIF1A expression inhibitor                |
|       |                         | 0.853                               | 0.009 | HIF1A expression inhibitor                |
|       |                         | 0.862                               | 0.008 | HIF1A expression inhibitor                |
|       |                         | 0.741                               | 0.013 | JAK2 expression inhibitor                 |
| 52    | Hypericin               | 0.855                               | 0.008 | HIF1A expression inhibitor                |
|       |                         | 0.778                               | 0.002 | NOS2 expression inhibitor                 |
|       |                         | 0.724                               | 0.015 | JAK2 expression inhibitor                 |
|       |                         | 0.709                               | 0.014 | Respiratory analeptic                     |
| 53    | Glabridin               | 0.778                               | 0.010 | JAK2 expression inhibitor                 |
|       |                         | 0.864                               | 0.008 | HIF1A expression inhibitor                |
|       |                         | 0.784                               | 0.005 | Anti-infective                            |
| 54    | Psoralidin              | 0.737                               | 0.014 | JAK2 expression inhibitor                 |
|       |                         | 0.810                               | 0.007 | JAK2 expression inhibitor                 |
|       |                         | 0.800                               | 0.002 | GABA C receptor agonist                   |
|       |                         | 0.776                               | 0.003 | GABA aminotransferase inhibitor           |
| 55    | Emodin                  | 0.741                               | 0.003 | Inulinase inhibitor                       |
|       |                         | 0.720                               | 0.018 | HIF1A expression inhibitor                |
|       |                         | 0.706                               | 0.005 | Platelet aggregation stimulant            |
|       |                         | 0.822                               | 0.007 | JAK2 expression inhibitor                 |
| 56    | Liquiritigenin          | 0.742                               | 0.005 | Insulysin inhibitor                       |
|       |                         | 0.730                               | 0.004 | GABA aminotransferase inhibitor           |
|       |                         |                                     |       |   |

**Table 1.** Continued

| S.No. | Compound Name     | Biological activity (Pa>Pi. Pa>0.7) |       |                               |
|-------|-------------------|-------------------------------------|-------|-------------------------------|
|       |                   | Pa                                  | Pi    | Activity                      |
| 61    | Thymohydroquinone | 0.840                               | 0.004 | Anti-infective                |
|       |                   | 0.814                               | 0.011 | HIF1A expression inhibitor    |
|       |                   | 0.754                               | 0.011 | Respiratory analeptic         |
|       |                   | 0.741                               | 0.013 | JAK2 expression inhibitor     |
| 62    | Thymol            | 0.829                               | 0.005 | Anti-infective                |
|       |                   | 0.808                               | 0.011 | HIF1A expression inhibitor    |
| 63    | Cinnamaldehyde    | 0.819                               | 0.007 | JAK2 expression inhibitor     |
|       |                   | 0.758                               | 0.011 | Complement factor D inhibitor |
| 64    | Myricitrin        | 0.911                               | 0.001 | Histamine release stimulant   |
|       |                   | 0.879                               | 0.007 | HIF1A expression inhibitor    |
|       |                   | 0.762                               | 0.009 | Anti-inflammatory             |
|       |                   | 0.733                               | 0.006 | Anti-infective                |
|       |                   | 0.704                               | 0.005 | Antiviral (Influenza)         |
| 65    | Corydine          | 0.793                               | 0.003 | Histamine release stimulant   |
|       |                   | 0.719                               | 0.013 | Respiratory analeptic         |
| 66    | Aloin             | 0.717                               | 0.005 | Antiviral (influenza)         |
| 67    | Catechin          | 0.883                               | 0.007 | HIF1A expression inhibitor    |
|       |                   | 0.791                               | 0.003 | Histamine release inhibitor   |
|       |                   | 0.785                               | 0.009 | JAK2 expression inhibitor     |

**Table 2.** Target Molecules for Phytochemical Compounds

| S.No. | Compound Name | Target                                     | Common Name            | Uniprot ID                  | Target Class                        |
|-------|---------------|--|------------------------|-----------------------------|-------------------------------------|
| 1     | Apigenin      | Cyclin-dependent kinase 5/CDK5 activator 1 | CDK5R1 CDK5            | Q15078 Q00535               | Kinase                              |
|       |               | Cyclin-dependent kinase 1/cyclin B         | CCNB3 CDK1 CCNB1 CCNB2 | Q8WWL7 P06493 P14635 O95067 | Other cytosolic protein             |
|       |               | Cyclooxygenase-2                           | PTGS2                  | P35354                      | Oxidoreductase                      |
|       |               | Cyclin-dependent kinase 6                  | CDK6                   | Q00534                      | Kinase                              |
|       |               | Tyrosine-protein kinase SYK                | SYK                    | P43405                      | Kinase                              |
| 2     | Curcumin      | Toll-like receptor (TLR7/TLR9)             | TLR9                   | Q9NR96                      | Toll-like and IL-1 receptors        |
| 3     | Kaempferol    | Tyrosine-protein kinase receptor FLT3      | FLT3                   | P36888                      | Kinase                              |
|       |               | Arachidonate 5-lipoxygenase                | ALOX5                  | P09917                      | Oxidoreductase                      |
|       |               | Estradiol 17-beta-dehydrogenase 2          | HSD17B2                | P37059                      | Enzyme                              |
| 4     | Orientin      | TNF-alpha                                  | TNF                    | P01375                      | Secreted protein                    |
|       |               | Interleukin-2                              | IL2                    | P60568                      | Secreted protein                    |
|       |               | Estradiol 17-beta-dehydrogenase 1          | HSD17B1                | P14061                      | Enzyme                              |
| 5     | Quercetin     | Insulin-like growth factor I receptor      | IGF1R                  | P08069                      | Kinase                              |
|       |               | Thrombin                                   | F2                     | P00734                      | Protease                            |
|       |               | Serine/threonine-protein kinase Aurora-B   | AURKB                  | Q96GD4                      | Kinase                              |
|       |               | Dopamine D4 receptor                       | DRD4                   | P21917                      | Family A G protein-coupled receptor |
|       |               | PI3-kinase p85-alpha subunit               | PIK3R1                 | P27986                      | Enzyme                              |
|       |               | Tyrosine-protein kinase SRC                | SRC                    | P12931                      | Kinase                              |
|       |               | Focal adhesion kinase 1                    | PTK2                   | Q05397                      | Kinase                              |
|       |               | Matrix metalloproteinase 3                 | MMP3                   | P08254                      | Protease                            |
|       |               | Arachidonate 15-lipoxygenase               | ALOX15                 | P16050                      | Enzyme                              |

**Table 2.** Continued

| S.No. | Compound Name | Target                                       | Common Name               | Uniprot ID                     | Target Class                        |
|-------|---------------|--|---------------------------|--------------------------------|-------------------------------------|
|       |               | Serine/threonine-protein kinase PLK1         | PLK1                      | P53350                         | Kinase                              |
|       |               | Cyclin-dependent kinase 1                    | CDK1                      | P06493                         | Kinase                              |
|       |               | Matrix metalloproteinase 9                   | MMP9                      | P14780                         | Protease                            |
|       |               | Matrix metalloproteinase 2                   | MMP2                      | P08253                         | Protease                            |
|       |               | Protein kinase N1                            | PKN1                      | Q16512                         | Kinase                              |
|       |               | Arachidonate 12-lipoxygenase                 | ALOX12                    | P18054                         | Enzyme                              |
|       |               | Serine/threonine-protein kinase NEK2         | NEK2                      | P51955                         | Kinase                              |
|       |               | Interleukin-8 receptor A                     | CXCR1                     | P25024                         | Family A G protein-coupled receptor |
|       |               | CaM kinase II beta                           | CAMK2B                    | Q13554                         | Kinase                              |
|       |               | ALK tyrosine kinase receptor                 | ALK                       | Q9UM73                         | Kinase                              |
|       |               | Serine/threonine-protein kinase AKT          | AKT1                      | P31749                         | Kinase                              |
|       |               | Serine/threonine-protein kinase NEK6         | NEK6                      | Q9HC98                         | Kinase                              |
| 6     | Thymoquinone  | Serine/threonine-protein kinase PLK1         | PLK1                      | P53350                         | Kinase                              |
| 7     | Myricetin     | Insulin receptor                             | INSR                      | P06213                         | Kinase                              |
|       |               | Cyclin-dependent kinase 5/CDK5 activator 1   | CDK5R1 CDK5               | Q15078 Q00535                  | Kinase                              |
| 8     | Luteolin      | Monoamine oxidase A                          | MAOA                      | P21397                         | Oxidoreductase                      |
|       |               | Cyclin-dependent kinase 1/cyclin B           | CCNB3 CDK1<br>CCNB1 CCNB2 | Q8WWL7 P06493<br>P14635 O95067 | Other cytosolic protein             |
|       |               | Lymphocyte differentiation antigen CD38      | CD38                      | P28907                         | Enzyme                              |
|       |               | Serotonin 1b (5-HT1b) receptor (by homology) | HTR1B                     | P28222                         | Family A G protein-coupled receptor |
| 9     | Cinanserin    | Serotonin 2a (5-HT2a) receptor               | HTR2A                     | P28223                         | Family A G protein-coupled receptor |
|       |               | Serotonin 2c (5-HT2c) receptor               | HTR2C                     | P28335                         | Family A G protein-coupled receptor |
| 10    | Carvacrol     | Cyclooxygenase-1                             | PTGS1                     | P23219                         | Oxidoreductase                      |

Figure 1.a)

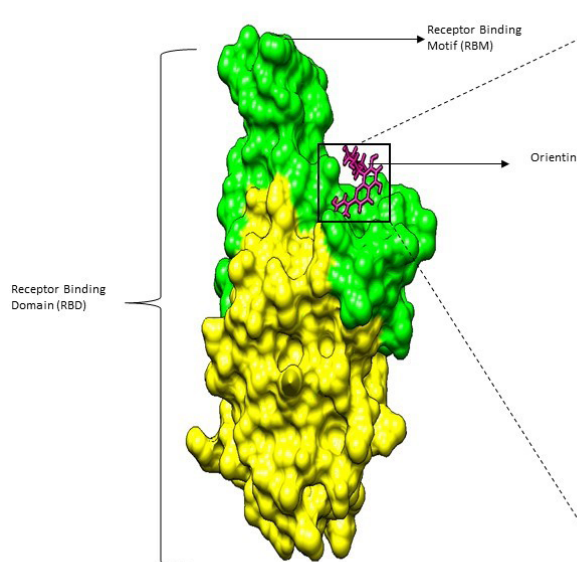
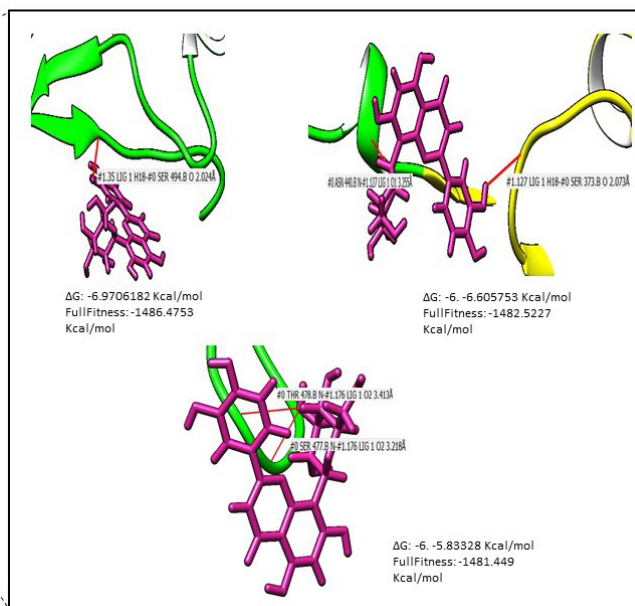


Figure 1.b)



**Figure 1. (a) Orientin Bound to Receptor Cavity in Receptor Binding Motif (RBM) of Spike Protein:** Region in green is RBM of Receptor Binding Domain, which is represented by both yellow and green. Orientin is colored in violet red. Orientin interacts with RBM, which is the main ligand for the ACE2 enzyme in humans. **(b) Amino Acid Residues Involved in the Hydrogen Bonding Between Orientin and RBM:** The red line marks the hydrogen bond. Labeling includes ligand cluster, ligand number, atom involved in the interaction at ligand side, an amino acid of RBM involved in the interaction, and the hydrogen bond length. Orientin specifically binds in three positions within RBM.

**Table 3.** Cellular Gene Expressions Induce by Phytochemical Compounds

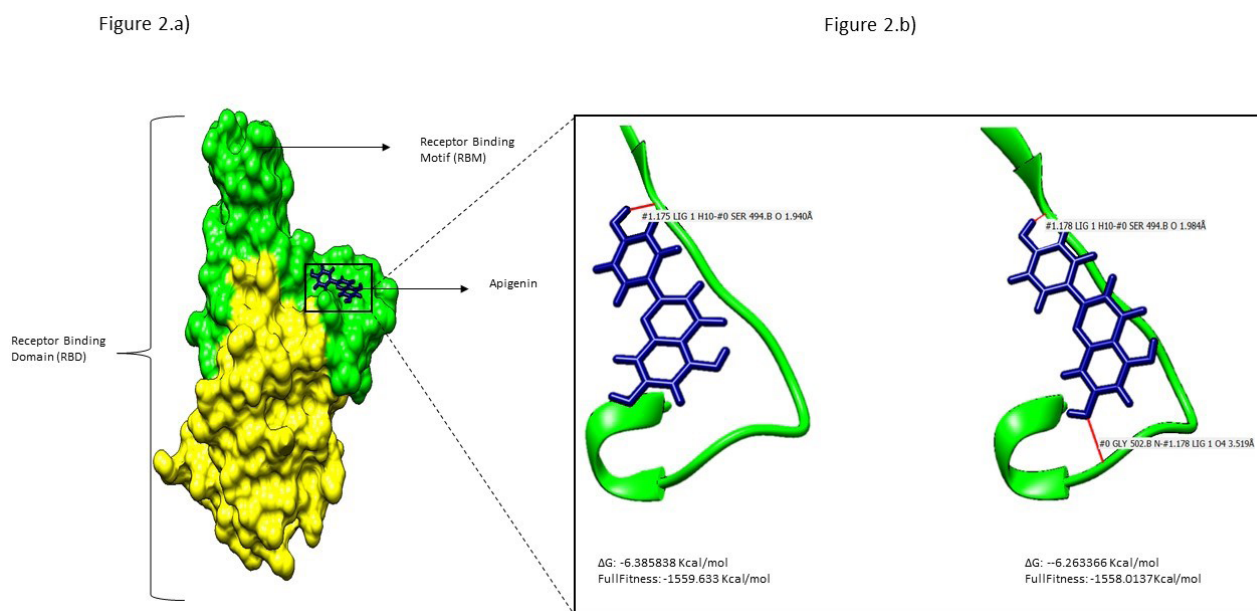
| S.No | Compound Names                                    | Pa    | Pi    | Regulation (Upregulation) |
|------|---|-------|-------|---------------------------|
| 1    | Apigenin  | 0.774 | 0.005 | PRDX2                     |
| 2    | Beta-sitosterol                                   | 0.659 | 0.029 | CD14                      |
| 3    | Bisdemethoxycurcumin                              | 0.639 | 0.101 | CD86                      |
|      |   | 0.585 | 0.087 | CCL2                      |
| 4    | Caleb in-A  | 0.551 | 0.066 | CD14                      |
|      |   | 0.572 | 0.117 | CD86                      |
| 5    | Cirsilineol                                       | 0.561 | 0.025 | PRDX2                     |
| 6    | Cirsimaritin                                      | 0.54  | 0.033 | PRDX2                     |
| 7    | Cordifolioside A                                  | 0.757 | 0.074 | CD86                      |
|      |   | 0.555 | 0.129 | CD83                      |
| 8    | Crategolic acid                                   | 0.546 | 0.14  | CD83                      |
| 9    | Curcumin  | 0.62  | 0.105 | CD83                      |
| 10   | Demethoxycurcumin                                 | 0.656 | 0.097 | CD86                      |
| 11   | Eriodictyol                                       | 0.55  | 0.03  | PRDX2                     |
| 12   | Flavonol glucoside                                | 0.672 | 0.056 | CD83                      |
|      |   | 0.54  | 0.125 | CD86                      |
| 13   | Isothymenin                                       | 0.615 | 0.014 | PRDX2                     |
| 14   | Isothymusin                                       | 0.615 | 0.014 | PRDX2                     |
| 15   | Kaempferol  | 0.851 | 0.003 | PRDX2                     |
| 16   | Oleanolic acid                                    | 0.58  | 0.107 | CD83                      |
| 17   | Pentadienoylpiperidine (1-Pentadienoylpiperidine) | 0.62  | 0.078 | CD83                      |
| 18   | Quercetin   | 0.874 | 0.003 | PRDX2                     |
| 19   | Rhamnetin   | 0.763 | 0.005 | PRDX2                     |
| 20   | Rosmarinic acid                                   | 0.621 | 0.074 | CCL2                      |
|      |   | 0.568 | 0.055 | CD14                      |
| 21   | Somniferine A (Somniferine)                       | 0.71  | 0.019 | CD14                      |
| 22   | Tinocordifolioside                                | 0.754 | 0.03  | CD83                      |
| 23   | Tinocordioside                                    | 0.685 | 0.052 | CD83                      |
| 24   | Ursolic acid                                      | 0.549 | 0.136 | CD83                      |
| 25   | Withanolide B                                     | 0.513 | 0.088 | CD14                      |
| 26   | Thymoquinone                                      | 0.598 | 0.043 | CD14                      |
|      |   | 0.556 | 0.127 | CD83                      |
| 27   | Eugenol   | 0.881 | 0.024 | CD86                      |
| 28   | Glycyrrhizin                                      | 0.665 | 0.058 | CD83                      |
| 29   | Anthraquinone                                     | 0.546 | 0.031 | PRDX2                     |
|      |   | 0.546 | 0.099 | CCL2                      |
|      |   | 0.523 | 0.159 | CD83                      |
| 30   | Honokiol  | 0.639 | 0.101 | CD86                      |
| 31   | Myricetin   | 0.85  | 0.003 | PRDX2                     |
| 32   | Andrographolide                                   | 0.526 | 0.082 | CD14                      |
| 33   | Naringenin  | 0.51  | 0.041 | PRDX2                     |
| 34   | 4'-O-methylbavachalcone                           | 0.624 | 0.104 | CD86                      |
| 35   | lambda-Carrageenan                                | 0.848 | 0.036 | CD86                      |

**Table 3.** Continued

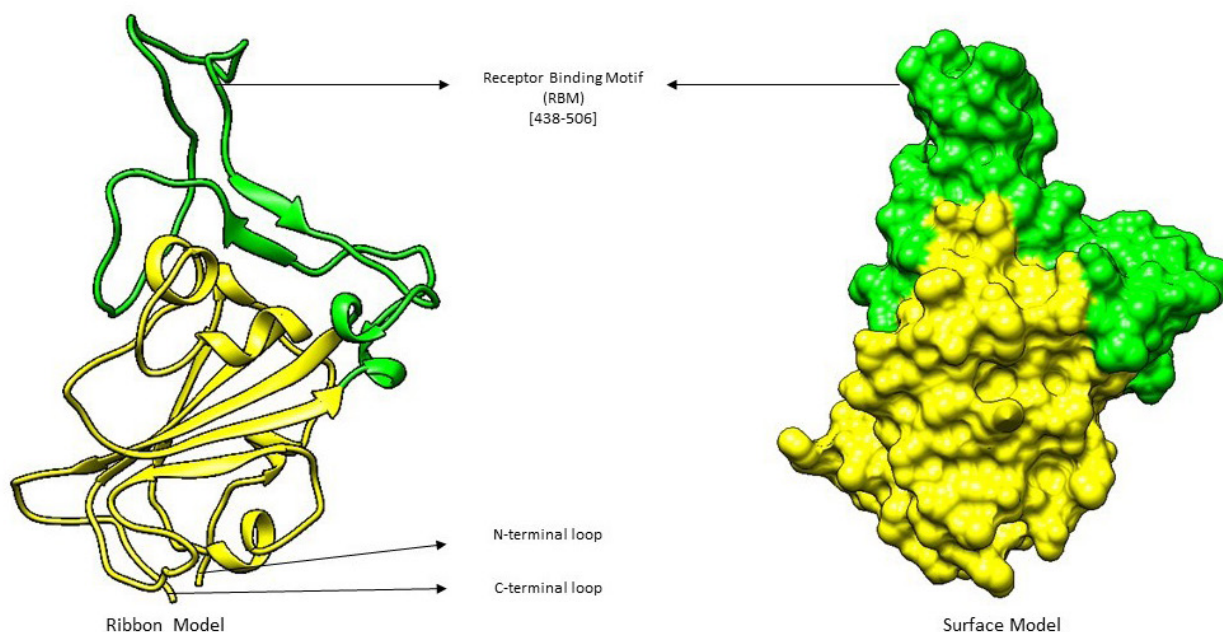
| S.No | Compound Names    | Pa    | Pi    | Regulation (Upregulation) |
|------|-------------------|-------|-------|---------------------------|
| 36   | beta-Carrageenan  | 0.616 | 0.08  | CD83                      |
| 37   | Nelfinavir        | 0.979 | 0.001 | CCL2                      |
|      |                   | 0.894 | 0.005 | CCL3                      |
| 38   | Luteolin          | 0.805 | 0.004 | PRDX2                     |
| 39   | Hibiscus acid     | 0.522 | 0.16  | CD83                      |
|      |                   | 0.708 | 0.043 | CCL2                      |
| 40   | Hydroxytyrosol    | 0.704 | 0.087 | CD86                      |
|      |                   | 0.608 | 0.04  | CD14                      |
| 41   | Saikosaponin      | 0.829 | 0.013 | CD83                      |
|      |                   | 0.868 | 0.029 | CD86                      |
| 42   | Cinnamic          | 0.754 | 0.025 | CCL2                      |
|      |                   | 0.724 | 0.039 | CD83                      |
|      |                   | 0.677 | 0.025 | CD14                      |
| 43   | Methyl cinnamate  | 0.653 | 0.064 | CCL2                      |
|      |                   | 0.605 | 0.041 | CD14                      |
| 44   | Thymohydroquinone | 0.57  | 0.115 | CD83                      |
|      |                   | 0.511 | 0.089 | CD14                      |
|      |                   | 0.517 | 0.111 | CCL2                      |
|      |                   | 0.628 | 0.104 | CD86                      |
| 45   | Thymol            | 0.554 | 0.096 | CCL2                      |
|      |                   | 0.535 | 0.15  | CD83                      |
| 46   | Cinnamaldehyde    | 0.927 | 0.009 | CD86                      |
|      |                   | 0.724 | 0.036 | CCL2                      |
| 47   | Allicin           | 0.55  | 0.097 | CCL2                      |
|      |                   | 0.532 | 0.104 | CCL2                      |
| 48   | Carvacrol         | 0.506 | 0.092 | CD14                      |
|      |                   | 0.535 | 0.15  | CD83                      |

## Discussion and Conclusions

The novel coronavirus has become a big challenge for the world. It has taken numerous lives within a span of a short time. After it, the whole world is developing a potential vaccine or drug against it but is not devised yet. Studies are being conducted to repurpose the known drugs used in many viral diseases and have shown varying results.<sup>22,23</sup> Various naturally occurring phytochemicals and other compounds in ancient medicines are also being extensively studied to confront the disease.<sup>24,25</sup> The main focus of all these medications is to inhibit the viral attachment with human receptors or to cease the replication of the viral genome inside the cell. In our study, we have more focused on the phytochemicals that could possibly attach to viral spike protein and thereby inhibit its entry inside the cell. The viral protein involved in the attachment of the virus with a cellular receptor, ACE2, is spike protein (S). It is an assembly of trimer on the surface of viral particles and contains two main functional domains, S1 and S2. The S1 domain at the N-terminal is responsible for receptor binding, and the S2 domain at the C-terminal is



**Figure 2. (a)** Apigenin bound to receptor cavity in Receptor Binding Motif (RBM) of spike protein. Region in green is RBM of receptor binding domain, represented by both yellow and green. Apigenin is colored in navy blue. Apigenin interacts with RBM, which is the main ligand for the ACE2 enzyme in humans. **(b)** Amino Acid Residues Involved in the Hydrogen Bonding Between Apigenin and RBM. The red line marks the hydrogen bond. Labeling includes ligand cluster, ligand number, atom involved in the interaction at ligand side, amino acid of RBM involved in the interaction, and the hydrogen bond length. Apigenin specifically binds in two positions within RBM.



**Figure 3.** Ribbon and Surface Structure of Receptor Binding Domain (RBD) in the Spike Protein of SARS-CoV-2. Region highlighted in green shows RBM.

responsible for membrane fusion.<sup>26</sup> The recognition of the receptor, ACE2, is achieved by an RBD in the spike protein, which stretches from amino acid 333 to 527.<sup>27</sup> Studies on the crystal structure of the protein showed that the RBD of SARS-CoV-2 contains a core RBM that mediates direct contact with ACE2 receptor.<sup>28</sup> The receptor-binding motif in RBD lies from 438 to 506 within the domain (Figure 3).

The motif has several amino acid sequences, which show a very high binding affinity with the ACE2 protein.<sup>29</sup> The main amino acid sequences involved in the interaction are G446, Y449, L455, F486, N487, Y489, Q493, S494, T500, N501, G502, and Y505. These specific amino acids enhance the efficiency of viral binding with ACE2.<sup>29,30</sup> The binding of the phytochemicals to this specific moiety can

possibly regulate the attachment of the virus to the host cell.

In our study, we have extracted 20 phytochemicals from 100 studied compounds on the basis of their physicochemical and pharmacokinetic properties, biological activities, possible target interactions, similar compounds in humans, and gene regulations using bioinformatic tools and have docked them with the RBD of the spike protein. This makes our effort novel as filtering these compounds through various criteria makes sure that the compound holds efficient drug-like properties inside our body and would possibly inhibit the viral attachment. To our surprise, we got overwhelming results as two of the phytochemicals were found to get bound with the amino acid sequences readily involved in the interaction of RBM in spike protein and ACE2. The bonding could be a robust test of an iterative framework of inhibiting virus-receptor interaction with the help of phytochemicals.

### Competing Interests

None.

### Supplementary Materials

Supplementary file 1 contains Table S1.

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