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Targeting COVID-19 through active phytochemicals of betel plant by molecular docking

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Betel leaf *(Piper betle)*, COVID-19 (SARS-CoV-2), Phytochemicals, Complex antibody protein, Molecular docking

Abstract: COVID-19 has reached pandemic proportions and is affecting people all across the world. Coronavirus 2 is responsible for causing severe acute respiratory syndrome. The *Piper betle* L. leaf, sometimes known as betel, has been used medicinally for centuries. The primary purpose of this docking study is to check the efficacy of the phytochemicals of Betel leaf *(Piper betle)* against COVID-19. Traditionally, it is used as a medicinal plant containing many bioactive constituents, which can be used to develop a drug for COVID-19. We have used molecular docking for the SARS-CoV2 receptor on a complex antibody protein with PDB ID-7BNV and PDB ID-7CM4. Betel leaf *(Piper betle)* contains various phytochemicals such as Eugenol, Alpha pinene, Alpha terpinene, Beta phellandrene, Terpinolene, Sabinene, Hydroxychavicol, Germacrene D, etc. All this data is collected from the PubChem database. All evaluations were carried out based on molecular docking of docking score of receptor interaction with the ligand. Using ligands, we were able to effectively molecular dock Betel leaf *(Piper betle)* phytochemicals on the SARS-CoV2 target (Eugenol, Alpha pinene, Alpha terpinene, Beta phellandrene, Terpinolene, Sabinene, Hydroxychavicol, Germacrene D). Based on molecular docking scores, we concluded that all the ligands showed significant activity for both the proteins of SARS-CoV2.

Introduction

COVID-19, also called SARS-COV2, is the disease that caused a pandemic outbreak just a few months ago (Rabaan et al., 2020). COVID-19 was first discovered in China (Wuhan city) and then spread throughout the world over a period of time. Many organizations have conducted various trials to develop effective vaccines, resulting in massive vaccination (Chauhan, 2020; De et al., 2023). The number of deaths caused by the Coronavirus is enormous; nearly 5 million people died due to the pandemic. The incubation or development period of this virus is approximately 7-14 days and can last up to 9 days, which means that during this time, this virus transmits from one person to another via various

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body cavities such as the nose, mouth, eyes, and so on (Abo-Zeid et al., 2020). This disease primarily manifested symptoms gradually, or in most cases, symptoms included fever, cough, cold, chills, body ache, shortness of breath, chest pain, and so on (Sathya et al., 2020).

Vaccine and antiviral development and social control measures to limit infections and inhibit the spread of infection in the community are all being pursued in the fight against the COVID-19 pandemic. However, developing a new antiviral would take a long time (Abo-Zeid et al., 2020). We used various natural medicinal plants during the pandemic as a home remedy, like tulsi, gugul, mirrah, ginger and gulvel juice. They have effective phytoconstituents in them which helps us fight against this virus. These medicinal plants boost our immunity, and they are almost chemical-free compared to synthetic drugs, which leads to almost no side effects (Sathya et al., 2020). There are various protein receptors available for COVID-19. We mainly selected two viral complex antibody proteins of severe acute respiratory syndrome coronavirus among them. Two crystal structures have been retrieved from the protein database: one with the SARS-CoV2 receptor binding domain in complex with antibody ION-300 (PDB ID-7BNV), and the other with the COVID-19 viral spike receptor binding domain in association with neutralizing antibody CT-P59 (PDB ID-7CM4). These proteins were derived from the organism Homo sapiens.

Betel leaf *(Piper betle)* belongs to the family Piperaceae, mostly called “paan" in India. It has various health benefits as it has various properties to cure complicated disease conditions. Diabetic patients mainly use it. From ancient times people have consumed Betel leaf *(Piper betle)* as it helps to flush out toxins and restore normal pH and helps in increasing appetite, and it correlates with current phytochemical research (Shivatare et al., 2023; Hajare et al., 2023). Some studies also show that different combination of essential oil with *Betel leaf (Piper betle)* extract with antibiotics potentiates antibacterial property (Nayaka et al., 2021). We have selected various phytochemicals of Betel leaf *(Piper betle)*, which have different roles and medicinal activities, like Eugenol, which shows excellent antioxidant activity (Chakraborty and Shah, 2011). Alpha pinene shows anti-inflammatory activity through mitogen-activated protein kinase restraint (Toprani and Patel 2013). Other constituents of Betel leaf *(Piper betle)* show good antimicrobial and antifungal activity (Sekar et al., 2022); constituents like Eugenol and Hydroxychavicol mainly show these activities. It is also seen that significant anti-proliferative activity is present in Betel leaf *(Piper betle)*, mainly shown by Hydroxychavicol (Amonkar et al., 1986). The main property which is shown by hydroxychavicol is anticarcinogenic activity (Das et al., 2016). Ethanolic extract of Betel leaf *(Piper betle)* shows radioprotective properties (Bhattacharya et al., 2005). By considering all the information, the research aimed to perform the docking study, in which we have selected some of the phytochemicals of Betel leaf *(Piper betle)*, which has tremendous medicinal properties.

Material and methods

Data collection

Structures of phytochemicals of plant betel are taken from PubChem database (https://pubchem.ncbi.nlm.nih.gov) which include eugenol (CID: 3314), alpha-pinene (CID: 6654), alpha terpinene (CID: 7462), beta phellandrene (CID: 11142), terpinolene (CID: 11463), sabinene (CID: 18818), hydroxychavicol (CID: 70775), germacrene D (CID: 6436582). The structures of proteins (PDB ID: 7BNV10.2210/pdb7BNV/pdb and PDB ID: 7CM410.2210/pdb7CM4/pdb) are retrieved from the protein database (https://www.rcsb.org).

Protein preparation

Protein databases are mined for their structural information. The antibody proteins against SARS-CoV-2 were created using the Schrödinger software's protein production wizard, which entails the following procedures: a) including hydrogen bonds absent from the disulfide b) Taking away the H_2O molecules c) Filling in any gaps with hydrogen molecules d) Complete the missing side chain e) Enhancing the strength of the hydrogen bonds to prevent steric interference f) Reducing the RMSD to 0.3A° via constrained reduction of the structure (Fatriansyah et al., 2022).

Ligand preparation

Schrödinger software is utilized for the ligand preparation process. Desalination and the incorporation of hydrogen molecules are steps in the ligand production process. Epic configuration at pH7 provides all the necessary ionization and tautomeric state. The OPLS3e force field was used, and the lowest penalty state was chosen for the rest of the procedure (Figure 1).

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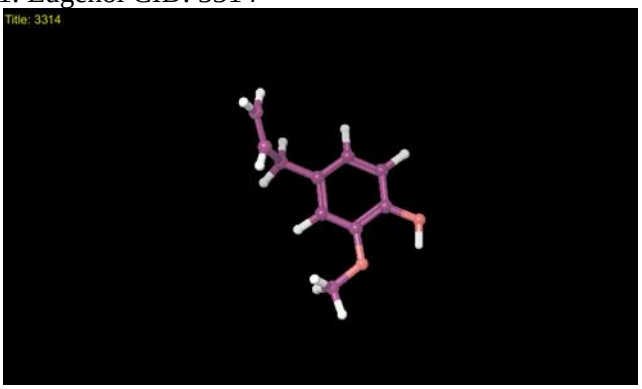
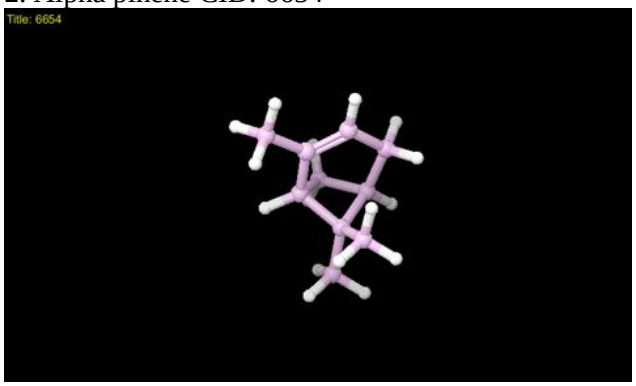
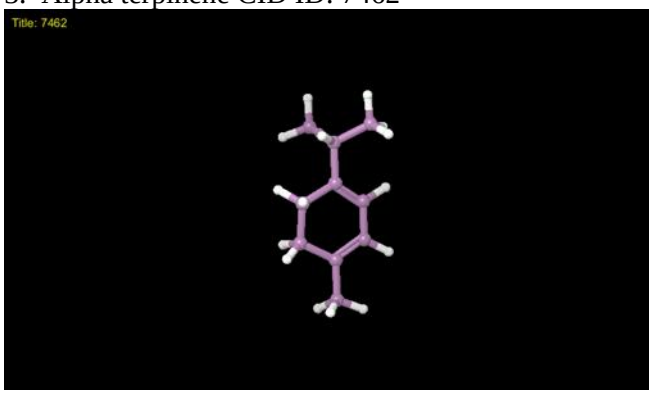
1. Eugenol CID: 3314



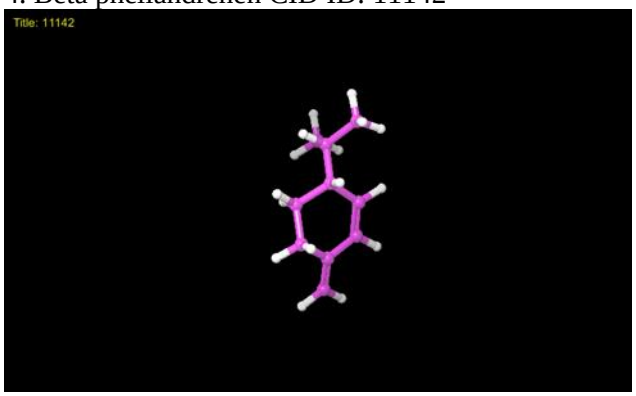
2. Alpha pinene CID: 6654



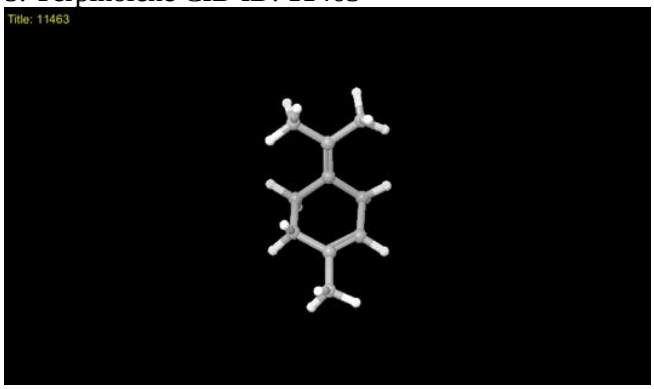
3. Alpha terpinene CID ID: 7462



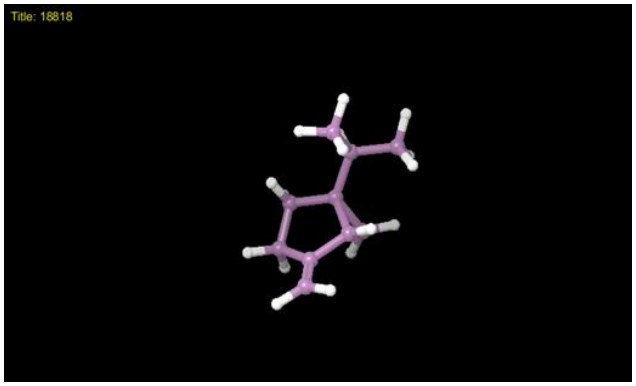
4. Beta phellandrenen CID ID: 11142



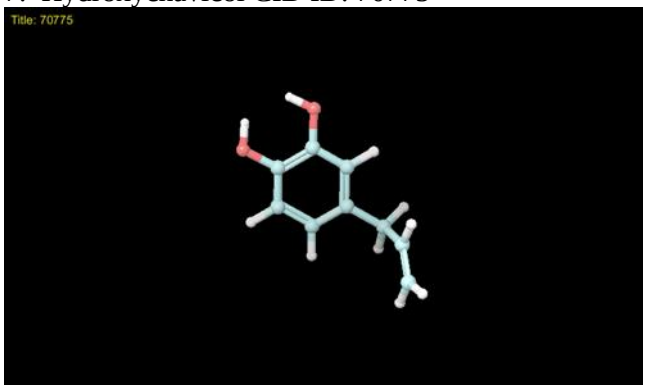
5. Terpinolene CID ID: 11463



6. Sabinene CID ID: 18818



7. Hydroxychavicol CID ID: 70775



8. Germacrene D CID ID: 643658

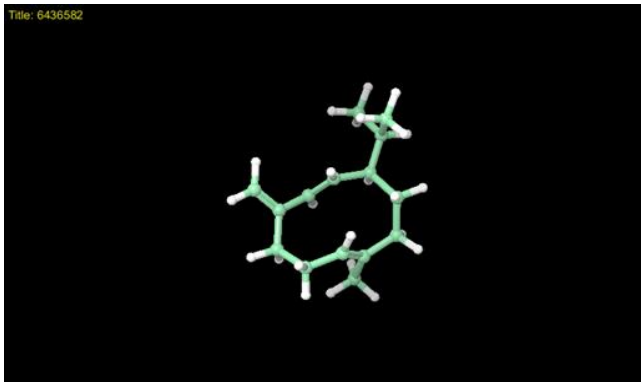


Figure 1. Ligand of betel plant (Source: Schrödinger software)

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Glide docking

The receptor for grid generation in Maestro was used to position the glide docking grid parameter at the protein's active site. The coordinates were X=17.500 Y= (-5.630) Z= (-5.320) for protein 7BNV and coordinates X= (-54.870) Y= (-74.170) Z= (-35. 360) for protein 7CM4, with the size of boxA^0. The Vander walls scaling was set to 1 to soften the potential for nonpolar parts of the receptor, and the partial charge was set to 0.25. The best ligand for active binding site was determined on the basis of D score, ligand having the most negative docking score shows the good binding.

Results and Discussion

The docking result of SARS COV-2 protein 7BNV

Eugenol shows hydrogen bonding interaction with residues Gly L:42 which has H bond distance-2.25217, acceptor angle-143.458, donor angle-128.578. and Gln L:43Which has H bond distance- 2.25217, acceptor angle-143.458, donor angle-128,578 respectively. with docking score-(-4.21).

Alpha pinene was correctly positioned into binding pocket constructed byILE-109, ALA-109, GLU-168, GLU-108, GLN-169, TYR-176, PRO-41, Lys-40, VAL-86, LEU-107, ALA-85, LYS-106 and PHE-84amino acids with docking score-(-4.45).

Alpha terpinene was appropriately positioned into the binding pocket constructed by GLN L-39, TYR H-95, GLN L-43, GLY L-42, LEU H-122, MET H -93, ALA H-92, PRO H-41, GLY H-42, MET H-40, GLN H-39, LYS L-40, PRO L-41amino acids with docking score- (-5.21).

Beta phellandrenen was appropriately placed into the binding pocket constructed by PRO L-41, GLN L-43, GLY L-42, MET H-93, LEU H-122, PRO H-41, ALA H-92, MET H-40, GLN H -39, GLY h-42, LYS H -43, GLN L-39, LYS L-40 and TYR H-95 amino acids with docking score- (-5.31).

Terpinolene was appropriately placed into the binding pocket constructed by PRO L-41, GLN L-43, GLY L-42, MET H-93, LEU H-122, PRO H-41, ALA H-92, MET H-40, GLN H-39, GLY H-42, LYS H-43, GLN L-39, LYS L-40 and TYR H-95 amino acids with docking score- (-4.70).

Sabinene was appropriately placed into the binding pocket constructed by GLY L-42, TYR H-95, GLN L-43, GLN L-39, PRO L-41, GLY H-42, MET H-40, GLN H-39, PRO H-41, MET H-93, LEU H-122, ALA H-92 and LYS H-43 amino acids with docking score- (-5.10).

Hydroxychavicol shows hydrogen bonding interaction with residues GLN L-43 which has H bond distance-2.21553, acceptor angle-139.682, donor angle-99.5508 and GLN L:43 Which has H bond distance- 2.07503, acceptor angle-168.02, donor angle-145.004 respectively with docking score-(-4.35).

Germacerne was appropriately positioned into the binding pocket constructed by GLN L-43, TYR H-95, GLY L-42, LYS L-40, GLN L-39, PRO L-41, GLY H-42, MET H-40, LYS H-43, GLN H-39, PRO H-41, MET H-93, ALA H-92, LEU H-122 and GLU H-162 amino acids with docking score- (-4.91) (Figure 2 and Table 1).

The docking result of SARS COV-2 protein 7CM4

Eugenol shows hydrogen bonding interaction with residues ASP L:86 which has H bond distance-1.69915, acceptor angle-173.64, donor angle-145.676 with docking score-(-4.30).

Alpha pinene was appropriately positioned into the binding pocket constructed By THR H-96, GLN H-41, PRO H-43, ALA H-93, PRO H-42, GLY H-44, LYS L-167, LYS H-45, GLN-39, PRO L-41, THR L-43, GLY L-42 amino acids with docking score- (-3.58).

Alpha terpinene was appropriately positioned into the binding pocket constructed by THR L-43, GLY L-42, LEU L-40, PRO L-41, GLN L-39, ASP L-86, TYR L-88, LYS L-167, LYS H-45, EDO L-302, GLY H-44, THR H-94, GLN H-41, ALA H-93, TYR H-96, PRO H-92, PRO H-43 amino acids with docking score- (-5.21).

Beta phellandren was appropriately positioned into the binding pocket constructed by ASP L-86, EDO L-302, LEU L-40, GLY L-42, GLN L-39, THR L-43, PRO L-41, TYR H-96, THR H-94, PRO H-42, PRO H-43, GLN H-41, LYS H-45, LYS L-167, GLY H-44 and TYR L-88, amino acids with docking score- (-4.51).

Terpinolene was appropriately positioned into the binding pocket constructed by GLN L-39, ASP L-86, TYR H-96, GLY L-42, THR H-94, THR H-123, PRO H-43, PRO H-42, GLN H-41, EDO L-302, GLY H-44, LYS L-167, LYS H-45, TYR L-88, GLN L-39 amino acids with docking score- (-4.06).

Sabinene was properly positioned into the binding pocket constructed by GLN H-41, ALA H-93, PRO H-42, PRO H-43, GLY H-44, ASP L-86, EDO L-302, TYR L-88, LYS H-45, LYS L-167, GLN L-39, GLY L-42, TYR H-96 and THR H-94 amino acids with docking score- (-4.06).

Hydroxychavicol shows hydrogen bonding interaction with residues ASP L-86 which has H bond distance-1.7076, acceptor angle-176.45, donor angle-162.199. and ASP L-86 Which has H bond distance- 1.6031, acceptor angle-177.215, donor angle-114.334 respectively with docking score-(-4.21).

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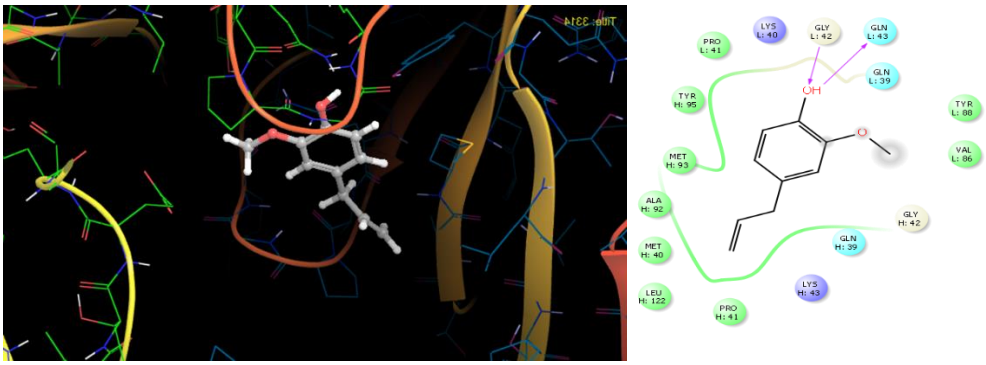
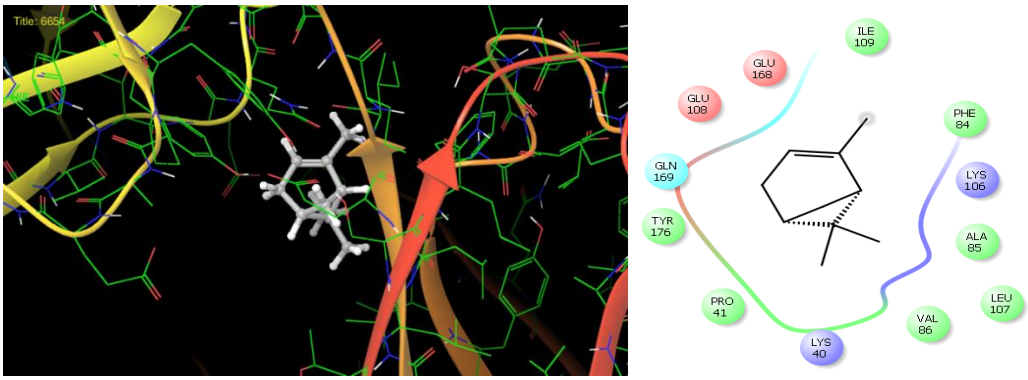
Molecular docking

Docking of ligands with PDB ID: 7BNV

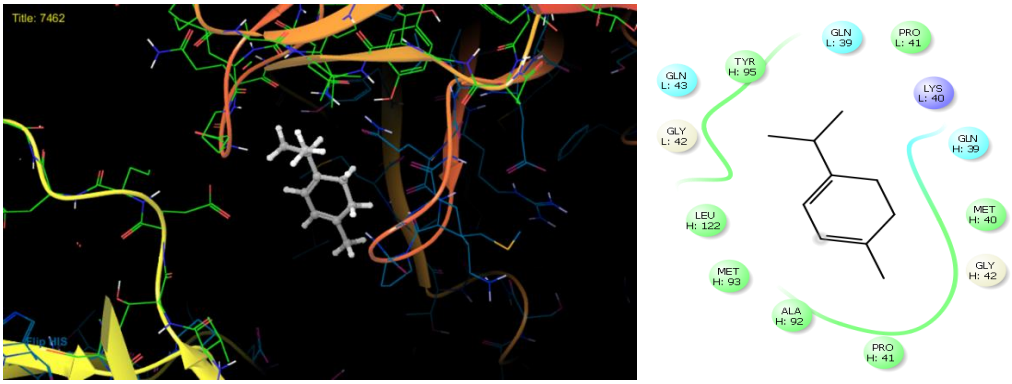
(a) Eugenol



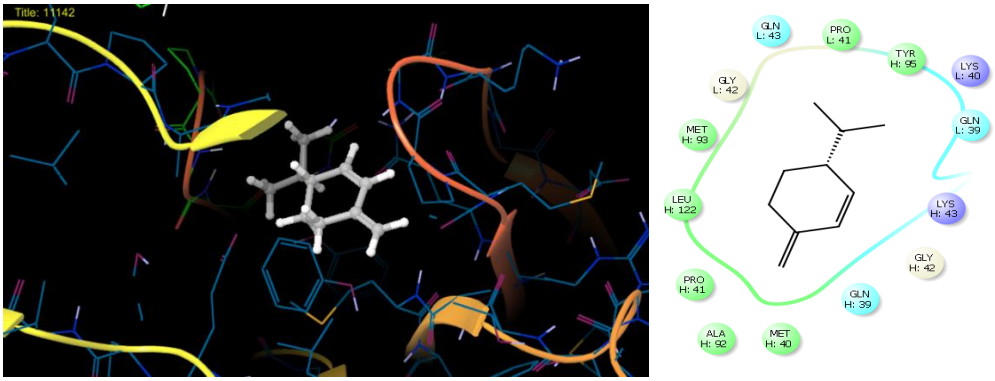
(b) Alpha pinene



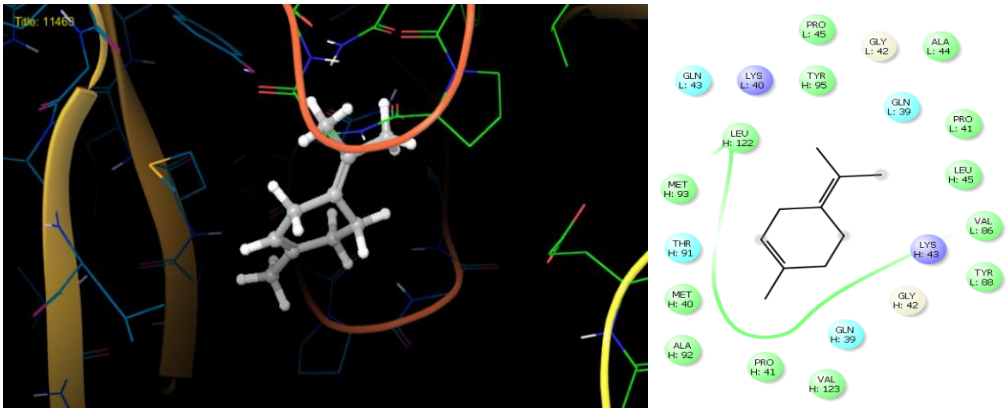
(c) Alpha terpinene



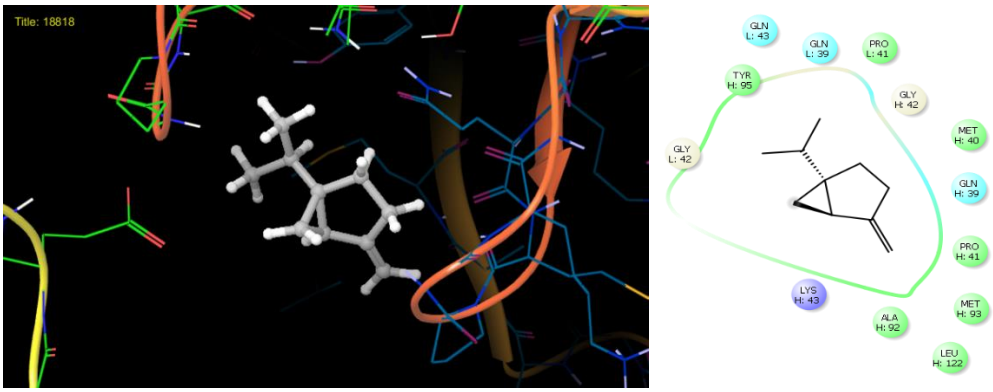
(d) Beta phellandrenen



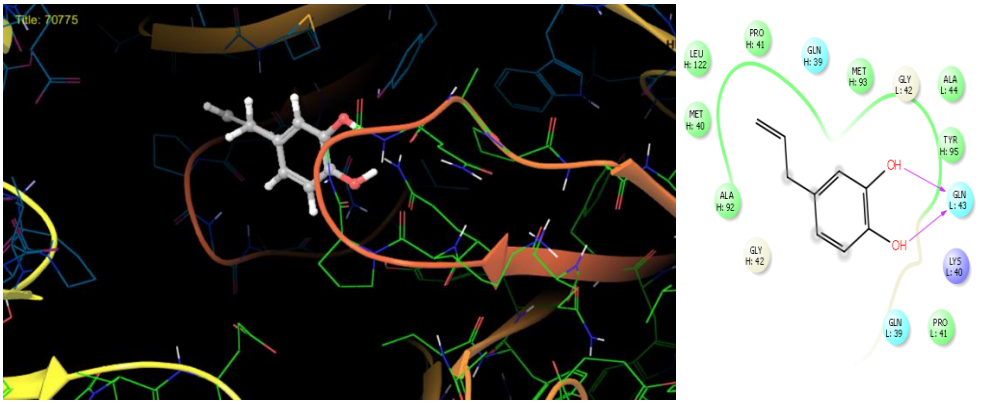
(e) Terpinolene



(f) Sabinene



(g) Hydroxychavicol



(h) Germacrene D

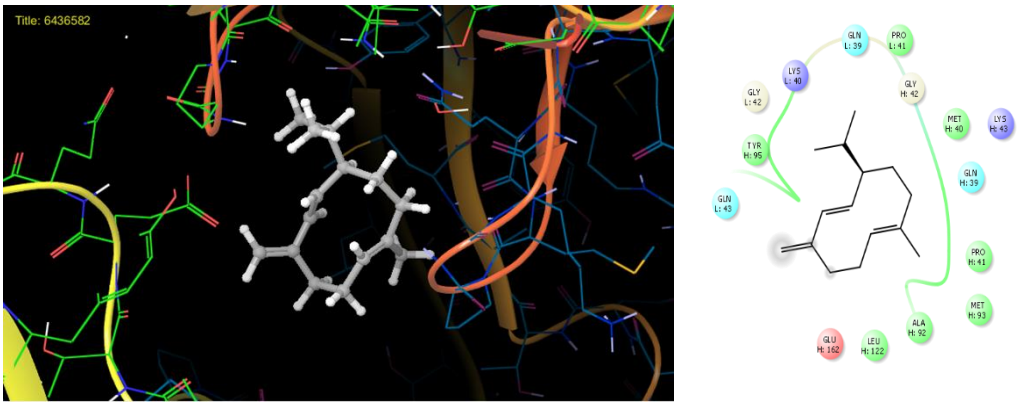
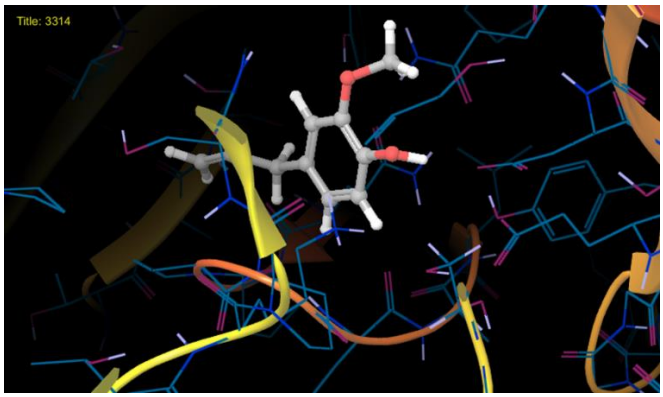
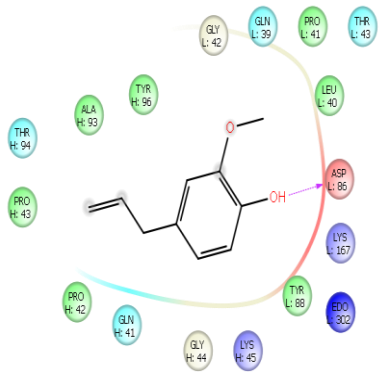


Figure 2. Docking results - 1(a) to1(h) Docking of ligands with PDB ID (7BNV)

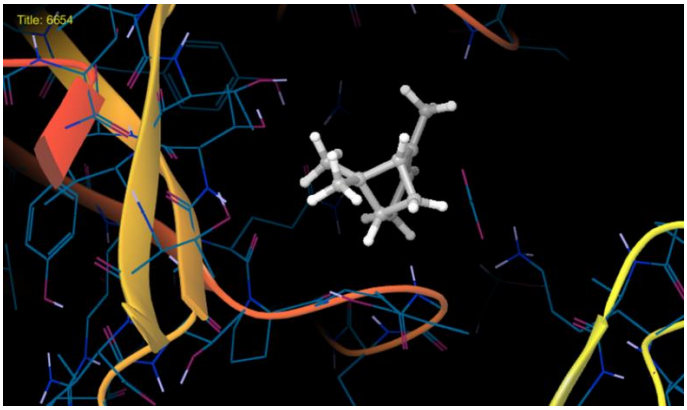
Docking of ligands with PDB ID: 7CM4

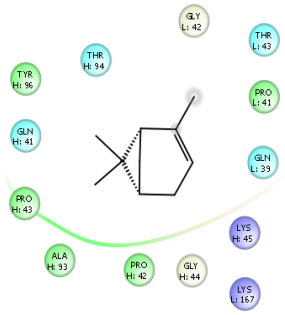
(a)Eugenol



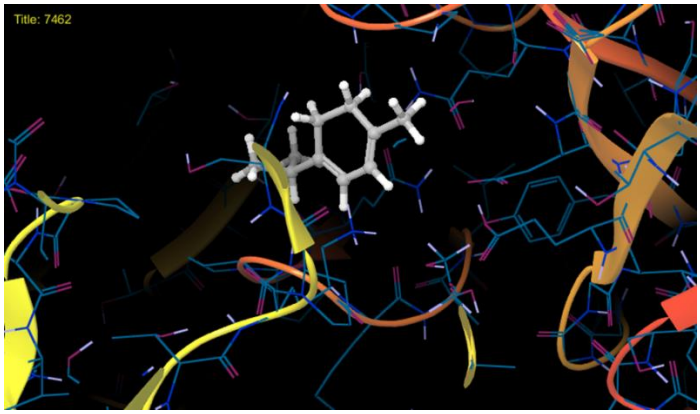


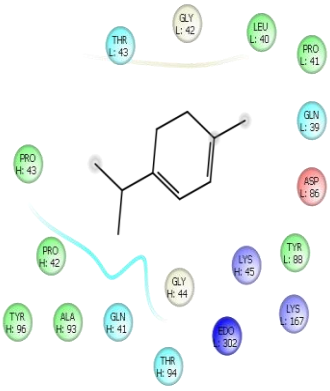
(b) Alpha pinene



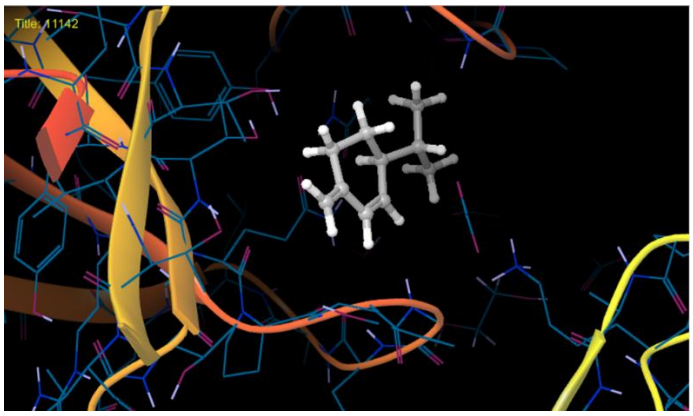


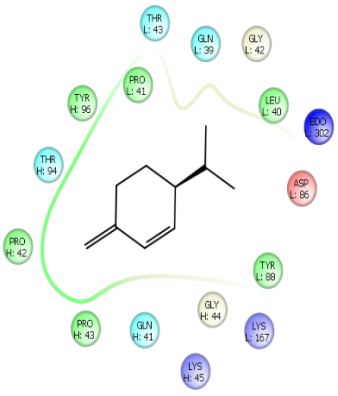
(c) Alpha terpinene



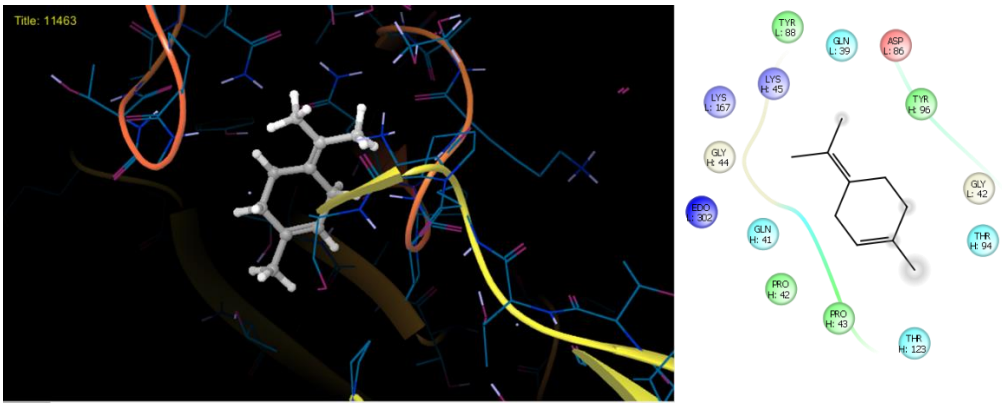


(d) Beta phellandrenen

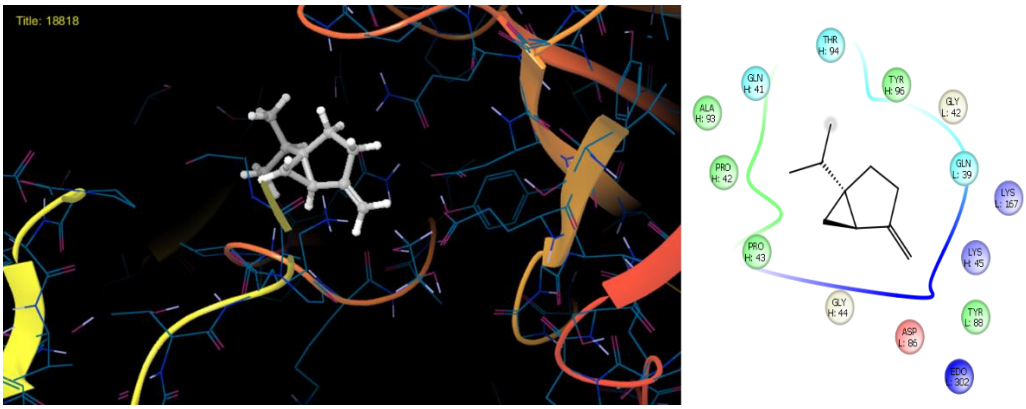




(e)Terpinolene



(f)Sabinene



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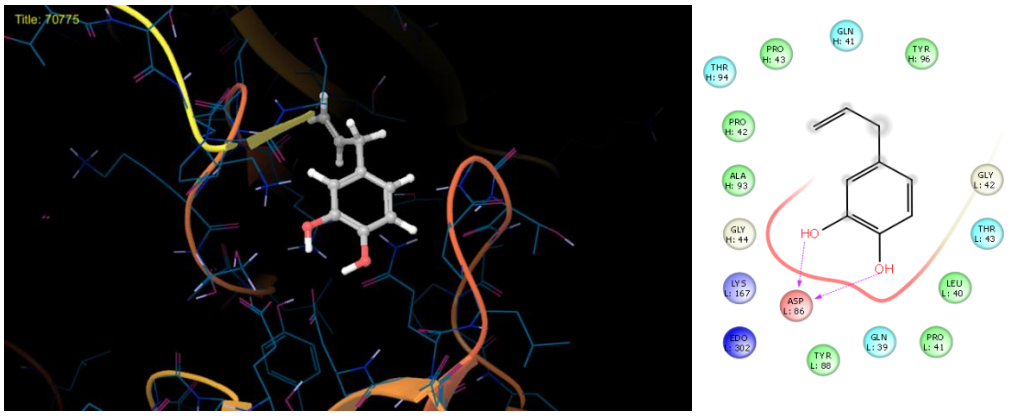

(h) Germacrene D

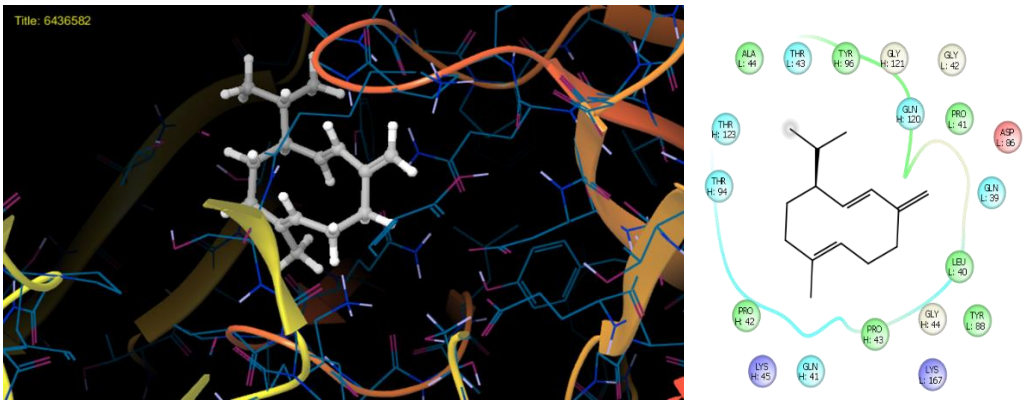

Figure 3. Docking Results- 2(a) to 2(h) Docking of ligands with PDB ID (7CM4)

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Germacerne D was properly positionedinto the binding pocket constructed by THR H-123, THR H-94, PRO H-42, LYS H-45, GLN H-41, PRO H-43, LYS L-167, GLY H-44, TYR L-88, LBU L-40, GLN L-39, ASP L-86, PRO L-41, GLN H-120, GLY L-42, GLYH-121, TYR H-96, THR L-43, ALA L-44amino acids with docking score (-4.40) (Figure 3 and Table 1).

Docking result for ligands of plant betel

Table 1. Comparative docking results

Ligands	PDB ID: 7BNV	PDB ID: 7CM4
Eugenol- (CID:3314)	-4.21	-4.30
Alpha pinene- (CID:6654)	-4.45	-3.58
Alpha terpinene- (CID:7462)	-5.21	-3.90
Betaphellandrenen- (CID:11142)	-5.31	-4.51
Terpinolene- (CID:11463)	-4.70	-4.06
Sabinene- (CID:18818)	-5.10	-4.06
Hydroxychavicol- (CID:70775)	-4.35	-4.11
Germacrene D- (CID:6436582)	-4.91	-4.40

Conclusion

The respiratory system, namely the lungs, serves as the principal site of infection for COVID-19, a viral illness. The current problem has now developed into a worldwide epidemic. The utilization of Betel leaf (*Piper betle*) as a medicinal plant date back to ancient times, owing to its notable antibacterial, anti-inflammatory, and antioxidative properties. By using ligands, the molecular docking of phytochemicals derived from Betel leaf (*Piper betle*) onto the SARS-CoV2 target was successfully accomplished. The specific phytochemicals docked include Eugenol, Alpha pinene, Alpha terpinene, Beta phellandrene, Terpinolene, Sabinene, Hydroxychavicol, and Germacrene D. Based on the molecular docking scores, it may be inferred that all the ligands exhibited substantial activity towards both proteins associated with SARS-CoV2. The docking score of Beta phellandrene is the highest among the other ligands, with values of -5.31 and -4.51 for the proteins with PDB ID-7BNV and 7CM4, respectively. This indicates that Beta phellandrene exhibits the most binding affinity with these proteins.

Conflicts of interest

There are no known conflicts of interest for the authors in the publication of this work.

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