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Molecular Docking and Antiviral Potential of Selected Medicinal Plants to Combat COVID-19

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Abstract

The current emergence of the COVID-19 virus has originated a global disaster due to the unavailability of any type of vaccine or drug which can be effective and determined to combat it. Naturally, various probabilities (such as herbal remedies with known medical importance) have been investigated by scientists. Research of systematic scientific (starting from silico research) of herbal medicine in specific and any type of drug in common is now possible that is building blocks (proteins) of COVID-19 which are already being identified. Mpro or 3CLpro is the main protease of the COVID-19 virus which have an important CoV enzyme and an attractive drug target because it plays a very important role in the viral replication and transcription. By using molecular docking scientist's aims to explore bioactive chemicals which are found in medicinal plants such as potential COVID-19 Mpro inhibitors. Molecular docking was performed by Autodock 4.2, and the Lamarckian Genetic Algorithm, for analyzing the possibility of a dock. Although, further research is needed here to investigate their uses of potential drug. And the search for new drugs, especially through the use of antiviral peptides, is a very possible and protein-protein docking were performed using silico methods to identify, test, and evaluate cell interactions and interactions of dermaseptin peptide molecules produced by Phyllomedusa frogs against SARS-CoV-2 spike protein macromolecule, with its effect on the surface attachment of the ACE-2 (Angiotensin Converting Enzyme-2) receptor. Therefore, it is hoped that the dermaseptin-S9 peptide molecule may continue to be studied in the formulation of antibodies to anti-virus peptides that will be able to control COVID-19 infectious diseases.

Keywords: COVID-2019; SARS-CoV-2 spike protein; Mpro; 6LU7; Medicinal Plant Compounds; Docking; Tinospora cordifolia; dermaseptin; antiviral peptide;

I. Introduction

Coronaviruses (CoVs) are etiologic agents in humans and animals for severe infections, which can cause disturbance not only in the digestive tract but also in the respiratory tract and system. Earlier CoV studies have reported that certain species of animals, including mammals, birds, and reptiles can infected CoVs. Since December

2019, the COVID-19 outbreak, which originated in China, has been a global catastrophe (Lu et al., 2020).

Corona in Latin means that Coronaviruses are derived from the crown belonging to the family Coronaviridae, which is a family of high-dose RNA viruses, which are covered with large viruses that affect humans and various animals (Xu et al., 2020). Tyrell and Bonne had previously reported coronavirus internally and facial specimens resembling a solar corona, a virus called corona. In 1966, who planted the virus in patients with common cold (Malik et al., 2020). According to their morphological features representing a round virion with a primary shell in its shape (Xu et al., 2020).

Coronaviruses have four genes that include α-, β-, γ- and Δ subtypes α and β CoVsare reported to be derived from mammals such as bats and γ and Δ viruses are mainly derived from pigs and birds (Aanouz et al., 2020). They range in size from 60-80 nm to genome size between 26 and 32 kb (Bogoch et al., 2020). In addition, SARS-COV-2, a large family of COVID-19, is sensitive to heat and ultraviolet (UV) radiation. In addition, they do not work56◦Cforhalfhourand can be stored at 80◦C for many years. In addition, 75% of chlorine, ethanol containing disinfectants and per-acetic acid that may be inactive for COVID-19. Often, the ultimate goal of preventing and controlling an infectious disease removes the source of disease and thus protects vulnerable people (Phan et al., 2020).COVID-19 is easily transferable and is already widespread. Symptoms are like the flu and can include muscle and body pain, fever, sore throat and cough. After 5-6 days of infection, symptoms may appear (Phan et al., 2020).

COVID-19 is a recent WHO disease that is originate by a new member of the "novel coronavirus" of this viral family (https://www.who.int/, Guo et al., 2020). Prior to its emergence in Wuhan China, in late December 2019 (Guan et al., 2020; Wang, Hu, et al., 2020), this new virus & disease have been never observed before in human history. The international committee on taxonomy of viruses, on February 11, 2020, reported the new coronavirus as “Severe Acute Respiratory Syndrome Coronavirus 2” (SARS-CoV-2) (Gorbalenya et al., 2020).

The use of blood, saliva, or a sample, COVID-19 can be detected in the same way as other conditions caused by a viral infection. Although, many experiments use a cotton swab to obtain a sample inside your nose. The Trusted Food and Drug Administration (FDA), on April 21, accepted the use of the first home screening tool for COVID-19. The Emergency Use Authorization stipulates that the diagnostic kit is licensed for utilization of that people who have been identified as COVID-19 suspect by health professionals (Benson & Daggett, 2012; Gajula et al., 2016).

Lungs tissue damage is quite obvious because COVID-19 is a respiratory disease, but there are also observed that other tissues and organs may also be affected. Since viral load in serum or plasma is common in respiratory infections but there is a potential for transmission of coronaviruses through the introduction of lean blood products (Corbin & Zeisel, 2012). According to the recent WHO report, that is released on August 10, 2020, 2, 86,000 COVID-19 cases have been reported in Pakistan. Globally, the number of reported cases has reached 20.3M, including 741K deaths (Wang et al., 2019).

Currently, no specific COVID-19 vaccinations are available and research into COVID-19 treatment is less (Neira et al., 2017). Faced with these difficulties, numerous countries have reported using herbal medicines for the treatment and prevention of COVID-19, ignoring the World Health Organization's warnings regarding conventional medicine's protection (Yan et al., 2020; Yan, Zhang, Li, et al., 2020).

In addition, Ethiopia is one of the countries that have been given a variety of medicinal plants. From medicinal herbs found in Ethiopia; *Nigella sativum, Allium cepa, Allium sativum, Brassica junce, Zingiber officinale, Curcuma longa, Capsicum annum, and Citrus sps* are mentioned in various literature on their antimicrobial activity (Amir et al., 2017; Neha S, 2019).

Nigella sativa, a Ranunculaceae family herbal medicine, has been evaluated on its own and gained worldwide recognition as a common and religious cure for various health issues (Gupta et al., 2020). Seeds of *N.sativa* were used to treat various ailments and weaknesses (Yimer et al., 2019; Majeed et al., 2020; Begum & Mannan, 2020). It is considered one of the best medicines in Islamic and Christian literature. The general use of black seeds is suggested in "Tibb-e-Nabwi" (Ahmad et al., 2013). Sowing N. Sativa has demonstrated good antibacterial properties when used against "Laryngotrachietis Virus (ILTV)" in Chicken Embryo Rough Cells (CER) at a concentration of 35µM (Begum & Mannan, 2020).

Quercetin isolated from ***Allium cepa*** can inhibit RNA polymerase; thus affecting the penetration, attachment, and replication of enterovirus and influenza virus in the center cell. On the other hand, organosulfur compounds such as ***ajoene, diallyltrisulide, and allicin*** are major chemicals that transport antibodies to ***A. sativum*** (Neha S, 2019). ***Tinospora cordifolia*** originally comes from the chemical components of its leaves, stem, root, flower, and seeds, among other things. Glycosides, alkaloids, phenolics, hormones, aliphatic compounds, essential oil polysaccharides, a mixture of fatty acids, or polysaccharides are all chemical elements found in various parts of the plant body, including the leaves are well documented in literature. (Sharma et al., 2019).

Small phyto constituents extracted from Tinospora cordifolia (Figure1) (https://www.drugbank.ca/drugs). These phytoconstituents were selected after using appropriate tests by examining their drug compatibility, pharma- co kinetics and lipophilicity properties set as guidelines for identifying potential drug combinations. After visual analysis, we examined their potential inhibitors of the main CoV-2 protease in the form of cell proliferation.

Leaf of Tinospora Cordiofolia **Stem of Tinospora Cordifolia**

Figure 1

II. Coronavirus diseases

2.1 Coronaviruses

Coronaviruses are a group of viruses that commonly infect humans and other mammals and their intestines (Li et al., 2020). Bacteria are closely linked to illnesses such as influenza, common cold, and disorders such as acute respiratory syndrome (SARS) and

respiratory syndrome in the Middle East (MERS). The official name of the Novel Corona virus is SARS-CoV-2. The official name of the disease created by SARS-CoV-2 is COVID-19. Coronaviridae is a family of coronavirus and its genus is Nidovirales.

2.2 Structure of SARS-CoV-2

Its genome consists of single stranded and non-segmented positive sense RNA strand. It forms nested subgenomic mRNA which is 26-32 kilo bases in length. Its capsid contains capsomeres that have helical shaped protein capsid and gives shape to virus. Its envelope generates from endoplasmic membrane of the host and viral proteins get embedded into it. It has host receptor binding proteins (spikes proteins).

2.3 Origin and Outbreak

COVID-19 outbreak was first observed in China's Wuhan Area at the end of December 2019, which rapidly spread to China and then to 209 countries around the world including America, Europe, Australia and Asia, including Pakistan. There are approximately 335 K deaths, and about 5.15 M people worldwide have been affected, though statistics are increasingly growing.

2.4 Symptoms

The symptoms of COVID-19 infection usually show up after about five days of incubation. Many of the commonest symptoms directly associated with COVID-19 include, having a cough that gets more severe over time, Shortness of breath, Fatigue, A low-grade fever that gradually increases in temperature, Repeated shaking with chills, Headache, Loss of taste, Muscle aches and pain, Loss of smell, Chills, Sore throat. In the most severe cases, patients may develop: Acute cardiac problems, Pneumonia, Multiorgan failure, acute respiratory distress syndrome

2.5 Causes

Coronaviruses are zoonotic, meaning they can spread from person to person. This implies that they evolve first in animals and then in humans. The virus spread from animals to humans, an individual must come into close contact with an infected animal. (Huang et al., 2020). This is a scientific term for the moist particles that pass through the air as your cough, sneeze, or speak. These droplets contain infectious content that can be inhaled into the respiratory tract (windpipe and lungs), where the virus can lead an infection. The coronavirus of 2019 has not been definitively related to a single species. The virus may have been spread to humans from bats to another animal, such as snakes or pangolins, according to the researchers. This transmission most likely actually occurred in the free food market in Wuhan, China.

2.6 Diagnosis

Similar to other disorders caused by viral infections, COVID-19 may be diagnosed: using a blood, saliva, or tissue sample. Many studies also use a cotton swab to get a sample from the inside of your nostrils. On April 21 the Trusted Source Food and Drug Administration (FDA) approved the use of the first home test kit COVID-19.

Your doctor will advise you on whether you should:

- stay home and monitor your symptoms
- come into the doctor’s clinic to be evaluated
- go to the hospital for more urgent care

III. Molecular docking

Cells are a type of bioinformatics model that involves the interaction of two or more molecules to provide a stable adduct. The main purpose of cell arrival is to detect the ligand-receptor complex with the prepared compound and for the purpose of having a small non-binding force (Agarwal et al., 2015). Chemical insertion is an attractive platform for understanding chemical drug interactions in rational drug formulation and discovery, as well as for technical research by placing a molecule (ligand) in a specific binding region of a specific DNA / protein (receptor) especially in an unconventional way to build a strong chain of potential much (Elokely KM and Doerksen RJ, 2013; Ferreira et al., 2015).

3.1 Advantages of molecular docking

1. Identify the target area.
2. Selection of "best" drugs (depending on the scoring process).
3. Enzymes and their processes.
4. Protein synthesis.
5. Vigorous chemical testing etc.

IV. Traditional medicines for COVID-19 treatment

In addition, Furthermore, chemicals isolated from these medications have recently been found to prevent coronavirus infection in numerous ethno botanical and molecular research (Siti et al., 2020). In various Insilco studies, several compounds from these drugs have shown inhibition of SARS-COV-2 main (M) protease, spike (S) glycoprotein, chymotrypsin-like protease (3CLpro), and angiotensin-converting enzyme-2 (ACE2) receptor.

As a result, the primary goal of this analysis is to provide additional information to researchers so that they can perform in vitro, in vivo, and clinical studies into chemicals classified by the following plant organisms, rather than to advise populations to use conventional COVID -19 drugs for treatment. Table 1.

Table 1: SARS-COV-2 inhibition and other antiviral effects of medicinal plants and their compounds.

Sr. no.	Scientific name	Vernacular name (Amharic)	Isolated compounds with potential anti-COVID-19 activities	Literatures supporting SARS-COV-2 inhibition	Other-viral infections treated
1.	Allium cepa	Key shin kurt	Quercetin epigallocatechin gallate	In silico study showed that quercetin and epigallocatechin gallate isolated from this plant found to be potential inhibitors of COVID-19 main (M) protease (Hanan P and Gillad L, 2020; Trina et al., 2020).	Enterovirus 71 (Saba et al., 2018; Neha S, 2019).
2.	Aloe barbadense miller	Eret	Aloenin aloesin aloe-emodin-aloin chrysophanol catechin isoaloresin aloin A	Aloenin extracted from this plant showed a greater binding affinity for COVID-19 protease (6LU7) using in silico study (Mansi P, 2020).	Influenza virus, Avian Paramyxo Virustype-1 (APMV-1), AI-H5N1, Newcastle Disease Virus (NDV), HSV-1 and 2, H1N1, and Egg- (EDSV) (Howaida et al., 2012; Ricio et a., 2019).
3.	Allium sativum L (tm 15)	Nech shinkurt	Allicin diallyltrisulide ajoene apigenin	Essential oils, Allicin, diallyltrisulideajoene, and apigenin have strong interactions with the host receptor of ACE2, and exhibited M protease inhibition by 70%	Herpes Simplex Virus (HSV-1 and 2) (Ha e al., 2017) Influenza A and B virus, HIV, Coxsackie Bl virus (CB1V), Infectious Bronchitis virus, Dengue virus
4.	Brassica oleraceavar	Broccoli	Kaempferol glucobrassicin	Glucobrassicin isolated from these plants showed a greater binding	Influenza A/H1N1 Virus (Lee et al., 2014; Zhansheg et al.,

				affinity for SARS-COV-2 6LU7 and 6Y2E proteases (Megha et al., 2020). Kaempferol extracted from Brassica oleraceavar. italic showed inhibition of SARS-CoV-2 M protease (Mpro) and Spike-(S) glycoprotein (Trina et al., 2020).	2019).
5.	Bambusa vulgaris	Shembeko		In chines traditional medicines preparation "yinqiao san", this plant is combined with other plants for the treatment of mild COVID 19 (Xu J and Zhang Y, 2020).	Measles virus, HSV-1, and yellow fever virus (Obi et al., 2016; Ojo et al., 2019).
6.	Camellia sinensis	Shay kitel		Epigallocatechin gallate with high oral bioavailability is also isolated from Camellia sinensis and endowed with good binding affinity for SARS-COV-2 S-glycoprotein and M Protease (Trina et al., 2020).	ADV, HBV, HCV, Influenza Virus, HIV, Bovine Coronavirus, Epstein-Barr virus, EV71, HSV, Chikungunya Virus (CHIKV), Laryngotracheitis Virus (ILTV) (Muhammad et al., 2016).
7.	Citrus limon	Lomi	Hesperidin	Computational studies indicate that the hesperidine, a flavonoid that is abundant in citrus peel, binding with the three key cellular receptors of the SARS-CoV-2 virus could act as a prophylaxis and treatment of COVID-19 (Utomo et al., 2020).	Common cold, HAV, HCV (Tahir et al., 2018; Worku AM, 2019).
8.	Lycopersicones culentum	Timatim	Rhoifolin	Rhoifolin is a compound extracted from this plants that showed inhibition	

				of SARS-COV-2 Spike and M protease (Amaresh et al., 2020).	
9.	Musa spp.	Muz	Rhoifolin	Rhoifolin from this plant species exhibited SARS-COV-2 3CLpro inhibition in molecular docking study (Leif EP, 2020).	Influenza Virus (Evelyn et al., 2020).
10.	Nigella sativa	Tikur azmud	Hederagenin nigelledine a-Hederin	Hederagenin is a constituent of N. sativa and several Cucurbitaceae vegetables making it again a potentially useful candidate for SARS-COV-2 treatment (Megha et al., 2020).	HIV, CMV, Avian Influenza, Chistosoma Mansoni Infection, Broad Bean Mosaic Virus, (Umar et al., 2016; Shamim et al., 2019).
11.	Phaseolus vulgaris	Bakela	Kaempferol	Flavonoids like Kaempferol Inhibit SARS-CoV 3CL protease.	HIV1, RSV and HSV-1.
12.	Piper nigrum	Kundo berbere	Piperine	In molecular docking studies, piperine isolated from this plant had inhibition of chymotrypsin-like COVID-19 virus protease (Ratish et al., 2020).	VSV, PIV, CVB3 (Priya et al., 2017).
13.	Spinaciaolerace a	Kosta	Kaempferol	Kaempferol isolated from this plants exhibited a better binding affinity for SARS-CoV-2 Mpro and Spike (S) glycoprotein (Neha S, 2020).	
14.	Vitis vinifera	Weyin fire	Resveratrol rhoifolin	Resveratrol effectively inhibits MERS-CoV infection (Lin et al., 2017).	HSV-1, PIV

V. Materials and methods

5.1 Preparation of the SARS-CoV-2 Spike Protein Macromolecule

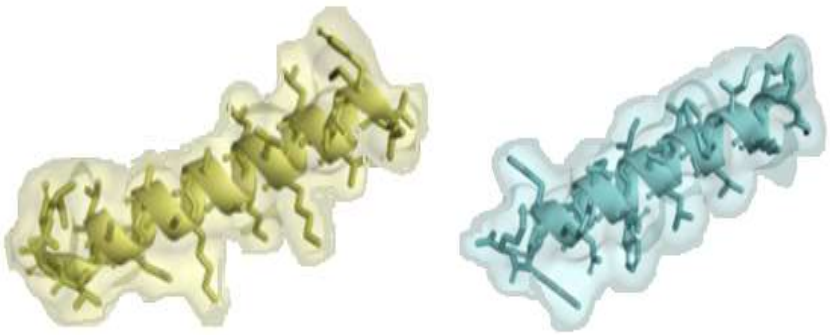
The Swiss-Model server was developed the 3D structure of the SARS-CoV-2 RNA-dependent-RNA polymerase (RdRp) enzyme. RCSB Protein Data Bank (http://www.rcsb.org/pdb) was made Angiotensin-converting enzyme 2 (ACE2) receptor (6VW1) and components of the SARS-CoV-2 spike protein model (6VSB) via -PDB ID 6LU7 (Wanget al., 2020).

5.2Ligand and drug scan

3-dimensional (3D) layouts are available at PubChem (https://pubchem.ncbi.nlm.nih.gov/), in .sdf format. PubChem is a biological and chemical activity that contains three details, including materials, details, bioassay data and compounds (Tahir ul Qamar, 2020). Drug-like properties have been estimated using Lipinski 's fifth law, which proposes that oral absorption and molecular permeation have a molecular weight of > 500, more than 5 donors of hydrogen bonds, C logP > 5 and more than 10 classes of consent (Shen et al., 2014). Lipinski's and Compliance and rule of five as measured using SWISSADME predictions (http:/www.swissadme.ch).

5.3 Preparation of the Antiviral Peptide Molecules

Here, the molecules used were dermaseptin-S4 and dermaseptin-S9 antiviral peptide sequence produced by Phyllomedusa frogs and tracked using PEPFOLD 3.5 (http://bioserv.rpbs.univ-paris-diderot.fr / PEP -FOLD /) (Figure 1). PEPFOLD 3.5 is a server used to mimic peptide sequences with amino acid values of between 5 and 50 into three-dimensional combinations using the no novo method (Lamiable et al., 2016; Shen et al., 2014; Thévenet et al., 2012). The results of the peptide cell model were then used to model peptide docking proteins.



Dermaseptin-S4, (GLRSKIWLWVLLMIWQESNKFKKM)

Dermaseptin-S9 (ALWMTLLKKVLKAAAKAALNAVLVGANA)

Figure.2

5.4 Preparation of ACE-2 Receptor Macromolecule

Now, the ACE-2 receptor macromolecule was obtained from Protein Data Bank (http://www.rcsb.org/pdb) via PDB ID 2AJF (Li et al., 2015). This macromolecule receptor was modified by removing water molecules, adding polar hydrogen atoms, and calculating Kollman's incomplete charge.

5.6 Active Sites determination

The amino acids in the active protein setting are calculated using the CASTp and Biovia Discovery Studio 4.5 Computated Atlas for Surface Topography of Proteins. Determining the amino acids on the site used was used to evaluate the Grid box and the effects of the tests for delivery. Discovery Studio is an offline life science programme offering protein, ligand, and pharmacophore modeing (Li et al., 2015).

5.7 Molecular docking

The AutoDock Vina software is used for all per-periment of docking, with the model configured as target docking. The experimental procedure is limited to the arrival of molecules, and molecular- dynamics mimics were not performed. Remdesivir and rizvirin are antagonists of RdRp. Remdesivir can work against the new coronavirus; however, rakuvirin is not approved.

5.8 The Simulations of Protein-Peptide Docking

In this study, HPEPDOCK was used to mimic protein-peptide docking (Yan et al., 2017; Zhou, Jin, et al., 2018; Zhou, Li, et al., 2018). The antiviral peptide molecules of docking simulations are matched and polar hydrogen atoms are inserted using the de novo method. Thereafter the complex protein-peptide type was selected by the RMSD 4.0 Å grouping. Connolly point shape on the surface of the molecule into various parts including convex, concave, and flat patch was produced with the HPEPDOCK algorithm. HPEPDOCK created, refined, transcribed, and re-selected the chain link interface on the top ten solutions.

5.9 The Simulations of Protein-Protein Docking

In this study, pyDockWEB was also used to mimic protein-peptide docking between two peptide-induced protein-peptide docking structures to ACE-2 receptor (Ahuja & Singh, 2016; Sable & Jois, 2015; Jiménez-García et al., 2013). The RMSD 4.0 group was used and selected a complex type of protein-protein. The local representation of Connolly's point from molecule to various components such as convex, concave, and flat patch is done with the pyDockWEB algorithm. pyDockWEB designed, refined, rewritten, and re-selected the chain link interface on the top side of 10 student solutions.

5.10 Compound screening using PyRx program

Cellular testing of all complex libraries was performed using the PyRx software by the autodock wizard as a stop engine. During shipping, ligands are considered flexible and proteins are considered rigid. The grid parameter configuration file is created using the Auto Grid engine in Pyrex (Chen et al., 2020).

5.11 Free binding Energy

Free binding energy is estimated using two methods: Poisson-Boltzmann Molecular Mechanics Surface Area (MMPBSA) and Molecular Mechanics-Generalized Born Surface Area (MMGBSA) embedded in the AMBER18 MMPBSA.py module (Lu et al., 2020). A total of 100 frames are processed from trajectories, and the following equation measures the power of the system;

$$\Delta GBinding = \Delta GComplex - \Delta GrReceptor - \Delta GInhibitor$$

VI. Docking of protein and peptide with COVID-19

6.1 The Simulations of Protein-Peptide Docking

Two of the antiviral peptides produced by Phyllomedusa frogs selected by the PEP-FOLD server were also identified and tested for their interactions and interactions with the SARS-CoV-2 spike protein macromolecule prepared by a protein-peptide mimic duplicate algorithm. –HPEPDOCK (Hui et al., 2020). The results of protein-peptide

docking simulations in Table 2 show that dermaseptin-S9 peptide has a better affinity with the active binding site of SARS-CoV-2 spike protein compared to dermaseptin-S4 peptide, with free energy values of 92792.93 kJ / mol and −692.43 kJ / mol, respectively.

Table 2: The affinity of the antiviral peptide molecules against the SARS-CoV-2 spike protein macromolecule (Fakih, T. M, 2020).

Peptide molecule	Binding free energy (kJ/mol)
Dermaseptin-S4	−692.43
Dermaseptin-S9	−792.93

Based on observations of the mimicry effects of protein-peptide docking, dermaseptin-S4 peptide and dermaseptin-S9 peptide show distinct cell interactions with the active site of SARS-CoV-2 spike protein. However, two peptide molecules can enter the polar center at the active binding site of the SARS-CoV-2 spike protein macromolecule (Figure 3) (Fakih, T. M, 2020). This is possible because the HPEPDOCK algorithm allows peptide molecules to move freely without tight bonds in the cellular suspension system used. In general, the dermaseptin-S4 and dermaseptin-S9 peptide molecules have a different affinity for the active site of the SARS-CoV-2 spike protein site.

Table 3. The interactions formed between antiviral peptide molecules and SARS-CoV-2 spike protein macromolecule (Fakih, T. M, 2020).

Peptide molecule	Number of interactions	Amino acid residues
Dermaseptin-S4	7	Leu335, Pro337, Phe338, Asn343, Val367, Ser373
Dermaseptin-S9	18	Tyr369, Asn370, Ala372, Ser375, Thr376, Lys378, Pro384, Lys386, Gly404, Asp405, Arg408, Gln414

6.2 The Simulations of Protein-Protein Docking

Subsequently, confirming the ability of each peptide-protein complex to prevent the attachment of the SARS-CoV-2 spike protein macromolecule to the surface of the ACE-2 receptor, identification, testing, and testing were performed using protein-docking methods. Excellent binding and strong and stable peptide-protein complex is expected to prevent the entry of SARS-CoV-2 into the cells and tissues of the host due to It is also important to identify amino acid residues that play a key role in preventing the formation of cellular interactions between the binding site of the SARS-CoV-2 spike protein macromolecule and the surface area of the ACE-2 receptor (Gabutti et al., 2020; Ton et al., 2020).

Table 4. The total energy of the peptide-protein complexes against ACE-2 receptor macromolecule (Fakih, T. M, 2020).

Peptide-protein complex	**Electrostatics (kJ/mol)**	**Desolvation (kJ/mol)**	**van der Waals (kJ/mol)**	**T.E**
Dermaseptin-S4+SARS-CoV-2 Spike Protein	183.17	42.74	77.96	303.87
Dermaseptin-S9 + SARS-CoV-2 Spike Protein	176.69	85.20	255.96	517.85

6.3 6LU7 and 2GTB Proteins

The composition and amino acids that was found in the active site packs of 2GTB and 6LU7 is shown in table 5. COVID-19 main protease (Mpro) is 6LU7 that was developed and repositioned in PDB and publicly available, from the beginning of February 2020. 2GTB is the major protease present in CoV associated with extreme respiratory failure syndrome (SARS), which is detectable by PDB and has been suggested as a possible drug target for 2019-nCov. (Xu et al. 2020) revealed that in 2019 nCov, the largest protease shares 96 percent close to SAR.

Table 5: Shows amino acids active site (Biovia Discovery Studio 4.5, 2019), protein target structures and the native ligand structure (Khaerunnisa et al., 2020)

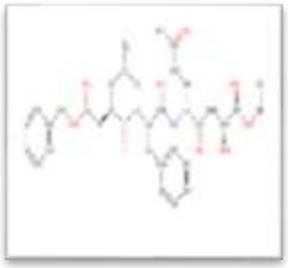
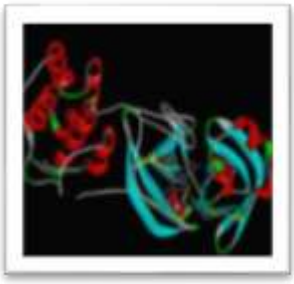
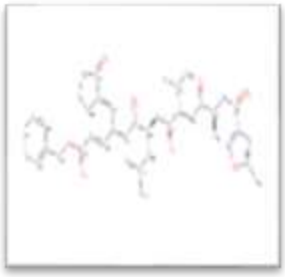
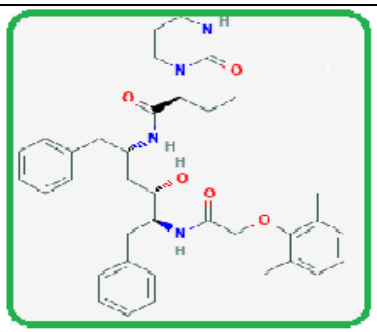
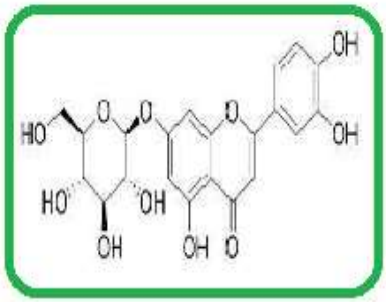
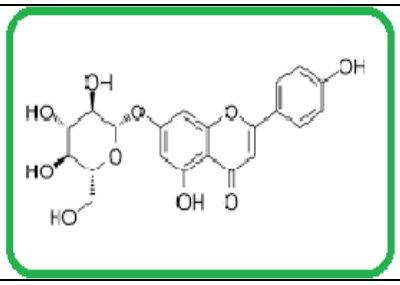
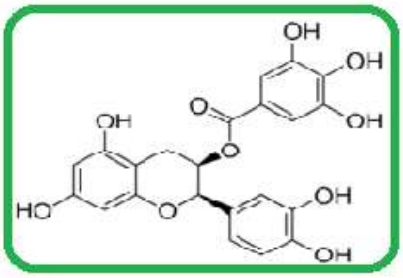
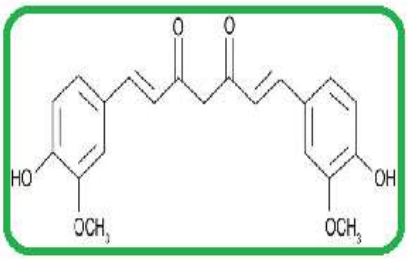
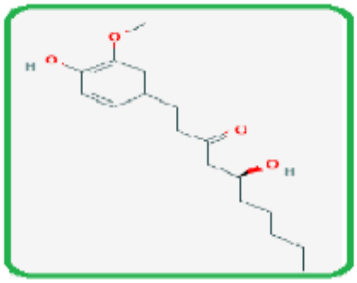
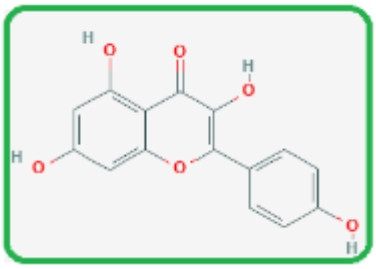
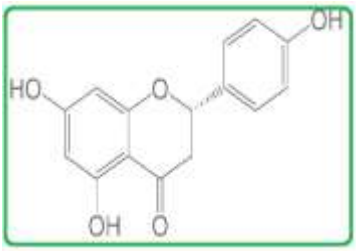
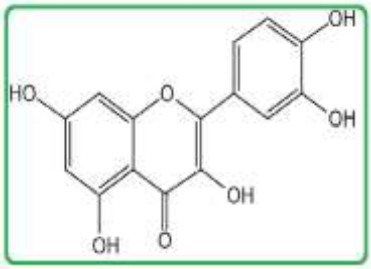
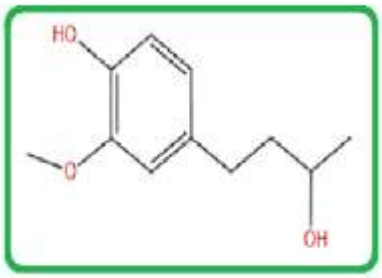
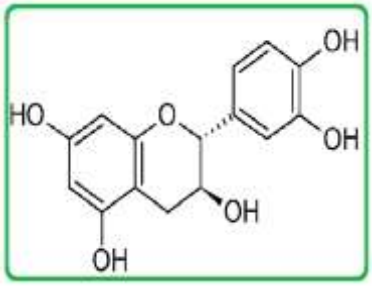
No.	PDB ID	Macromolecule	Native ligand	Active site
1.	2GTB			ALA7, HIS4, TYR54, TYR126, LYS5, SER144, LEU141, THR25, MET49, GLY143, CYS145, LEU167, MET165,
2.	6LU7			PHE140, HIS163, THR26, GLY143, HIS172, CYS145, HIS164, THR24,GLU166, ASN142

Table 6: Shows the molecular docking analysis results for various compounds against 6LU7, including ligand efficiency, binding energy/Gibbs Energy, inter-molecular energy, inhibition constant, and van der Waals (VDW)-H Bond de-solvation energy (Khaerunnisa et al., 2020).

Sr No	Compound	Molecular formula	Molecular structure and interaction with 6LU7	Lipinski's rule of five	
1.	Lopinavir	C37H48N4O5		Properties	Values
				LogP (<5)	4.37
				Molecular weight (<500 Da)	628.8
				Violations	1

				H.bond acceptor (<10)	5
2.	Luteolin-7-Glucoside	C21H20O11		LogP (<5)	0.16
				Violations	2
				Molecular weight (<500 Da)	448.38
				H.bond acceptor (<10)	11
3.	Apigenin-7-glucoside	C21H20O10		Molecular weight (<500 Da)	432.34
				Violations	0
				LogP (<5)	1.57
				H.bond acceptor (<10)	8
4.	Epicatechingallate	C22H18O10		LogP (<5)	1.23
				Violations	1
				Molecular weight (<500 Da)	442.37
				H.bond acceptor (<10)	8
5.	Curcumin	C21H20O6		LogP (<5)	3.03
				Violations	0
				Molecular weight (<500 Da)	368.38
				H.bond acceptor (<10)	6

6.	Gingerol	C17H26O4		Molecular weight (<500 Da)	294.39
				Violations	0
				LogP (<5)	3.13
				H.bond acceptor (<10)	4
7.	Kaempferol	C15H10O6		LogP (<5)	1.58
				Violations	0
				Molecular weight (<500 Da)	286.24
				H.bond acceptor (<10)	6
8.	Naringenin	C15H12O5		Molecular weight (<500 Da)	272.25
				Violations	0
				LogP (<5)	1.84
				H.bond acceptor (<10)	3
9.	Quercetin	C15H10O7		LogP (<5)	1.23
				Violations	0
				Molecular weight (<500 Da)	302.24
				H.bond acceptor (<10)	5

10.	Zingerol	C11H16O3		LogP (<5)	1.86
				Violations	0
				Molecular weight (<500 Da)	196.2
				H.bond acceptor (<10)	3
11.	Catechin	C15H14O6		LogP (<5)	0.85
				Violations	0
				Molecular weight (<500 Da)	290.27
				H.bond acceptor (<10)	6

The current study focused on major proteases in coronaviruses (3CLpro / Mpro), specifically PDB ID 6LU7, as proteins that may be targeted for COVID-19 treatment. 6LU7 is a COVID-19 Mpro redeveloped in PDB and made available to the public from early February 2020. The proteins are the potential target for inhibition of coV replication, and the SARS-CoV Mpro and 2019-nCoV Mpro protein sequences are identical to 96 percent, and the active sites in both proteins remain unchanged. Mpro amino acids Tr24, Tr26 and Asn119 can play a role in drug interactions (Z. Xu et al., 2020; A. Zhavoronkov et al., 2020).

Table 7: Source of various compounds belong to medicinal plants (Khaerunnisa et al., 2020).

Compounds	**Species names**	**Sources**
Quercetin	*Foeniculum vulgare* *Oregano vulgare* *Allium cepa*	Fennel leaves Oregano Onion
Kaempferol	*Anethum graveolens* *Sauropus androgynous* *Spinacia oleracea*	Dill Katuk Spinach
Demethoxycurcumine	*Curcuma xanthorriza* *Curcuma longa*	Curcuma Tumeric
Apigenine-7-glucoside	*Lycium chinense* *Olea Europaea L*	Goji berries Olives
Allicin	*Allium sativum*	Garlic
Luteolin-7-glucoside	*Capsicum annum* *Olea Europaea L*	Chilli pepper Olive
Epicatechin gallate	*Camellia sinesis*	Green tea
Gingerol	*Zingiber officiale*	Ginger
Oleuropein	*Olea Europaea L*	Olive
Curcumin	*Curcuma xanthorriza* *Curcuma longa*	Curcuma Turmeric

VII. Conclusion

Currently, COVID-19 is human and is a major threat to global health, worldwide. However, there is currently no prescriptive drug that will stop the flow of emotions. The current drugs for the treatment of COVID-19 primarily act on a large protease (Mpro). The purpose of this study was to test the plant-derived chemicals that can be used to prevent the COVID-19 infection process. In the present study, we studied the effectiveness of antibodies against other phytoconstituents extracted from a specific plant plant: Tinospora cordifolia that fights SARS-CoV-2 infections. Tinospora cordifolia is the source of a wide variety of bioactive compounds including alkaloids, steroids, glycosides, aliphatics.

The highlight of the current study is finding the essential drug for the disease COVID19 using the antiviral activity of these compounds. As a result, nelfinavir and lopinavir have been proposed as possible therapeutic alternatives, while kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, and epicatechin-gallate are highly recommended compounds present

in medicinal plants that can serve as potent COVID-19 Mpro inhibitor. However, further research is needed to see whether medicinal plants containing these compounds may be useful. In this study, we used PyRx and Autodock-Vina to identify FDA-approved potent inhibitors against COVID-19 Main Proteases that play a key role in the distribution of Coronavirus. And the dermaseptin-S9 peptide molecule can form stable and strong molecular interactions with the active binding site of the SARS-CoV-2 spike protein macromolecule. Therefore, it has been proven that the dermaseptin-S9 peptide molecule has the potential to be a member of the SARS-CoV-2 spike protein macromolecule inhibitor in controlling COVID-19 infection.

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