Research Article

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Unveiling *Acacia farnesiana* phytochemicals as Angiotensin Converting Enzyme (ACE) inhibitors via *in-silico* drug design, molecular docking, and bioavailability predictions: An illustration against SARS-CoV-2 spike protein

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ABSTRACT

Angiotensin-converting enzyme 2 (ACE2) is a transmembrane protein that functions as a receptor for coronavirus spike protein. When spike protein fragments as the ligand binds with ACE2 protein, this ACE2 protein functions as a virus receptor, participating in the biological process known as the viral particle entry in the host cell. Hence, an *in-silico* study was carried out since it is faster and less expensive than trial and error methods based on experimental investigations. To study the effect of *Acacia farnesiana* phytochemicals on spike protein, molecular docking analyses were carried out. In this study, twelve phytochemicals from *Acacia farnesiana* have been selected as small molecules based on their ACEI and anti- inflammatory nature to evaluate molecular interaction between spike protein of SARS-CoV2 with ACE2 of the human complex molecule. Gallic acid, methyl gallate, kaempferol, Rhamnocitrin, naringenin, apigenin, ellagic acid, ferulic acid, myricetin, Diosmetin, Caffeic acid, and Quercetin were chosen as competent natural compounds from *Acacia farnesiana* as potent small molecules against COVID-19 and further ADME analysis were carried out. The result indicated that due to the presence of ACEIs and anti-inflammatory phytochemicals in *Acacia farnesiana*, the bound structure of ACE2 and spike protein becomes unstable. Therefore, these natural compounds can show antiviral activity by destabilizing spike protein binding with the human host ACE2 receptor.

Keywords: *Acacia farnesiana*, ACE2, Molecular docking, Phytochemicals, SARS-CoV-2

INTRODUCTION

The recent global pandemic disease which emerged in the year 2019 named as COVID-19 or Coronavirus disease 2019 belongs to Family Coronaviridae, Torovirus genera, and Nidovirales order is an acute respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. Among all the coronavirus family, SARS CoV-2 is the seventh member to infect humans, and it was first seen in Wuhan city of China in December 2019 [3]. In humans, these viruses can infect the lower respiratory tract and cause a serious respiratory illness causing symptoms such as fever and dyspnea [4,5]. The severity of the disease varies, from asymptomatic infection to multi-organ failure and death [6,7]. CoVs are grouped into four genera as the biggest known RNA viruses with an average size of 30kb: alpha-coronavirus, beta-coronavirus, gamma-coronavirus, and delta-coronavirus. Six human coronaviruses (HCoVs) have been found so far, including the alpha-CoVs HCoVs-NL63 and HCoVs-229E, as well as the beta-CoVs HCoVs-OC43, HCoVs-HKU1, severe acute respiratory syndrome-CoV (SARS-CoV), and Middle East respiratory syndrome-CoV (MERS-CoV) [8].

SARS-CoV-2 is spherical in shape having a spike protein projecting from the surface of the virus. Helically symmetrical nucleocapsids are found within the envelope, which is unusual among positive-sense RNA viruses [9]. An N-terminal S1 subunit and a C-terminal membrane proximal S2 subunit make up the spike protein. S1A, S1B, S1C, and S1D domains make up the S1 subunit. The spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins, which are encoded at the 3' end of the genome, are the four primary structural proteins of coronavirus particles whereas, Non-structural proteins, which are necessary for virus replication, make approximately two-thirds of the coronaviral genome that includes RdRp (RNA-dependent RNA polymerase), proteases, and helicase [10]. The S1B domain, also known as the receptor-binding domain (RBD), interacts with the human ACE-2 receptor [11]. As a result, cells expressing ACE2 may

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behave as target cells, making them susceptible to infection by 2019-nCoV; such cells include type II alveolar cells (AT2) in the lungs. To obtain cell entrance, SARS-CoV-2 employs its trimeric spike protein to attach to the host angiotensin-converting enzyme 2 (ACE2) and fuse with the cell membrane [12] assisting in the synthesis of transmembrane Protease Serine 2 (TMPRSS2) followed by RdRp-mediated replication within the host cell for virus replication [13]. ACE2 is a zinc-containing type I membrane enzyme found on the surface of endothelial cells in the lungs, as well as other cell types and organs resulting in damage, inflammation, and respiratory distress [14,11]. It is important in maintaining blood pressure homeostasis and controlling blood pressure as well as known for its function in hypertension, in addition to its position as a receptor for SARS-CoV-2 [15]. Inhibiting viral entrance into cells and replication, as well as regulating the immune system, might be a therapeutic therapy target [16].

To treat SARS-CoV-2 illness, several potential techniques have been tested, including protein-based vaccine design, ACE2 receptor inhibition, and the influence of phytochemicals on spike protein interaction with its ACE2 receptor. Drug design with phytochemicals is a well-known strategy among the several therapeutic options that have been offered for the treatment of SARS-CoV 2 infection [17]. Medicinal plants have long been a natural source of many phytoconstituents, which have unavoidably been exploited as current medications in modern therapeutic procedures. Due to the presence of phytochemical ingredients, they are utilized to heal and cure human illnesses [18].

Acacia farnesiana (L.) Wild (family: Fabeceae), commonly named as sweet acacia or Huizache [19] is a medicinal shrub that grows in tropical areas of the Indian subcontinent, particularly in sandy soils of river beds in Northern India and portions of Tamil Nadu, and has a wide range of traditional uses. Its blossoms create "cassie" a scent widely used in European perfumery [20]. The bark is used to cure coughs and has therapeutic effects [21]. The seeds and pods of *A. farnesiana* (L) Willd are used in Mexican traditional medicine to treat diarrhoea, TB, and as antispasmodics and astringents. The presence of phenolic acids, flavonoids, tannins, alkaloids, and terpenes in different Acacia species was found to be responsible for a variety of pharmacological effects, including hypoglycemic, anti-inflammatory, anti-bacterial, anti-platelet aggregation, anti-hypertensive, analgesic, anticancer, and anti-atherosclerotic activity [22]. Phytochemicals must be docked against SARS-structural CoV-2's protein in order to develop medicines against the virus.

Molecular docking studies can be performed using several servers and software to understand and predict inter-molecular interactions, finding likely binding modes, and energetically, predicting binding affinity. It has a wide variety of uses and applications in the field of drug discovery that includes finding potential leads by virtual screening, providing binding hypotheses, chemical mechanism studies, and performing structure-activity studies [23]. Molecular docking is usually performed between the protein receptor called macromolecules and ligands in a variety of orientation, conformations, and locations [24]. Virtual screening based on molecular descriptors and physical features of (in)active ligands is extremely beneficial for identifying hits and leads in screening databases. When utilized as the final stage in virtual screening, molecular docking aids in generating three-dimensional (3D) structural hypotheses about how a ligand interacts with its target. Several tools include AutoDock, Dock, flexX, GOLD, ICM, and PyRx which help users to perform molecular docking [25].

In the present study, molecular docking studies and pharmacokinetics studies were employed to examine the effects of potential phytochemicals such as Gallic acid, Naringenin, Kaempferol, Rhamnocitrin, apigenin, Ellagic acid, Ferulic acid, Methyl gallate, Myricetin, Quercetin, Diosmetin, and Caffeic acid from *Acacia farnesiana* as angiotensin converting enzyme inhibitors, anti-inflammatory and anti-oxidant agents against SARS-CoV-2 spike protein. The study's purpose is to find out how efficient the active chemical is in inhibiting the target protein., which is critical for viral entrance into the host. furthermore, this research will aid in the development of a COVID-19 antiviral medicine and offer information to the public on how to use natural materials in daily intake as a COVID-19 illness prevention strategy

MATERIALS AND METHOD

Target selection and preparation

Three-dimensional structures of spike protein (PDB ID: 6VXX) and human ACE2 (PDB ID: 6M0J) were downloaded via the RCSB Protein Data Bank (https://www.rcsb.org/) in .pdb format. The retrieved PDB structure was further visualized and edited by eliminating the non-standard amino acid residues connected to the protein using Pymol and Chimera software [26].

Protein structure validation

Using the MOLPROBITY online tool, the protein structure was refined and validated. The Ramachandran plot was used to examine the improved protein structures of spike protein and ACE2, which revealed the percentage of residues in favored and allowed regions.

Ligands selection and preparation

The two-dimensional structure of the ligands i.e., Gallic acid, Naringenin, Kaempferol, Rhamnocitrin, apigenin, Ellagic acid, Ferulic acid, Methyl gallate, Myricetin, Quercetin, Diosmetin, and Caffeic acid were chosen from *Acacia farnesiana* were retrieved from IMPAAT (Indian Medicinal Plants, Phytochemistry and Therapeutics) database and PubChem database in .sdf file format. For performing molecular docking, a three-dimensional structure in .pdb format is needed. So, the downloaded .sdf ligands coordinates were converted into .pdb format after adding hydrogen bonds using a free access tool Open Babel (http://openbabel.org/). Also, the geometric augmentation of the ligands was improved using Argus Lab 4.0.1 (http://www.arguslab.com/).

Swiss ADME prediction

To analyze the individual ADME (absorption, distribution, metabolism and excretion) behavior of the selected phytochemicals and interpret the results, in-silico ADME prediction of phytochemicals was performed. The compound's Simplified Molecular Input Line Entry System (SMILES) format was pasted on the Swiss ADME webpage (Swiss Institute of Bioinformatics, Switzerland) to create bioavailability radar, pharmacokinetic profile, and drug-likeness metrics [27].

Protein-protein docking between ACE2 and Spike protein

The ClusPro web tool was used to conduct molecular docking experiments between human ACE2 and the SARS-CoV-2 Spike protein. From a total of 30 models, we chose the one with the lowest binding energy. The following equation was used to compute cluster scores and predict the lowest binding energy.

$$E= 0.40E_{rep} + -0.40E_{att} + 600E_{elec} + 1.00E_{DARS}$$

The repulsive and attractive contributions to the van der Waals interaction energy are denoted by E_{rep} and E_{attr}, respectively. Electrostatic energy is referred to as E_{elec}. DARS is denoted as Decoys as the Reference State which represents desolvation contributions [28].

Molecular docking study of phytochemicals obtained from *Acacia farnesiana*

Molecular interaction and docking studies were performed using the PyRx v0.8 open access docking program to investigate the interaction between the binding structure of Spike protein and ACE2 against phytochemical substances. The PDB files were uploaded in PyRx for further docking process. Active site regions were covered with a Grid box; the grid box was set for the specified binding site residues to produce the optimal orientation with the minimum binding affinity values (kcal/mol) [29].

RESULTS

Protein structure validation

The Spike proteins and ACE2 were validated using MOLPROBITY. The Ramachandra plot for spike protein and ACE2 shows that 98% of all residues are in favored. 100% of all residues were in allowed region for Spike protein and about 99.8% of all residues are in allowed regions for ACE2. As a result, the proteins are more stable, allowing for further molecular docking research. Table 1 and Figure 1 shows the proportion of residues in the preferred, permitted, and outlier areas of all three proteins.

Ligand selection and Preparation

The antioxidant, anti-inflammatory, and antiviral characteristics of the ligands were chosen and downloaded from IMPAAT and PubChem. Table 2 lists the phenolic and flavonoid characteristics of the chosen ligands with 2D structure (Figure 2).

Swiss ADME prediction

The result obtained from In-silico ADME predictions performed in SwissADME web server shows that out of thirteen phytochemicals only myricitrin have one Lipinski violation with low Gastro Intestinal (GI) absorption, Ferulic acid penetrates the BBB while others have high GI absorption and no BBB permeant properties (Table 3). These phytochemicals are suitable for druggable compound as it shows minimum violation.

Protein-protein docking interactions

The molecular docking studies of spike protein fragments with their receptor in human hosts, human ACE2 (PDB ID: 6M0J) was used as a receptor protein. Human ACE2 receptor docking structure connects with SARS CoV2 spike protein fragment with binding energy of -991.2 kcal/mole using ClusPro web server. A conformational shift occurs when the ACE2 receptor protein interacts to a Spike protein fragment. The therapeutic focus for SARS-CoV2 therapy is the bound structure of the SARS CoV2 spike protein fragment with the ACE2 receptor protein.

Molecular docking interactions between phytochemicals and bound structure of ACE2 and spike protein

Table 4 and Figure 3 provides a clear interpretation of the study's findings. The lowest comparable binding affinity was written down after considering the best-docked posture of all the molecular docked compounds. PyMol and discovery studio tools were used to display and analyze the docked compounds, which highlighted the surrounding labeled binding residues.

Gallic acid - complexed Spike protein and ACE2: With a binding energy of -5.7 kcal/mol, gallic acid binds to the complex structure of Spike protein and ACE2. Gallic acid binds to the A chain of ACE2 at positions 562, 564, 566, and 210, respectively, with the amino acids LYS, GLU, TRP, and ASN.

Methyl gallate - Spike protein and ACE2: The binding energy of methyl gallate with the complex protein is -6.7 kcal/mol, which is higher than gallic acid (-5.7). The docked structure is maintained by two conventional hydrogen bonds with bond lengths of 2.40 Å and 2.43 Å at ALA 1056 and GLY 1059, respectively. In the C chain of Spike protein, methyl gallate binds to the amino acids ALA: 1056 and GLY: 1059.

Kaempferol - Spike protein andACE2: After docking with the complex structure of Spike protein and human ACE2, kaempferol had a binding energy of -7.7 kcal/mol. Kaempferol interacts with the B chain of spike protein, with the binding residues ASN:317, GLN:314 and GLN: 957. Three typical hydrogen bonds with bond lengths of 2.91 Å, 2.78 Å, and 2.17 Å correspondingly stabilize the structure.

Rhamnocitrin - spike protein and ACE2: Rhamnocitrin, a phytochemical, binds to the docked structure of spike protein and ACE2, with a binding affinity of -7.6 kcal/mol. Rhamnocitrin binds to the B and C chains of Spike protein with the amino acids ASN:317, THR:315, and ARG: 765. Four conventional hydrogen bonds stabilize the structure. With ASN:764 and ARG: 765, it also displays one pi-donor hydrogen link and two pi-alkyl bonds.

Naringenin -spike protein and ACE2: With the greatest binding energy of -8.2 kcal/mol, Naringenin binds to Spike protein and ACE2. It forms two conventional hydrogen bonds with the Spike Protein's C chain, with ILE: 742 and ARG: 1000 amino acids, with bond lengths of 2.47 Å and 2.49 Å.

Apigenin - of Spike protein and ACE2: Apigenin is a flavonoid having a binding energy of -7.2 kcal/mol with Spike protein and ACE2. Apigenin binds to the amino acids TYR 196, GLN 98, LYS 562, and GLU 564 with bond distances of 2.02 Å, 2.62 Å, 2.46 Å, and 2.32 Å, respectively.,

Ellagic acid - spike protein and ACE2: When docked with Spike protein and ACE2, ellagic acid has a binding energy of -7.8 kcal/mol and forms two conventional hydrogen bonds for stability with ARG:514 and HIS:378 at distances of 2.51 Å and 2.87 Å.

Ferulic acid-spike protein and ACE2: Ferulic acid forms three conventional hydrogen bonds with spike protein and ACE2 with a binding energy of -7 kcal/mol, one with PHE:374 amino acid position with bond length 2.49 and two with THR:415 amino acid position with bond length 2.10 Å and 2.39 Å.

Myricetin-spike protein and ACE2: Myricetin makes five conventional hydrogen bonds with the complex structure of spike and ACE2 protein, with a binding affinity of -8.6. Myricetin binds to both the A and B chains of spike protein with the amino acids at positions THR: 415, GLN:414, TYR:369, and LEU:368 correspondingly, forming bond lengths of 2.34 with THR, 2.50 and 1.86 with GLN, 2.22 and 2.70 with TYR and LEU.

Diosmetin -spike protein and ACE2: Diosmetin's stability is demonstrated by the amino acids PHY:374 creating bond length 2.63 Å, LEU:368 producing bond length 2.75 Å, ARG:408 forming bond length 2.61 Å, and GLN:414 forming bond length 2.73 Å with the A and C chains of spike protein. Diosmetin and the bound structure of spike protein and ACE2 have a binding affinity of -8.6.

Quercetin -spike protein and ACE2: Quercetin makes five conventional hydrogen bonds with three amino acids, one with the C chain and two with the B chain of spike protein, with a binding affinity of -8.1. The structures containing amino acids PHE: 1042 and ASP:1041 formed four interactions with bond lengths of 2.58 Å and 2.37 Å, 2.07 Å and 2.10 Å, respectively. The C chain of the spike in amino acid GLN:784 has one contact with bond length 2.58 Å.

Caffeic acid -spike protein and ACE2: Caffeic acid and the complex structure of spike protein and ACE2 have a binding affinity score of -6.7, generating one carbon hydrogen bond with GLY:416 and four conventional hydrogen bonds with THR:415 (bond length 2.41), TYR: 369 (bond length 2.94), and two with PHE:374 (bond length 2.78 and 2.58).

DISCUSSION

Acacia farnesiana, sometimes known as Huizache or sweet acacia, is a medicinal shrub. According to the study, it has anti-oxidant and topical ant-inflammatory compounds that might be utilised to treat dyspepsia, diarrhoea, and skin irritations. The pods, stem, leaves, and branches of *Acacia farnesiana* contain phytochemicals such phenols, flavonoids, gums, and tennis, which have health-promoting properties. Despite the presence of numerous phytochemicals, we focused on those with antioxidant, anti-inflammatory, and antiviral properties. These qualities are found in gallic acid, methyl gallate, kaempferol, naringenin, apigenin, ellagic acid, myricetin, caffeic acid, quercetin, diosmetin, and ferulic acid. Gallic acid and methyl gallate, according to various studies, have strong immunomodulatory characteristics [30,31]. Shivraj Hariram Nile in 2016 found that the compounds Ferulic acid and caffeic acid have promise anti-inflammatory effect and that their bioavailability is nontoxic. Following the selection of phytochemicals, ADME characteristics were used to assess their pharmacokinetics. Myricetin has a low GI (gastrointestinal) absorption and one Lipinski violation: NHorOH>5, whereas Gallic acid, methyl gallate, kaempferol, naringenin, apigenin, ellagic acid, caffeic acid, quercetin, diosmetin, and ferulic acid have better GI absorption. The active substance should have no more than one violation, according to the Lipinski rule [27]. Ferulic acid was shown to be permeant to the BBB (blood-brain barrier), while the rest of the phytochemicals were found to be permeability negative (Table 3). The bioavailability radar for oral bioavailability prediction revealed that the colorful zone is the best physicochemical space for oral bioavailability when flexibility, lipophilicity, saturation, size, polarity, and solubility are taken into account. Except for the instauration component, all phytochemicals fall within the colored part of the bioavailability radar (Table 3). The ADME result indicates that the discovered compounds can be utilized as drugs, however they cannot be ingested orally.

The chosen chemical has the greatest binding affinity with the complexed structure of spike protein and ACE2, according to the present study's findings. All of the chosen phytochemicals have a high binding affinity value (ΔG), but four have the highest. The stronger the bond between the target molecule and the ligand, the lower the binding affinity [29]. Myricetin and Diosmetin > naringenin> quercetin> ellagic acid> kaempferol> Rhamnocitrin> apigenin> ferulic acid> caffeic acid> methyl gallate> gallic acid, classified by affinity (ΔG). Rhamnocitrin, apigenin, and ferulic acid have -7 and higher binding affinity(ΔG). Myricetin and Diosmetin have the highest binding affinity with the chosen receptor spike protein and ACE2 (-8.6), whereas naringenin and quercetin had -8.2(ΔG) and -8.1 (ΔG) respectively (Table 4). Apart from the recent sickness affecting public health, Al-Nour *et al*. stated in 2019 that Ellagic acid, Kaempferol, and Quercetin from different plant of same species, *Acacia nilotica* can contribute to therapeutic activity can be used to treat cancer, multidrug-resistant bacterial infections, diabetes mellitus, and chronic inflammatory systemic disorders. According to Laksmiani *et al*. (2020), phytochemicals such as naringenin, kaempferol, myricetin, and quercetin have a negative binding energy, indicating affinity for receptors such as ACE2 as well as other receptors such as RdRp, TMPRSS2, 3CLPro, and PLPro, which will obstruct viral entry in the host. Thus, the bioavailability radar and phytochemical features of A. farnesiana key phytochemicals revealed drug-like potential for anti-SARS-CoB-2 drug development. As a consequence, the findings can be used to support further research into using these drugs to treat SARS-CoV-2 proteases.

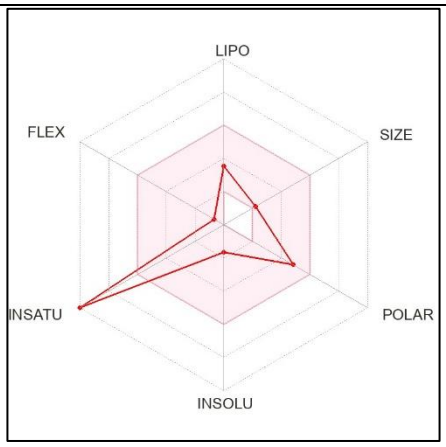
Table 1: MolProbity score of Spike protein and ACE2

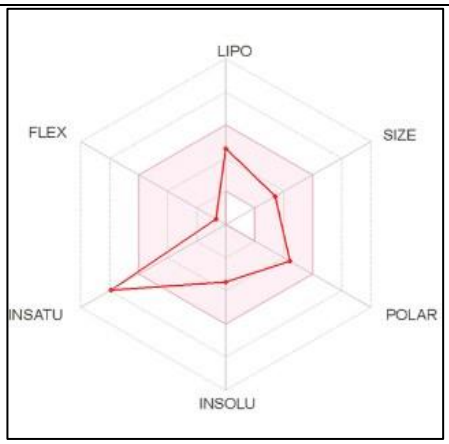
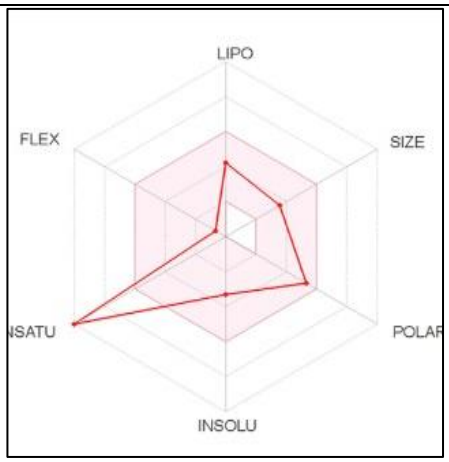
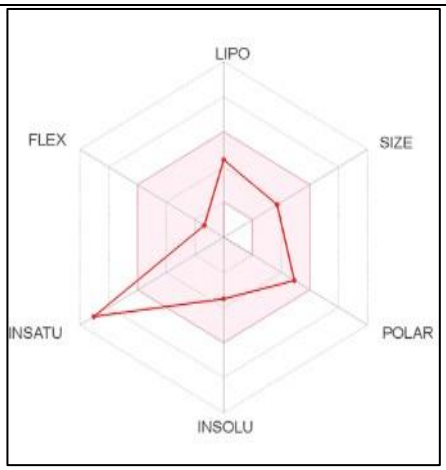
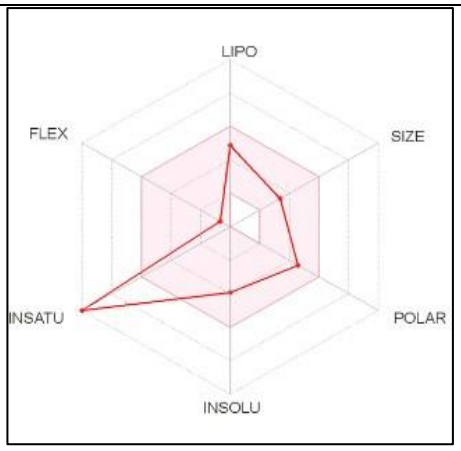
S. No	Target Protein	Number of residues in the Favored region (%)	Number of residues in the allowed region (%)	Number of residues in the outliner region (%)
1	Spike protein	97.6	100.0	0.00
2	ACE2	98.0	99.8	0.17

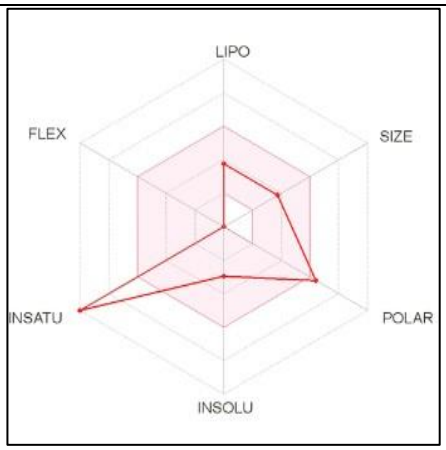
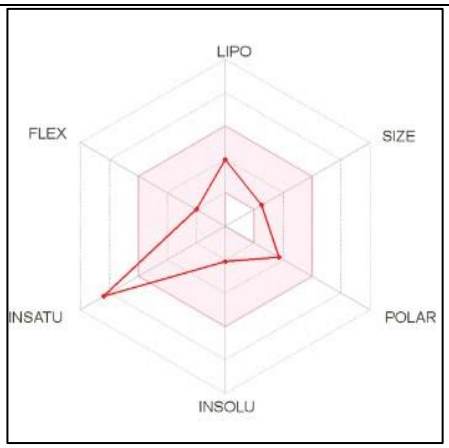
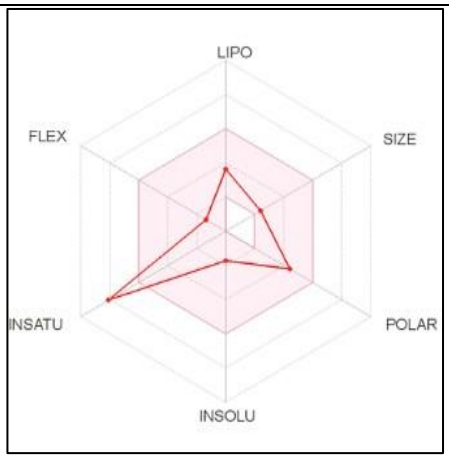
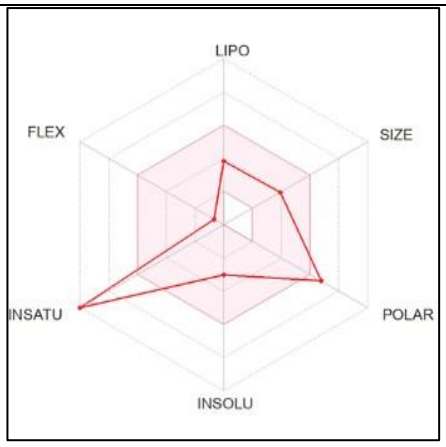
Table 2: Structural and chemical information of selected phytochemicals of *Acacia farnesiana*

Acacia farnesiana **phytochemicals**	**Chemical formula**	**Molecular weight (g/mol)**	**Chemical class of phytochemicals**
Gallic acid	$C_7H_6O_5$	170.12	Phenolic
Methyl gallate	$C_8H_8O_5$	184.15	Phenolic
Kaempferol	$C_{15}H_{10}O_6$	286.24	Flavonoid
Rhamnocitrin	$C_{16}H_{12}O_6$	300.26	Flavonoid
Naringenin	$C_{15}H_{12}O_5$	272.25	Flavonoid
Apigenin	$C_{15}H_{10}O5$	270.24	Flavonoid
Ellagic acid	$C_{14}H_6O_8$	302.19	Polyphenol
Ferulic acid	$C_{10}H_{10}O_4$	194.18	Phenolic
Myricetin	$C_{15}H_{10}O_8$	318.23	Flavonoid
Diosmetin	$C_{16}H_{12}O_6$	300.26	Flavonoid
Quercetin	$C_{15}H_{10}O_7$	302.23	Flavonoid
Caffeic acid	$C_9H_8O_4$	180.16	Phenolic

Table 3: SwissADME prediction of *Acacia farnesiana* phytochemicals

Phytochemicals	**GI absorption**	**BBB permeant**	**Lipinski rule**	**Bioavailability radar**
Gallic acid	High	No	Yes, 0 violation	

Naringenin	High	No	Yes, 0 violation	
Kaempferol	High	No	Yes, 0 violation	
Rhamnocitrin	High	No	Yes, 0 violation	
Apigenin	High	No	Yes, 0 violation	

Ellagic acid	High	No	Yes, 0 violation	
Ferulic acid	High	yes	Yes, 0 violation	
Methyl gallate	High	No	Yes, 0 violation	
Myricetin	Low	No	Yes; 1 violation: NHorOH>5	

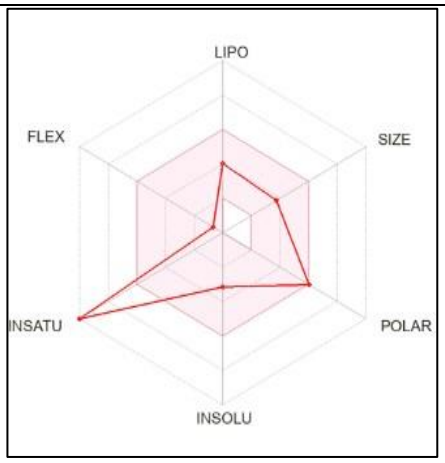
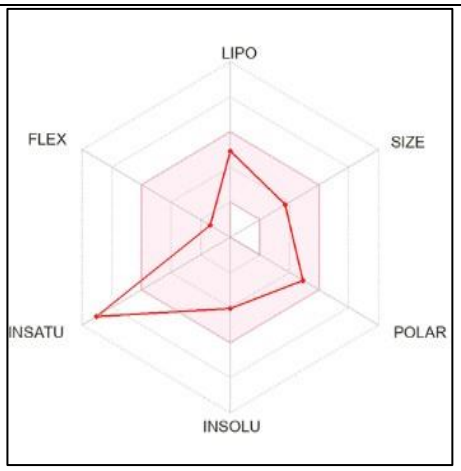
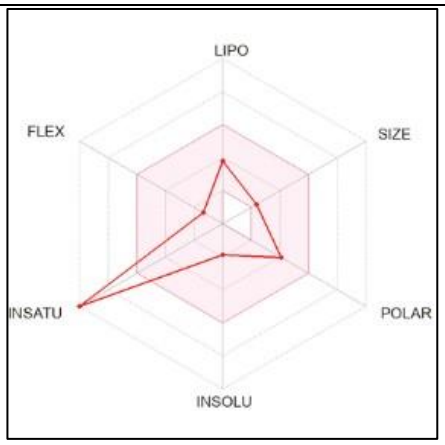
Quercetin	High	No	Yes, 0 violation	
Diosmetin	High	No	Yes, 0 violation	
Caffeic acid	High	No	Yes, 0 violation	

Table 4: The interacting amino acid residues in docking structures of ACE2 bound with spike protein fragment as receptor with various *Acacia farnesiana* phytochemicals

S. No	Phytochemicals	Binding residues	Binding affinity
1	Gallic acid	LYS A:562, GLU A:564, TRP A: 566, ASN A: 210	-5.7
2	Methyl gallate	ALA C: 1056, GLY C: 1059	-6.7
3	Kaempferol	ASN B:317, GLN B:314, GLN B: 957	-7.7
4	Rhamnocitrin	ASN B:317, THR B:315, ARG C: 765	-7.6
5	Naringenin	ILE C: 742, ARG C:1000	-8.2

6	Apigenin	TYR: 196, GLN: 98, LYS 562, GLU: 564	-7.2
7	Ellagic acid	ARG:514, HIS:378	-7.8
8	Ferulic acid	PHE A:374, THR C:415	-7
9	Myricetin	LEU B:368, TYR B:369, THR A: 415, GLN A:414	-8.6
10	Diosmetin	PHE A:374, LEU A:368, ARG C: 408, GLN C: 414	-8.6
11	Quercetin	PHE B:1042, ASP B:1041, GLN C: 784	-8.1
12	Caffeic acid	THR A:415, TYR B:369, PHE B: 374	-6.7

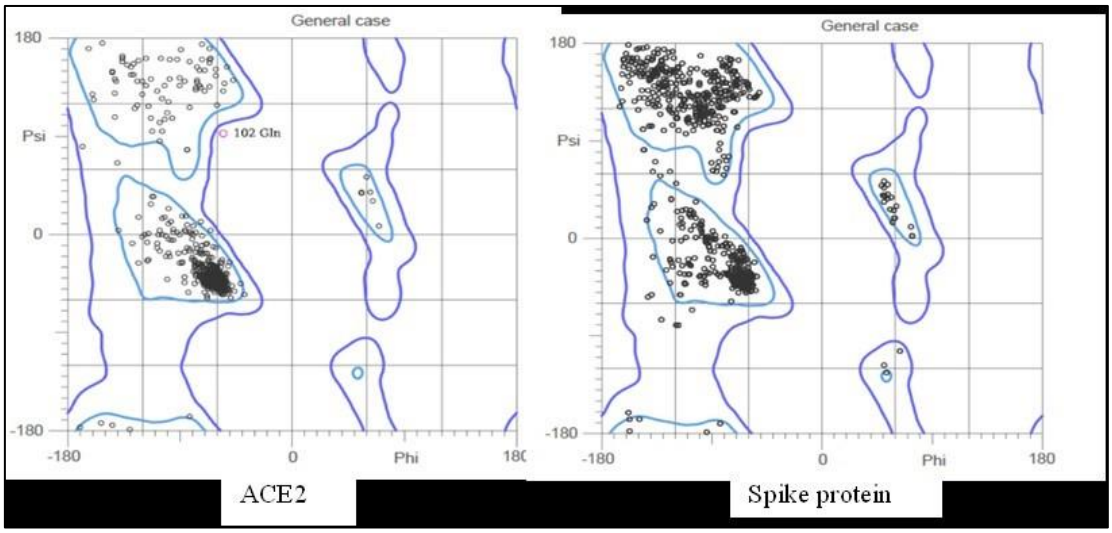


Figure 1: 3D structure of ACE2 (left side) and Spike protein (right side) Ramachandran plot from MolProbity server.

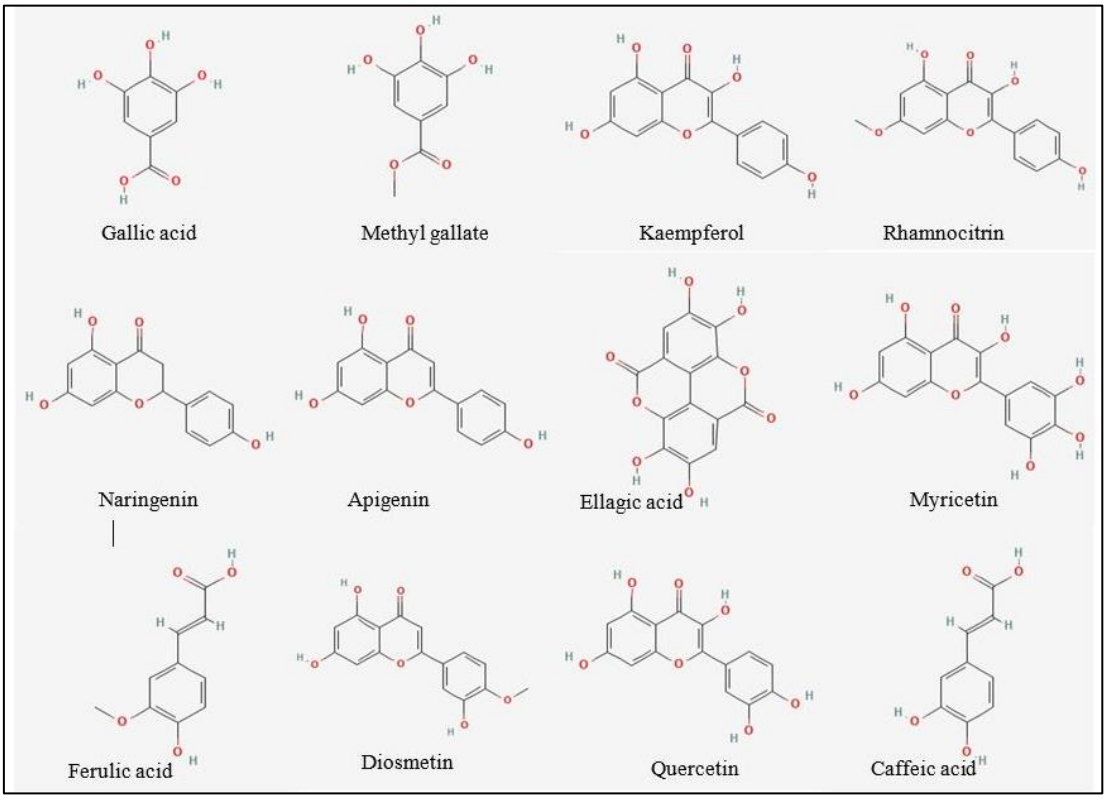


Figure 2: 2D structure of Acacia farnesiana Phytochemicals obtained from PubChem web server.

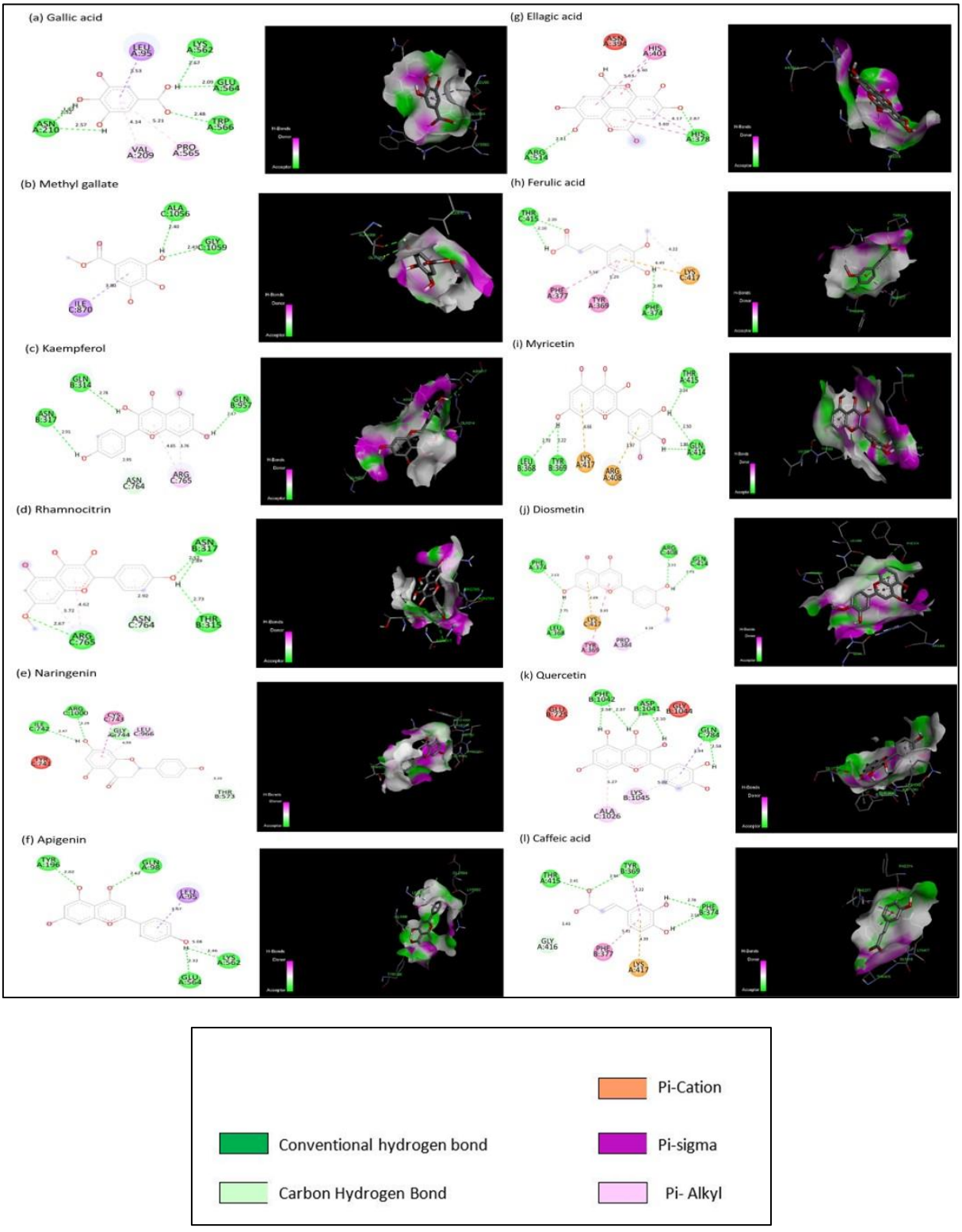


Figure 3 (a-l): Docking structure of Acacia farnesiana phytochemicals in presence of bound structure of ACE2 and spike protein generated using Discovery studio tool in 2D (left) and 3D (right) visualization.

CONCLUSION

We found some possible antiviral inhibitors using various in-silico approaches, which might serve as a starting point for stopping SARS-CoV-2 replication by reducing the binding with human ACE2. These inhibitors were produced from *Acacia farnesiana,* a well-known medicinal shrub. This research made use of a molecular docking investigation. From the virtual screening technique, the top lead compound demonstrates that several phytochemicals interact with the active site of SARS-CoV-2 with good binding energy. According to the findings, Myricetin and Diosmetin (among the twelve phytochemicals) had the greatest binding affinity (-8.6 ΔG) in conjunction with the SARS-CoV-2 spike protein. Important residual interaction was observed, such as LEU 368, TYR 369, THR 415, GLN 414 in myricetin with A and B chain of spike protein, PHE 374, LEU 368, ARG 408, GLN 414 in diosmetin with A and C chain of Spike protein. Naringenin, quercetin, ellagic acid,

Rhamnocitrin, kaempferol, apigenin and ferulic acid also shows good binding affinity above -7 ΔG. We concluded from the study that these phytochemicals from *Acacia farnesiana* have anti-inflammatory, antioxidant, and antiviral effects, and that they can play a critical role in preventing SARS-CoV-2 entrance into the host cell. This research will aid researchers in the identification of a possible SARS-CoV-2 medication.

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Conflict of Interest

We declare that we have no conflict of interest.

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