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In silico analysis of quranic and prophetic medicinal plants for the treatment of infectious viral diseases including corona virus



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ABSTRACT

Coronavirus disease (COVID-19) is an infection of the respiratory system caused by single standard RNA viruses named as Severe Acute Respiratory Syndrome 2 (SARS-CoV-2). The disease appeared as a serious problem and the leading cause of death in human beings throughout the world. The main source of different phytochemicals are plants, which helps in the development of new drugs against various ailments. Islam is comprehensive religion and a complete code of life for Muslims. The teaching of Islam, according to the Holy Quran and Hadith are universal for the benefit of humanity. Islam believes that every ailment is from God and who made the disease definitely made its medication. There is a complete guideline with regard to taking measures against infectious diseases such as quarantine and seeking medicinal treatment. The research objective is to gather the knowledge of medicinal plants described in the Holy Quran or utilized by the Prophet (SAW) for the treatment of different ailments or advised to use them to boost immunity and strengthen the body. Scientists across the globe have found these plants beneficial for many diseases and have antiviral potential. In present study, the six plant species including *Olea europaea*, *Nigella sativa*, *Allium Sativum*, *Allium cepa*, *Zingiber officinale* and *Cassia senna* were selected which contain phytochemicals like Calcium Elenolate, Thymoquinone, S-Allylcysteine, Dipropyl Disulfide, Sesquiterpene, Monoterpene, Pelargonidin 3-Galactoside ion and Kaempferol. The phytochemicals monoterpene (from *Zingiber officinale*) shows best interaction with target proteins RdRP, 3CLPro, ACE2. Calcium Elenolate (from olive) bonds with 3CLPro, ACE2 and Kemoferol and Pelargomidine (from Senna Makki) bonds with RdRP, ACE2. The ligands show a unique set of intersections i.e. hydrogen bonding, and alkyl interaction. These medicinal plants can be utilized immediately for the treatment of COVID-19 as their safety is already established. This treatment can enhance recovery when combined with other

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treatments. Furthermore, the screening of bioactive compounds or phytochemicals found in these plants can be utilized to design new therapeutic drug to treat COVID-19 pandemic.

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1. Introduction

According to the current statistics, COVID-19 pandemic has infected more than 16.5 million people and 0.6 million deaths were recorded up till 31st July 2020 and the number is increasing every day (WHO). It is typical pneumonia caused by a novel single standard virus, SARS CoV-2. It was named as Corona Viruses Disease 2019 (COVID-19) by the World Health Organization (WHO) on January 30, 2020 (see Table 1).

Symptoms of COVID-19 are non-specific range from no symptom to severe pneumonia and death. Different studies have reported different symptoms, including fever, cough, fatigue or myalgia and atypical symptoms include hemoptysis, diarrhea, headache and sputum. Other symptoms include lymphocytopenia and all patients had pneumonia (Huang et al., 2020). Various studies have reported different fatality rates in different age groups. In one research it is presented that patients greater than 60 are at higher risk than younger one (Jordan et al., 2020). In another report, it is investigated that patients of age group 30–79 years appeared to more vulnerable to COVID-19 (Wu et al., 2020). The complete sequence of SARS-2 has been obtained and disease can be diagnosed by RT-PCR and sample is collected from both lower or upper respiratory tract or by counting the total number of leucocyte and lymphocytes (Corman et al., 2020; Jin et al., 2020). In China, it is reported in a preliminary study that SARS-CoV-2 has gained a number of mutations. The high mutation rate of coronavirus can cause problems for process of vaccine development. It is investigated that intense quarantine and social distancing measures are helpful in controlling the outbreak. Some of the allopathic medicines (Chloroquine, Lopinover, Oseltamivir and Retenover etc.) used for other purposes like malaria have proved effective for corona but their efficacy is not yet established. In China, traditional herbal treatment was also adopted against COVID-19 and has shown good results. Herbal decoctions were suggested by the National Health Commission of China. (Luo et al., 2020; Ho et al., 2020).

UK Deputy Chief Medical Officer Professor Jonathan Van-Tam reportedly told that the vaccine developed by Oxford University and AstraZeneca could be ready for deployment in January, while Sir Jeremy Farrar, a member of the Sage Science Advisory Council and Director of the Wellcome Foundation, said that at least one of the UK vaccine portfolios could be ready by spring. Up to now, three COVID-19 vaccines have been licensed for use by several national regulatory authorities. None of the WHO EUL/PQ approvals have yet been issued, but we foresee an evaluation of the Pfizer vaccine and other candidates soon. Trials of 5 vaccine candidates for effectiveness and safety effects, including these three (and for Moderna and AstraZeneca), have been widely announced via press releases, but only one (AstraZeneca) has published findings in peer-reviewed literature. There are several new vaccine candidates currently under production for COVID-19. Once the vaccines have been proven to be safe and reliable, they must be licensed by national authorities, developed to exacting specifications and delivered. WHO is partnering with stakeholders around the world to help plan crucial measures in this process, and to promote equal access to secure and reliable COVID-19 vaccines for the billions of people who will need them (Mahase, 2021)

Human beings have been using medicinal plants since ancient times. The ethnobotanical literature presents various medicinal plants having an antiviral activity (Jassim and Naji 2003). The Holy Quran described everything for human beings including different scientific knowledge. The teaching of Islam pays special stress on health and nutrition (Azarpour et al., 2014).

The concept of quarantine and hygienic practices were introduced by the Prophet Muhammad peace be upon him, fourteen centuries ago when no one knows about infectious diseases. In the case of infectious disease patients were advised to quarantine themselves so that the disease may not spread (Goje, 2017).

The Prophet, peace be upon him, narrated that: “If you hear that there is a plague in a land, do not enter it; and if it (plague) visits a land while you are therein, do not go out of it” (Sahih Bukhari, 5728; Muslim, 2218).

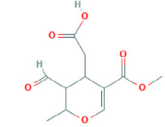
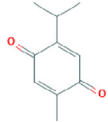
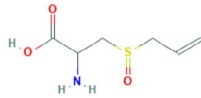
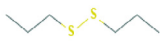
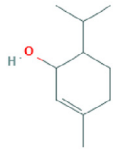
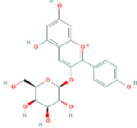
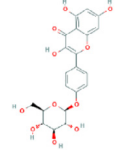
The Holy Quran also described plant knowledge regarding many crops, including the grains, seeds and fodder, their process of germination and development is also described in different Surahs. Plants are considered as a gift of God and several botanical terms and parts of plants are stated in the Quran. In the Quran, the names of many important medicinal herbs and plants used as food are also described such as olives, ginger, tamarisk, grapes, pomegranates, figs, bottle gourds, date palms, camphor, christ's thorns and others. The Holy Quran also describes different botanical terms in a different situations to explain different Quranic verses. In these verses, the Holy Quran invites human beings to think about the Allah's creation. Prophet of Allah, Muhammad (SAW), has ordered, “If the end of the world approaches and one of you has a seedling (or plant) in his hand, if he can plant it before the end comes, let him do it.” He also says, “If a Muslim plants a tree or sows seeds, and then a bird, a person or an animal eats from it, it is regarded as a charitable gift for him until the day of judgment”. (Sahih Bukhari, 2320; Rahman, 2017).

The use of natural plants as medicines were started in ancient times. Hazrat Muhammad (SAW) used a number of plants and plant products for the treatment of many diseases in His life. Different scholars have compiled a number of books on the subject (Sajid et al., 2019). Scientists and researchers are constantly exploring and compiling these medicines after the demise of the Holy Prophet Muhammad (SAW) throughout the world (Ahmad et al., 2009; Yari et al., 2011). The Prophet Muhammad (SAW) advised to use a healthy diet and by Himself used many plants for the cure of many diseases centuries before the researchers or scientists have evaluated their importance (Syed, 2003; Deuraseh, 2006).

It is therefore, imperative to review the ethnobotanical medicines prescribed by the Prophet Muhammad (SAW). Hence, this study emphasizes the therapeutic potentials of prescribed medicinal plants and their bioactive compounds to alleviate various incurable human diseases. Many Plants contain bioactive compounds having antiviral potential for various viruses. These active compounds show different mechanisms to control or prevent viruses. (Amber et al., 2017).

The study objective is to identify the plants having medicinal importance mentioned in the Holy Quran and Hadith. The identification of active phytochemicals having antiviral properties that can be used for the cure of respiratory and other contagious viral diseases including COVID-19 (see Figs. 1 and 2).

Table 1
Molecular formula, molecular weight and 2D structures of active phytochemicals of chosen medicinal plants.

Plant Name	Scientific Name	Compound Name	Molecular Formula	Molecular Weight	2D-Structure
Olive	<i>Olea europaea L</i>	Calcium Elenolate	$C_{11}H_{14}CaO_6^2$	282.3 g/mol	
Black Seed	<i>Nigella sativa L</i>	Thymoquinone	$C_{10}H_{12}O_2$	164.2 g/mol	
Garlic	<i>Allium Sativum</i>	S-Allylcysteine	$C_6H_{11}NO_3S$	177.22 g/mol	
Onion	<i>Allium cepa L</i>	Dipropyl Disulfide	$C_6H_{14}S_2$	150.3 g/mol	
Ginger	<i>Zingiber officinale Rosc</i>	Monoterpene	$C_{10}H_{18}O$	154.25 g/mol	
Senna Makki	<i>Cassia senna L</i>	Pelargonidin 3-Galactoside Ion	$C_{21}H_{21}O_{10}^+$	433.4 g/mol	
		Kaempferol	$C_{21}H_{20}O_{11}$	448.4 g/mol	

2. Materials and methods

Islam is comprehensive religion and gives great value to health. The Holy Quran is surely the guidance and health book. It provides different guidelines for human health. The important steps involved in identification and screening are:

2.1. Identification and phytochemical analysis

The phytochemicals of (these Quranic) selected plant species were identified from the literature and the 3D structures of the selected plants were retrieved from PubChem (Kim et al., 2016) and those chemical compounds were selected which meets the rule of 5 and had anti-viral activity. The phytochemicals of the selected medicinal plants were screened based on their ADMET properties and drug toxicity prediction, through the SWISSADME server. Pharmacokinetics and pharmacological properties of the phytochemicals, i.e. gastrointestinal (GI) absorption, blood–brain barrier (BBB) penetration, Lipinski's rules and solubility (ESOL) were analyzed. The adopted criteria for the screening of compounds were: GI absorption = High or Moderate; Lipinski's violations = 0; Toxicity = Zero/Nil; BBB-permeability = No and Solubility = High; (Hamza et al., 2019; Daina et al., 2017).

2.2. Drug targets identification

The drug targets were identified from current literature and protein complexes were retrieved from Protein Databank with resolution: 2.50–3.0 Å for the docking studies having PDB Id's 1P9S, 3BGF, 6 M71. The mutation of selected proteins was verified from the coronavirus proteome. The 3D structures of these proteins were analyzed in PYMOL and Discovery studio and prepared for docking. The downloaded PDB files of the targeted proteins were checked for mutation analysis. During the preparation of receptor protein, the incomplete atoms and residues are amended by adjacent residues. And remove the unwanted chains of the protein from the protein complex (Berman et al., 2000; Chopade et al., 2015).

2.3. Identification of drug targets (Proteins)

Aftab et al., (2020) identified RNA-dependent RNA polymerase (RdRp) as a novel COVID-19 drug target, which controls viral replication, acting as a possible therapeutic target to prevent viral infection. The viral 3-chymotrypsin-like cysteine protease (3CLpro) enzyme regulates coronavirus replication and is necessary for its life-cycle. 3CLpro is a proven drug development target for extreme

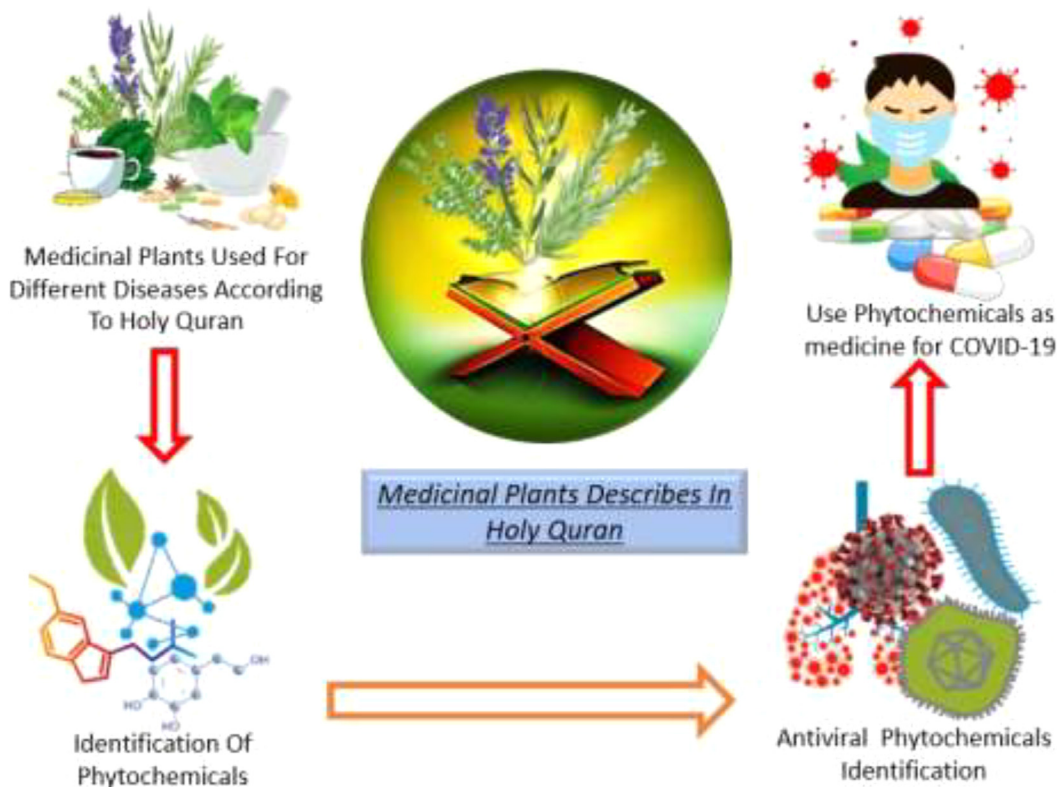


Fig. 1. Graphical representation of screen phytochemical use for the cure of COVID-19.

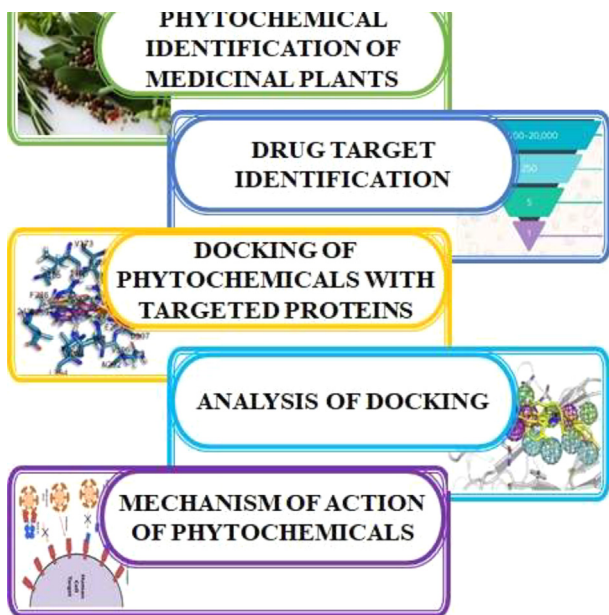


Fig. 2. Diagrammatic representation of computational work.

acute respiratory coronavirus syndrome (SARS-CoV) and Middle East respiratory coronavirus syndrome (MERS-CoV) (Qamar et al., 2020). ACE2 is a potential target for developing specific drugs, antibodies, and vaccines, as SARS-COV2 spike protein binds with ACE2 for replication (Ni et al., 2020). Therefore, these three proteins were selected as drug targets for docking analysis.

2.4. Docking of phytochemicals and COVID-19 proteins

All eight virtually screened phytochemicals were docked with targeted COVID-19 proteins, based on their antiviral properties and performed molecular docking for each of the phytochemicals (ligands) from the selected plants with the active sites of targeted proteins. Docking was performed by the online server PATCHDOCK for rigid protein and small peptide docking. PATCHDOCK is based on a geometry-based molecular docking algorithm, which finds docking transformations and results in the best-docked complex of receptor and ligand (Schneidman-Duhovny et al., 2005).

2.5. Analysis of docking and mechanism of action of phytochemicals

Analysis of docking was done in PYMOL and Discovery Studio. All docking complexes from eight compounds and three proteins were analyzed separately in the PYMOL and Discovery Studio to visualize the best molecular geometry of ligand–protein interaction. Docked scores were analyzed for the distinction of good or bad docked conformation (Chopade et al., 2015).

3. Result and discussion

Al-Quran is the Holy book that described the importance of plants in different Surahs. Plants are considered as the blessing of God. The Holy Quran invites human being to think about God’s creation including plants. Present research work focused on ethnobotanically important medicinal plants mentioned in the Holy Quran or used by the Prophet Muhammad (SAW) in his life as food or for the treatment of various diseases. Researches proved that these plants are an important source of nutrients, vitamins and phytochemicals effective against many diseases. Our Prophet Muhammad (SAW) said that, “Allah has not made a disease

without appointing a remedy for it, with the exception of one disease, namely old age” (Sunan Abi Dawud 3855 : Book 29, Hadith 1).

3.1. Quranic plants identification and description

In the present research work, detailed information of ethnomedicinal important plant species having antiviral potential for corona and other respiratory diseases which are described in the Holy Quran and Hadith was collected by reviewing the Holy Quran, Hadith, different Islamic books, and research articles. These plants were identified with the help of the flora of Pakistan (Nasir and Ali, 2001, 1972–1994). After a thorough review of different books and research papers, six plant species having the anti-viral potential to use against COVID-19 and other viral diseases were selected for the present investigation.

3.1.1. *Olea europaea* L

Olea europaea L. is a small tree up to 7 m in height, greyish-green bark, belongs to family Oleaceae consisting of 25 genera and 600 species (Wallander and Albert, 2000). The olive was originated probably in Asia Minor. Since ancient times, the plant has been cultivated throughout the Mediterranean region. Now it is found in the subtropical region of the entire world. It is one of the oldest known cultivated trees in the world - being grown before the written language was invented. Olive plant is the first thing that appeared after Noah (AS) flood. In the Bible, it is narrated that after the great flood, Noah (AS) sends a bird (dove) to know the condition of water if it has subsided. The dove came back with having fresh leaf of olive in her beak and after then the dove has been known as a symbol of peace (Ghaznavi, 2014). Olives have been found in Egyptian tombs from 2000 years BC. In Pakistan olive is cultivated in Baluchistan province and northern areas. Fruit and oil are used as food and medicines. Olive oil has also been used to anoint the dead in many cultures. Since ancient time olive leaves and oil have been used as ethnomedicine for the treatment of fever, influenza T.B, rheumatoid arthritis, inflammation, as analgesic, in stomach problem and many other diseases like hypertension, diabetes and cancer. (Ghaznavi, 1996; Sharique et al., 2018)

The oleuropein is an important active constituent isolated from the leaves of *Olea europaea*, having a wide range of health-promoting and pharmacologic properties including immune stimulant, hypotensive, spasmolytic, cardioprotective, antihyperglycemic, anti-inflammatory, anti-arrhythmic, and antimicrobial effects (Chebbi Mahjoub et al., 2011). Oleuropein is metabolized into hydroxytyrosol and elenolic acid. Hydroxytyrosol is a highly effective anti-oxidant and it protects nerve cells in the spinal cord and brain. Due to the presence of elenolic acid, olive leaves are effective antiviral agent and can prevent and control many viruses. Quercetin is flavonoid that has anti-cancer properties and oleocanthal also known to possess anti-inflammatory and antioxidant properties (Sharique et al., 2018).

The benefits and importance of the olive tree and its fruit has been narrated many times in the Holy Quran, Hadith and other Holy books revealed to other Prophets of Allah. In Islam olive is considered a sacred plant. In Holy, Quran Olive is narrated as Zaiytoon in a number of verses. The translation of few verses are mentioned here:

“Allah is the Light of the heavens and the earth. The parable of His Light is as (if there were) a niche and within it a lamp, the lamp is in glass, the glass as it were a brilliant star, lit from a blessed tree, an olive, neither of the east (i.e., it neither gets sun-rays only in the morning) nor of the west (i.e., nor does it get sun-rays only in the afternoon – but it is exposed to the sun all day long), whose oil would almost glow forth (of itself), though no fire touched it. Light upon Light! Allah guides to His Light whom He wills. And Allah sets forth parables for

mankind, and Allah is All-Knower of everything” [Surah al-Noor, 24:35].

“And a tree (**olive**) that springs forth from Mount Sinai, that grows oil, and (it is a) relish for the eaters” [Surah al-Muminoon, 23:20].

“And He it is who causes gardens to grow, [both] trellised and untrellised, and palm trees and crops of different [kinds of] food and olives and pomegranates, similar and dissimilar. Eat of [each of] its fruit when it yields and give it due [zakah] on the day of its harvest. And be not excessive. Indeed, He does not like those who commit excess” [Surah al-Anaam, 6:141].

Abu Aseed (RA) narrates: The Prophet Muhammad (SAW) said: “Eat the oil and use it on your hair and skin, for it comes from a blessed tree.” (Al-Tirmidhi, 1775; see also Saheeh al-Jaami).

Hazrat Alqama Bin Amir (R.A) narrates that The Prophet Muhammad (SAW) said, “There is olive oil for you, eat it, massage over your body, since it is effective in hemorrhoids (Piles)”.

Khalid Bin Saad (R.A.) narrates, “I came to Madinah with Ghalib Bin Al Jabr. Ghalib became ill during the journey. Ibn Abi Ateeq came to see him and told a narration from Hazrat Aisha (R.A.) that the Prophet Muhammad (SAW) told about the cure in Kalonji. We crushed a few seeds of Kalonji and mixed it with olive oil and dropped in both nostrils, after which Ghalib became healthy”.

Hazrat Abu Huraira (R.A.) narrated that Prophet Muhammad (SAW) said “Eat the olive oil and massage it over your bodies since it is a holy (mubarak) tree”(Farooqi, 1998)

Hazrat Abu Hurairah (R.A) narrates that the Prophet Muhammad (SAW) stated, “Eat the olive oil and apply it (locally), since there is cure for seventy diseases in it, one of them is Leprosy” (Farooqi, 1998). The Prophet Muhammad (SAW) declared olive effective against respiratory diseases (Ghaznavi, 1996).

Olive is one of the plants among the plants and fruit described in Holy Quran having the lowest amount of sugar i.e. 0.54 g and the highest amount of fat (15.32 g) (Azarpour et al., 2014). Recent research proved that olive leaves and oil is a source of many phytochemicals, which are effective against virus, bacteria and fungi. Olive leaf extract has been used to combat many ailments like cough, fever and cystitis in Egypt (Şahin and Bilgin, 2018). Leaf extract of olive to contain oleuropein has antibacterial, antiviral, antitumor, blood pressure, and blood lipid-reducing factor, anticancer, and cardioprotective activities (Ghanem et al., 2019).

Ronald Hoffman reported that oleuropein from the leaf extract of olive plant is one of the excellent antiviral agents. Dutch researchers recognized that it has antifungal, antibacterial and antiviral activities. It is studied that it has antiviral ability against every known virus. Upjohn pharmaceutical company 1970 conducted research on salt made of olive leaf extract (Calcium elenolate) and reported that it is a safe and effective antiviral agent. No side effects were reported even in the doses several hundred times higher than the recommended. Leaf extract was an effective treatment against diseases of viruses, retroviruses, bacteria and protozoan. It blocks virus-specific system of host cells. It prevents protein synthesis of the virus. It inactivates viruses in many ways. It prevents penetration of virus in a cell, prevents virus replication and stimulates the immune system to kill them (Miller, 2009).

3.1.2. *Nigella sativa* L

Nigella sativa known as black seed is an annual herbaceous plant, belongs to family Ranunculaceae. The plant is 15–50 cm in height, the stem is erect, with bluish purple or white flower. It is also known as black cumin, small fennel, black caraway, Habibul-Sauda in Arabic, shooneez in Persian, Kalonji in Urdu and many other names (Nasir et al., 2014). It is believed that the plant *Nigella sativa* originate in Mediterranean countries but now it is cultivated widely Middle Eastern Europe, North Africa and Asia. The seeds of the plant are extensively used as spices in various foods like bread, pickles, salad and sauces. The plant is widely used ethnobotanically

for centuries for the treatment of different ailments like respiratory diseases, headache, rheumatism, fever, influenza and different types of inflammations (Venkatachallam et al., 2010.)

Medicinal uses of the plant were started after the Prophet Muhammad (SAW) mentioned its therapeutic importance. Hazrat Abu Hurairah narrated - "I have heard from the Prophet (SAW) that there is a cure for every disease in black seeds except death".

With reference to Abdullah Bin Omar Salim Bin Abdullah narates that the Prophet Muhammad (SAW) said, "Let fall these black seeds upon you, these contain cure for all diseases except death" and many other books of Hadith contain the same narration. Prophet (SAW) has used *Nigella* for different medicinal purposes, but He used it with syrup of honey. (Ghaznavi, 1996)

It is not possible to enlist the complete medicinal uses of this plant.

Observations of the scholars of Hadith reported a number of uses of *Nigella*. e.g. It is used to remove the obstacle in any body part, ejects the gases and reinforces the stomach. It is Diuretic, Lactogogue and Emmenagogue. It is an effective treatment of chronic cold, asthma, dog biting, in paralysis, cough, flu, in stomach and pancreas diseases, diabetes, in inflammation and several skin and other diseases. (Ghaznavi, 1996)

Seeds of *Nigella* contain two types of oils; 37.5% non-volatile oil, while 1.5% volatile oil. In addition to these organic acids, mineral elements (Mg, Ca, Cu, Mn, K) terpene, many amino acids, albumen, sugar, organic acids, enzyme lipase, many alcohol-soluble organic acids, fats and water-soluble vitamins. Nigellimine is also reported in research. Other important active components of seed of *Nigella* include thymol, thymohydroquinone, and dithymoquinone (Morikawa, et al., 2004, Ghaznavi, 1996, Nasir, et al., 2014).

Thymoquinone (TQ) is one of the important active constituents of oil and seed, which is an effective treatment of many inflammations. It also possesses immune modulatory properties, enhancing T cells and natural killer's immune response. Seeds of *Nigella sativa* contain more than 100 compounds, many of them are not yet studied (Salem, 2005).

Modern research has proved that *Nigella sativa* is very useful because it is effective against almost all diseases of a human being. It is widely used as an antioxidant, antifungal, antibacterial, antispasmodic, antidiabetic, analgesic, anticarcinogenic and mutagenic agent, hepatoprotective agent. *Nigella sativa*, also possesses immune modulatory properties, nephroprotective & neuroprotective activity (Nazir et al., 2018)

A number of research studies have proven that *Nigella sativa* improves the immune system of the human body by improving the ratio between suppressor T-cells and helper T-cells and it also increases the natural killer cell activity (Arafat, 2008).

Many modern researches have also proven that the immune system is the only system which can combat diseases and produce cells that kill viruses. As *Nigella sativa* can boost the immune system, therefore it can be concluded that *Nigella* seeds can combat viruses and cure every disease. Based on saying of the Holy Prophet we believe that this wonderful plant has healing ability in it. It is needed to learn about proper dosage and method to use it.

3.1.3. *Allium Sativum L*

Allium sativa is the scientific name of garlic. It is one of the oldest plants, belongs to the family Liliaceae. The plant is cultivated throughout Europe, USA and Asia, including India, Pakistan and China. The workers of the Egyptian pyramids were given garlic in their lunch. The clay models of garlic bulbs were excavated by western archeologists, in Tutankhamen's Tomb in Egypt. Ancient Hindus have used garlic to treat different ailments. The Sanskrit word for garlic is mahoushuddh, which means a panacea, or "cure-all." (Ghaznavi, 1996). In folk medicine, garlic has been used to treat different gastrointestinal diseases, respiratory problems,

anti-fungal, antiseptic, flatulence, leprosy, hypertension, diabetes and is also found effective for warts and nervous diseases (Kumar et al., 2010).

In the Holy Quran garlic is narrated as Fūm in Surah e Baqra, verse 61, Chapter No.1 as: And [recall] when you said, "O Moses, we can never endure one [kind of] food. So call upon your Lord to bring forth for us from the earth, its green herbs and its cucumbers and its garlic and its lentils and its onions. (Rafai, 1990).

Mahdan Bin Abu talah narrates that the Hazrat Muhammad (SAW) said those who eat onion and garlic should eat them in the cooked form (Khan, 2001). Hazrat Ali (RA) narrated that Hazrat Muhammad (SAW) said "Eat garlic and use it for the treatment of diseases. It cures 70 diseases". (Ghaznavi, 2001).

Garlic is an important and safe source of bioactive constituents (Mikaili et al., 2013). Active compound present in garlic is antifungal, antibacterial and decreases blood clotting. The characteristic odor is due to the presence of volatile oil which is released when garlic is crushed or cut. This releases an enzyme that causes the formation of allicin, the component responsible for garlic's odor and therapeutic activity (Sajid et al., 2019). It also possesses antioxidant properties due to the presence of a sulfur compound S-allylcysteine diallyl disulphide (DDS).

A. sativum has proved as an effective antiviral agent. Garlic extract is effective against many human viruses i.e. influenza B virus, vesicular stomatitis virus, Cytomegalovirus (HCMV), vaccinia virus, Herpes simplex virus type 2, Herpes simplex virus type 1, human Rhinovirus type 2, Parainfluenza virus type 3, and common cold virus (Ankri and Mirelman, 1999). Aged garlic fructans possess immune modulatory activities *in vitro*. Extracts of garlic are also effective against interferon (INF)- γ gene expression of stimulated lymphocytes and proliferation of interleukin (IL)-2 (Hanieh et al., 2012). Garlic extracts result in the formation of nitric oxide (NO) which causes the reduction of macrophage infection. (Gamboa-León et al., 2007). Due to the presence of biologically active compounds that are safe and effective against many viruses it can be used for the treatment and development of drugs against COVID-19 and other viruses.

3.1.4. *Allium cepa L*

Allium cepa L. (onion) belongs to the family Liliaceae. It is distributed in Pakistan, Russia, America, India, Europe, and China. In medicines, its seeds, leaves and rhizome are used. For more than 6000 years, *Allium cepa* has been cultivated and is used as a nutrient. The bulb is commonly utilized as a food component to give flavour and aroma to a number of dishes. Ethnobotanically its fresh juice is used for pain and swelling, as a treatment for bee or wasp stings. It also acts as anti-inflammatory and anti-asthmatic agents. Its extract or oil is effective against different microbes, intestinal worms, fungi and bacteria (Wetli, 2004). It is also used for treating neurological and cardiovascular diseases. Onion is ethnobotanically used as: throat infection, stomach diseases, antidote, baldness, ear pain, common cold, diarrhea, cholera, cough, menstruation, clear face, fever, eye diseases, hepatitis, intestinal diseases, piles, constipation, influenza, and skin spots, appetizer, headache, and improve sperm production (Khan et al., 2009).

Onion is mentioned in the Quran with the name of Basel in verse (2:61) of chapter (2) *sūrat l-baqarah*. And [recall] when you said, "O Moses, we can never endure one [kind of] food. So call upon your Lord to bring forth for us from the earth, its green herbs and its cucumbers and its garlic and its lentils and its onions." [Moses] said, "Would you exchange what is better for what is less? Go into [any] settlement and indeed, you will have what you have asked. And they were covered with humiliation and poverty and returned with anger from Allah [upon them]. That was because they [repeatedly] disbelieved in the signs of Allah and killed the prophets without right. That was because they disobeyed and were [habitually] transgressing".

In this verse, onion is considered inferior to the Manna-o-Salwa of paradise food sent to Bani Israel. Due to its bad odour onion and garlic are forbidden to eat before going to the mosque or any meeting. As the bad odour create trouble for other people. Therefore, it is advised to use it after cooking. Jabir bin Abdullah narrated: The Prophet Muhammad (SAW) said, "Whoever eats garlic or onion should keep away from our mosque or should remain in his house".

Mahdan Bin Abu Talah narrates: The Prophet Muhammad (SAW) said, "those who eat onion and garlic should eat them in cooked form".

Narrated Aisha, Ummul Mu'minin (R.A.): Khalid (R.A.) said: Abu Ziyad Khiyar ibne Salamah (R.A.) asked Aisha (R.A.) about onions. She replied: "The last food which the Apostle of Allah (SAW) ate was some which contained onions" (Ghaznavi, 2014).

Onion is source of several phytochemicals like thiosulfonates, fructo oligosaccharides (FOS), and flavonoids; different phenolic compounds and many other sulfur compounds. Onion possesses antioxidant properties and are effective against degenerative diseases due to the presence of high levels of phenolic compounds (Slimestad et al., 2007; Griffiths et al., 2002). Flavonols in the form of quercetin and kaempferol are found abundantly in the concentration 280–400 mg/kg. In the red onion anthocyanin in the form of anthocyanidins is also present in onion bulb insufficient amount. Other FOS compounds found in the onion bulb are inulin, kestose, mystose and fructofuranoses slynstose. The characteristic odour and flavor of onion are due to the presence of sulfur compounds. These compounds are also effective as antimicrobial agents (Loredana et al., 2017). Lee et al., 2012 reported that *Allium fistulosum* extract has an inulin-type polysaccharide that possesses good anti-influenza activity. The polysaccharide seemed to help in the enhancement of the host immune system.

3.1.5. *Zingiber officinale* Rosc

Zingiber officinale Rosc is a herbaceous plant species with an underground perennial rhizome commonly called ginger. It is a member of the family Zingiberaceae. It consists of about 85 species and is cultivated in different parts of the world, including Asia, Central, South America and Africa. The underground stem Rhizome is widely used as ethnomedicine throughout the world for centuries. (Ding et al., 2013). Ginger is widely used as flavoring in food and it is extensively used in Unani-Tibb, Ayurvedic, and Chinese medicines. Recent research has proved that it acts as antimicrobial, antioxidant, antiplatelet aggregation, blood pressure-lowering agent, chemo preventive, anti-inflammatory, cholesterol-lowering agent and hypoglycemic properties. The unique flavor and medicinal importance of ginger is due to presence of a number of phenolic compounds called gingerols in its rhizome (Gunathilake and Rupasinghe, 2015).

Other ethnobotanical uses include anorexia, stomach disorders, intestinal pain, dog bite, headache, constipation, sexual weakness, digestive stimulant, diarrhea, intestinal swelling, cooling effect on the body, dyspepsia, increase urine production (Rehman and Fatima, 2018).

The Holy Quran described ginger as one of the drinks of Paradise. In Holy Quran ginger is narrated as *Zanjabil* in Surah Ad-Dahr, Verse 17. Allah says the ginger drink will be given to believers to refresh them in paradise: "And they will be given to drink there of a cup mixed with *Zanjabil*".

Ginger was given the status of heavenly herbs because it was used by the Prophet Muhammad (SAW) and due to its medical importance. During the time of the Prophet Muhammad (SAW) the Prophet received a jar of pickled ginger as a gift from Byzantine Emperor. The Prophet Muhammad (SAW) ate from the jar and shared a piece with each of his Companions. Many of the health benefits of ginger were also described in book, "The Prophetic Medicine by Ibn Qayyim El-Jawziyyah".

Ginger comprises magnesium, zinc and vitamin C. More than 50 components in ginger oil are studied and it was observed that these compounds are mainly monoterpenoids and sesquiterpenoids. The research revealed that more effective antiplatelet agents are the gingerol compounds and their derivatives than aspirin under similar conditions (Gunathilake and Rupasinghe, 2015). Due to the presence of phytochemicals sesquiterpene hydrocarbons and monoterpene i.e. β -sesquiphellandrene, β -bisabolene, *ar*-curcumene and α -zingiberene in the essential oil extracted from rhizome of ginger it is confirmed as antimicrobial agent. Ginger is widely used to treat numerous inflammatory diseases since ancient times in different parts of the world due to its broad anti-inflammatory properties (Srivastava and Mustafa, 1992). Ginger products, are good antiviral agent due to the presence of different potent plant compounds. In research, it is proved that ginger extract possesses antiviral properties against many viruses such as feline calicivirus (FCV), and avian influenza, RSV, as comparable to human-norovirus (Aboubakr et al., 2016). In addition other compounds in Zingerber like gingerols and zingerone, are reported to stop replication and prevent the virus from entering host cells. Ginger possesses Anti-influenza agents (TNF- α). The fibrinolytic activity of *Zingerber officinalae* is due to the presence of alliscins which reduces platelet aggregation. The antioxidant enzyme like dismutase and glutathione peroxidase are reported from ginger which is beneficial in inflammatory reactions triggered by viral infections (Arora et al., 2010).

3.1.6. *Cassia senna* L

Cassia senna L. (synonym *Casia angustifolia* Vahl.) is a perennial herb up to 90 cm tall with compound leaves. Inflorescence terminal or axillary receme. Flower pedicilate. It is an important traditional medicinal plant. It is distributed in hot and dry region of Africa and Asia including Pakistan, India, Algeria, Egypt, Sudan, Somalia, and Arabia (Nasir and Ali, 2001, 1972–94).

The dried fruits and leaves have been used for the treatment of different diseases. Ethnobotanically it is used in the treatment of gout, rheumatism, haemorrhoids, ophthalmic, ringworm infection, liver disorders, skin diseases, constipation, leprosy, and against intestinal worms. (Shivjeet et al., 2013).

Various parts of the plant contain active constituents like anthraquinones which are classified as sennosides A to F. Sennosides are converted into anthrones in the digestive system. It helps to regulate peristalsis movement in the intestine by inhabiting water absorption. It also contains isorhamnetin, its glucoside kaempferin, further sterol glucosides, yellow flavonol kaempferol, mucilage polysaccharides, resin, naphthopyrone glycosides, phenolic compounds, calcium oxalate, tetram 6-hydroxy musizin glycoside, and Pelargonidin 3-Galactoside (Wu et al., 2007; Franz, 1993; Ganapaty et al., 2002).

The Prophet Muhammad (SAW) also used to take Senna leaves and it is a part to treat diseases. Ibraheem ibn e abi laila narrates that Prophet Muhammad (SAW) says "necessarily use Sena and sanoot; because there is a cure in both of them from every disease except the "saam" someone asked ya Rasulallah what is saam? Replied that death!" (Ibn e Majah 3457).

3.2. Proteins of COVID-19 used for docking with these phytochemicals

All of the eight phytochemicals were docked against RDRP, 3CLPro and ACE2, the results shows that each of the compound expressed different behavior with the proteins. A threshold value of binding affinity -8 kcal/mol was set for the screening of the best docked phytochemicals, and best orientations for docking confirmation of ligand-receptor complexes. Docked scores were analyzed for the distinction of good or bad docked conformation (Hamza et al., 2020; Chopade et al., 2015). The Quranic plants are the best

source of beneficent phytochemicals. All of our selected phytochemicals are individually screened and only the ones which shows best interaction are selected and carefully studied for the docking properties. The docking results show that these phytochemical will bond accurately with the mutant COVID-19 proteins. Especially the phytochemicals of *Olea europaeae L*, *Zingiber officinale Rosc*, *Cassia senna* (Senna Makki) shown the best results with proteins.

3.2.1. RdRp

The RNA-dependent RNA polymerase (RdRp also named nsp12) is the transcription machinery and vital part of corona viral replication and it appears to be a main target for the antiviral drug. The 3D structure of RdRp is cryo-electron microscopy structure and full-length nsp12 in complex with a resolution of 2.9Å and cofactors of nsp7 and nsp8. In addition to the conserved design of the polymerase center of the viral polymerase family, nsp12 has a recently recognized β -hairpin domain at its N terminus. A similar analysis of the model shows how drug compounds binds to the polymerase. This RdRp viral structure provides a basis for the design of new antiviral therapies (Gao et al., 2020). The 3D structure of 3CLPro is shown in Fig. 3.

3.3. Docking of medicinal plants with selected protein

As RdRp is the basis for the design for the new therapies to cure COVID-19 we dock it with some of the phytochemicals and it shows best interaction with three compounds namely Kemoferol, Monoterpene and S-Allylcysteine. The amino acid MET₈₇ made a bond with multiple atoms of kemoferol with a bond distance of 1.85 Å to 2.28 Å showing hydrogen bonding and also made other specific hydrophobic interactions with other amino acids ASN₄₁₄, ASN₄₁₆, GLN₁₈, GLN₁₉, SER₁₅, ASP₈₄₆, LYS₄₁₁, PRO₄₁₂, TYR₅₄₆ ligand completely fits into the hydrophobic surface with the bond energy of -7.0 kcal/mol the 3D dock pose shows in Fig. 4. The second best docking interaction of RdRp is with Monoterpene showed H-bonding with SER₁₅ and Alkyl bonding with LYS₄₁₁, MET₈₇ the ligand interact with bond energy of -4.7 kcal/mol 3D dock pose shows in Fig. 5. The last best interaction of RdRp is with S-Allylcysteine having hydrogen bonding with ARG₅₅₃, SER₆₈₂, alkyl bonding with ALA₅₅₈, the ligand interact with a bond energy of -5.0 kcal/mol the best dock pose is shown in Fig. 6. The ligands effectively docked with the mutated amino acids of the target protein.

1. RDRP with Kemoferol
2. RDRP with Monoterpene

RDRP with S-Allylcysteine

1. 3CLpro

The viral main proteinase is called 3CLpro, which controls the replication activities of the coronavirus. Crystal structures were determined for human-coronavirus (strain 229E) 3CLpro and porcine coronavirus (transmissible gastroenteritis virus TGEV) 3Cpro for an inhibitor complex. A homology model for SARS coronavirus (SARS-CoV) 3CLpro was also constructed. The structures disclose a remarkable degree of conservation of the substrate-binding sites, which is further supported by recombinant SARS-CoV 3CLpro-mediated cleavage of a TGEV 3CLpro substrate. This docking result suggests that the available rhinovirus 3CLpro inhibitors may be adapted to make them useful for treating SARS (Anand et al., 2003). The 3D structure of 3CLPro is shown in Fig. 7.

3CLPro shows effective binding with three chemical compounds namely Calcium Elenolate, Monoterpene and S-Allylcysteine. Cal-

cium Elenolate made Alkyl and hydrogen bonding with LYS₁₅₂ bond distance with 2.98 Å, hydrogen bonding with GLU₂₉₁ bond distance 3.0 Å, PHE₁₁₁ bond distance 2.60 Å. The bond energy of the complex is -7.0 kcal/mol dock pose shows in Fig. 8. S-Allylcysteine shows hydrogen bonding with ASN₁₁₂, GLN₈, ASN₁₅₀ bond distance of 3.29 Å, 2.68 Å, 2.75 Å respectively. The bond energy of the complex is -5.5 kcal/mol the 3D dock pose shows in Fig. 9. Monoterpene shows hydrogen bonding with GLY₁₁₀ with a bond distance of 2.19 Å and Alkyl bonding with LYS₁₅₂ bond energy of -6.4 kcal/mol shows in Fig. 10 (see Fig. 11).

3CLpro with Calcium Elenolate

3CLpro with S-Allylcysteine

3CLpro with Monoterpene

2. ACE2 (S protein)

The angiotensin-converting enzyme 2(ACE2) or spike (S) protein of SARS-CoV is responsible for the attachment of host cell and fusion of host cell membranes. Inside the S receptor-binding domain (RBD) intervenes the interaction with the angiotensin-converting enzyme 2(ACE2). Both RBD and S protein are extremely immunogenic and found to elicit neutralizing antibodies. RBD-F26G provides a prime instance of the structural properties of this Fab Complex antibody that is triggered by the SARS-CoV immune response or any of its components. This structure suggests that the RBD level admits by F26G19 significantly overlaps with the level accepted by ACE2 and, thus, reveals that F26G19 could potentially block the interaction of the host cell of the virus by inactivating SARS-CoV. The coronavirus S protein is an important antigenic carcinogen and antibodies against S that neutralize several coronaviruses. During the initial work on SARS, the mice were vaccinated with synthetically inactive SARS-CoV, which was used to prepare a panel of clonal antibodies based on cell culture. The effectiveness test was able to prevent infection. Many of them govern in opposition to S-protein.

ACE2 shows effective binding with three chemical compounds namely Calcium Elenolate, Monoterpene, Dipropyl Disulfide, Pelargonidin 3-Galactoside, Thymoquinone. The ACE2 has multiple mutations, the phytochemicals bond with protein and helps to cure COVID-19. Calcium Elenolate shows effective hydrogen bonding, with PHE₈₃, GLN₁₆₆ bond distance 1.94 Å and 2.28 Å, and Alkyl bonding with LYS₁₀₃ the bond energy is -5.8 kcal/mol which shows in Fig. 12. Dipropyl Disulfide shows Alkyl bonding with TYR₄₇₅, PRO₄₆₂, PRO₄₇₀ with bond distance 2.40 Å, 3.10 Å, 2.98 Å respectively, with bond energy of -4.6 kcal/mol and dock pose shows in Fig. 13. Monoterpene also shows Alkyl bonding with LYS₁₀₃, ILE₁₀₆ and bond energy is -5.6 kcal/mol shows in Fig. 14. Pelargonidin 3-Galactoside shows conventional hydrogen bonding with GLN₁₆₆, PHE₈₃, Carbon hydrogen bonding with SER₈₀ and Alkyl bonding with LYS₁₀₃, PRO₄₀ and ASP₁₆₅. Bond energy for this ligand complex is -8.6 kcal/mol and is shown in Fig. 15. Thymoquinone shows Alkyl bonding with PRO₄₀, LYS₁₀₃, ILE₁₀₆, PHE₈₃ with a bond distance of 3.4 Å, 2.4 Å, 3.0 Å, 3.12 Å respectively. Bond energy for this dock complex is kcal/mol 3D pose of the dock complex is shown in Fig. 16.

The plant compounds used here having antiviral properties and they block the activity of COVID-19 by covering active sites of ACE2. The phytochemicals of *Cassia senna L*. inhibit the activity of ACE2 which blocks the interaction of viral protein. Similarly, the RdRp protein also shows the best interaction with the phytochemicals of *Cassia senna L*. at multiple atoms which also inhibits the activity of the targeted proteins. These natural phytochemicals were proven less toxic and have no side effects. The phytochemicals Pelargonidin 3-Galactoside and Kemoferol from *Cassia senna L*. were reported for the first time as novel COVID-19 inhibitor.

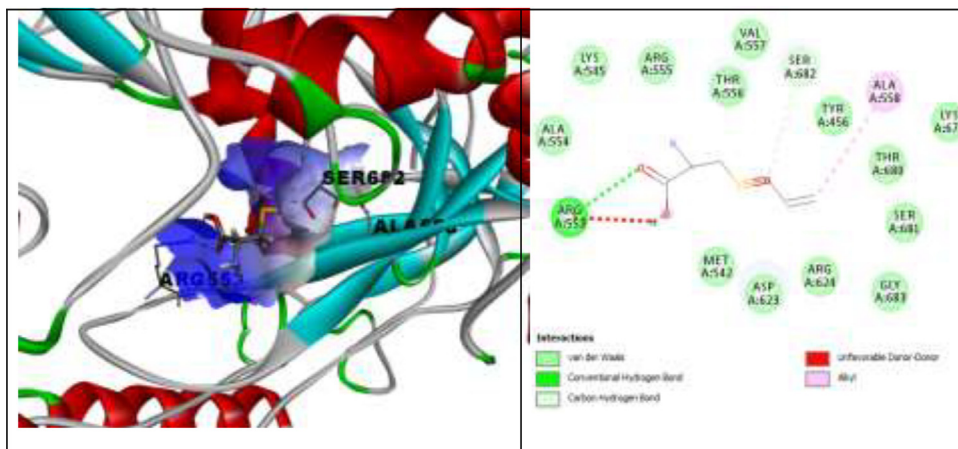


Fig. 6. S-Allylcysteine shows conventional hydrogen bonding, Carbon hydrogen bonding and Alkyl bonding with ARG₅₅₃, ALA₅₅₈, SER₆₈₂.

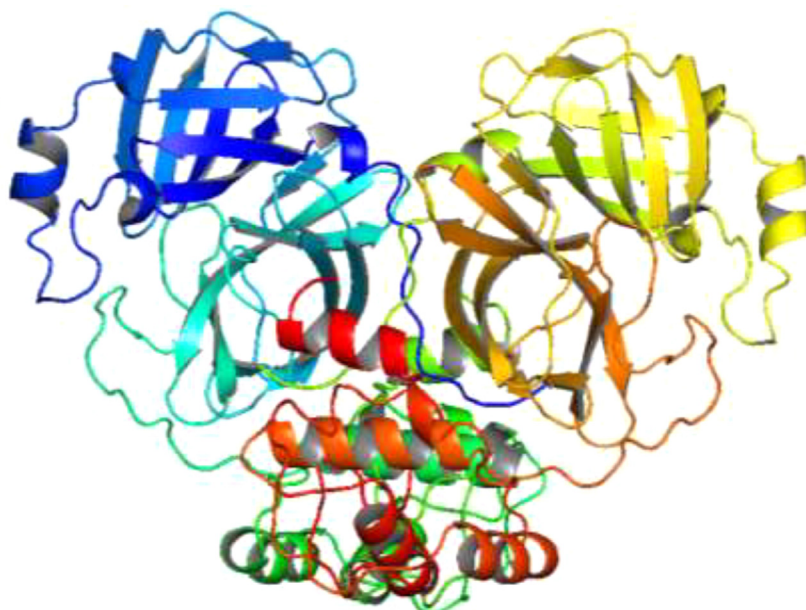


Fig. 7. Structure of 3CLpro protein.

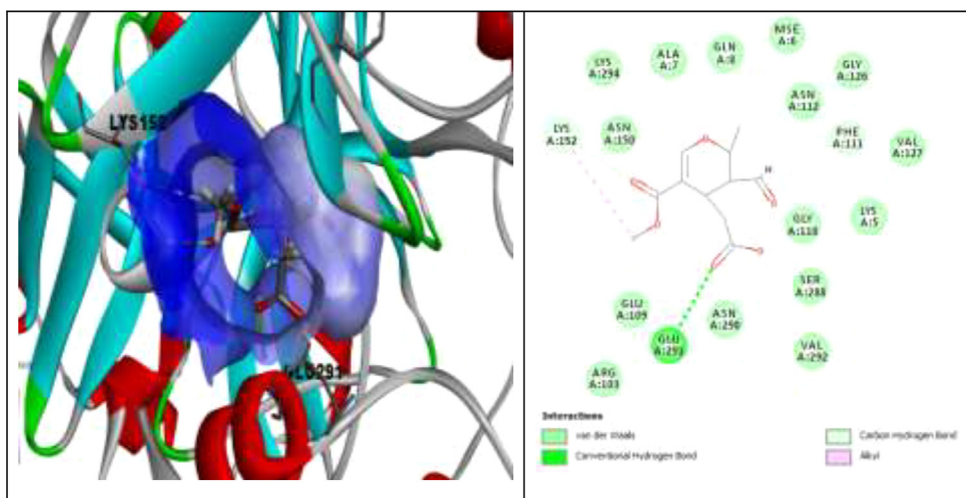


Fig. 8. Calcium Elenolate shows conventional hydrogen bonding, Carbon hydrogen bonding and Alkyl bonding with LYS₁₅₂, GLU₂₉₁, PHE₁₁₁.

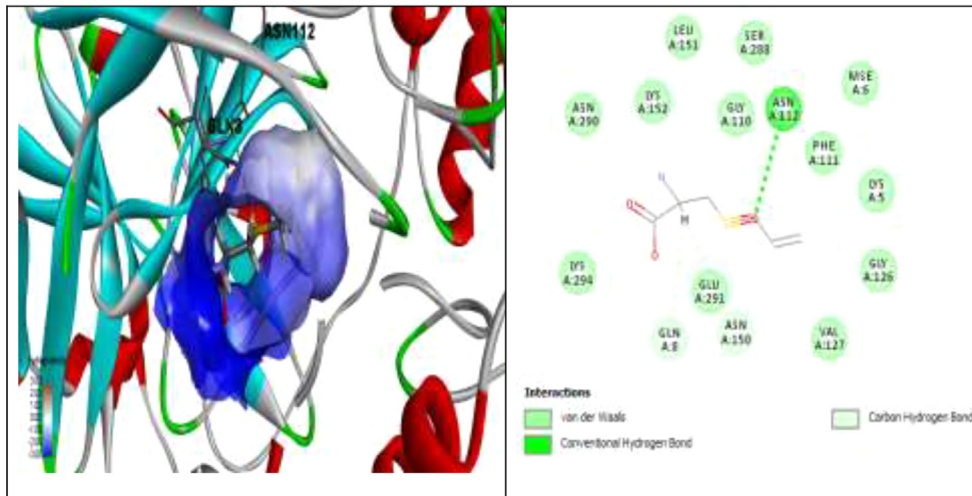


Fig. 9. S-Allylcysteine shows conventional hydrogen bonding, Carbon hydrogen bonding with ASN₁₁₂, GLN₈, ASN₁₅₀.

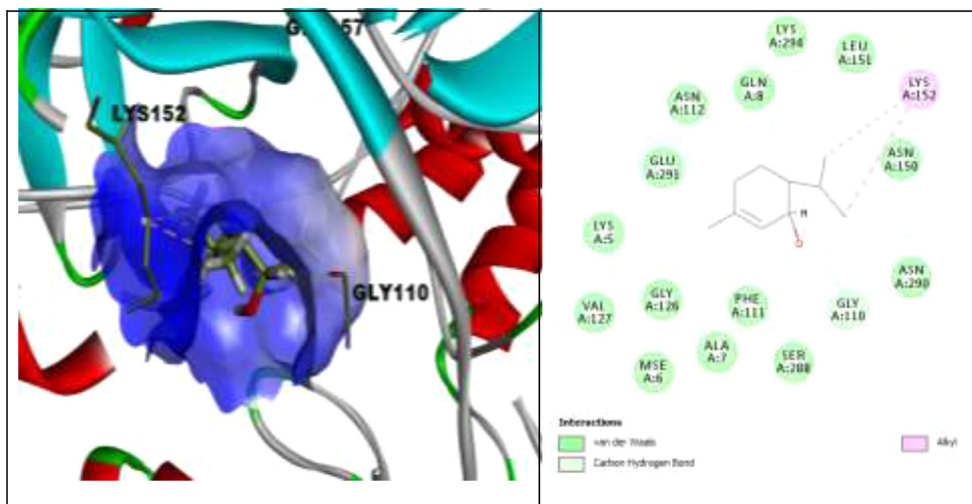


Fig. 10. Monoterpene shows carbon-hydrogen bonding, Alkyl bonding with GLY₁₁₀, LYS₁₅₂.



Many of them govern in opposition to S-protein.

Fig. 11. Structure of ACE2 (S protein).

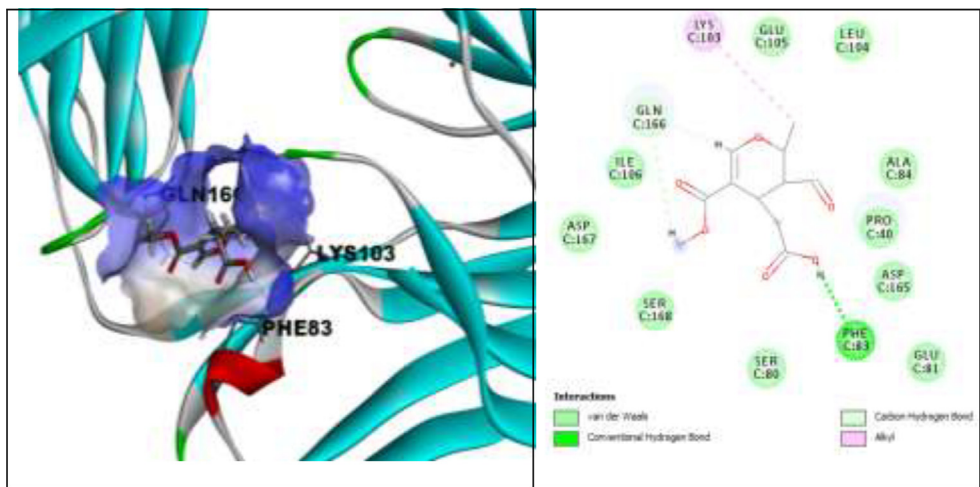


Fig. 12. Calcium Elenolate shows conventional hydrogen bonding, Carbon hydrogen bonding and Alkyl bonding with PHE₈₃, GLN₁₆₆, LYS₁₀₃.

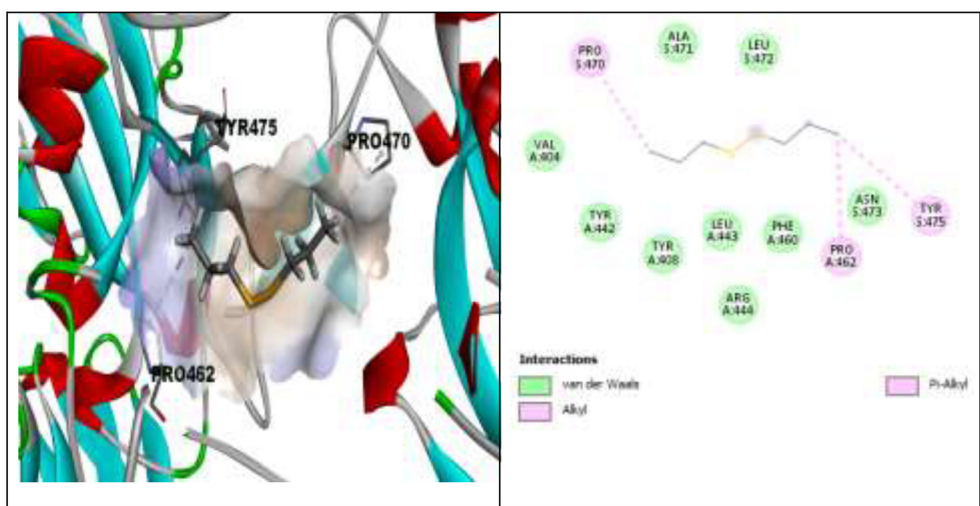


Fig. 13. Dipropyl Disulfide shows Alkyl bonding with TYR₄₇₅, PRO₄₆₂, PRO₄₇₀.

ACE2 with Monoterpene

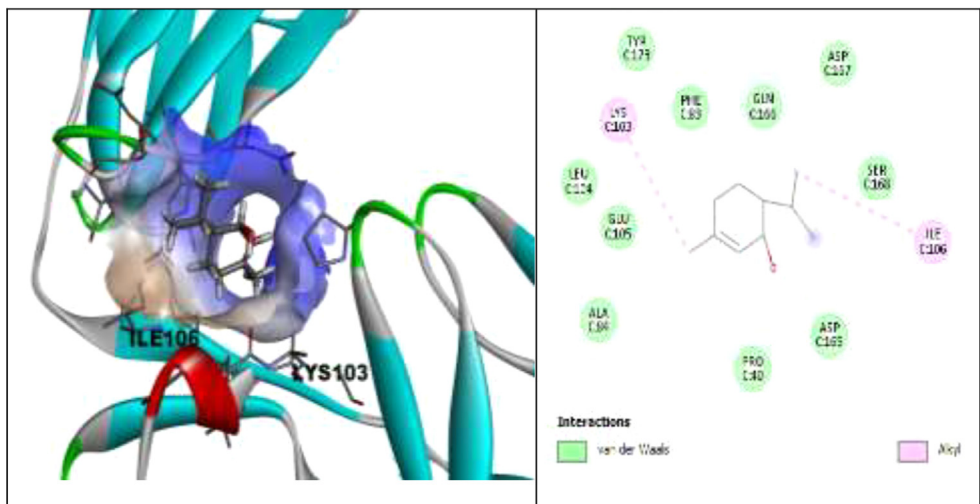


Fig. 14. Monoterpene shows Alkyl bonding with LYS₁₀₃, ILE₁₀₆.

ACE2 with Pelargonidin 3-Galactoside

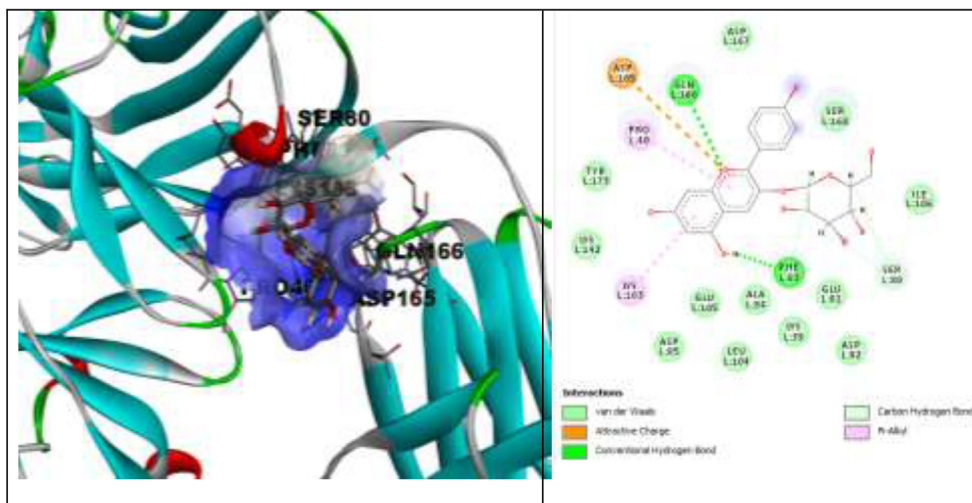


Fig. 15. Pelargonidin 3-Galactoside Ion shows conventional hydrogen bonding, Carbon hydrogen bonding and Alkyl bonding with GLN₁₆₆, PHE₈₃, SER₈₀, LYS₁₀₃, PRO₄₀, ASP₁₆₅.

ACE2 with Thymoquinone

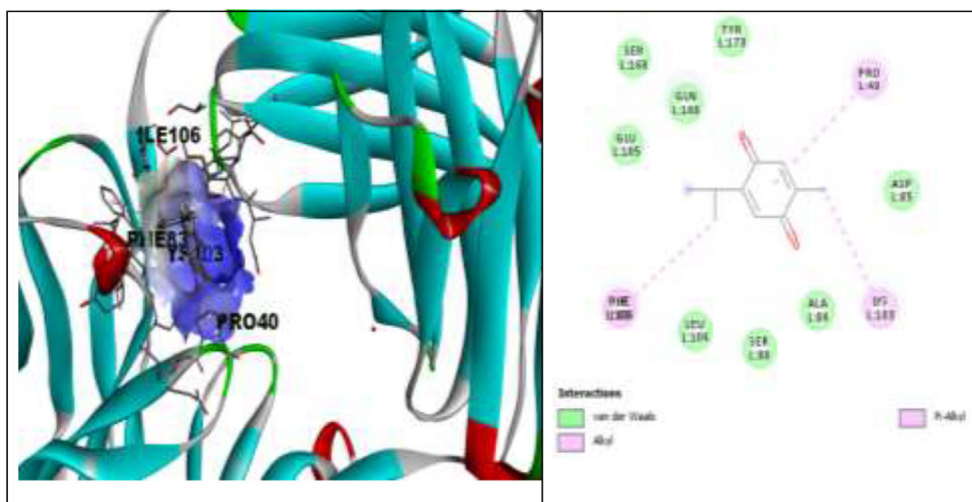


Fig. 16. Thymoquinone shows Alkyl bonding with PRO₄₀, LYS₁₀₃, ILE₁₀₆, PHE₈₃.

- ACE2 with Calcium Elenolate**
- ACE2 with Dipropyl Disulfide**
- ACE2 with Monoterpene**
- ACE2 with Pelargonidin 3-Galactoside**
- ACE2 with Thymoquinone**

4. Conclusions

COVID-19 is declared as a pandemic by WHO and has resulted in numerous deaths in our country and other parts of the world. In China and other parts of the world, some of the allopathic medicines (Cholroquine, Lopinover, Oseltamivir and Retenover etc.) used for other purposes like malaria have shown good results against coronavirus. But their efficacy is not yet established. The process of drug development is time consuming and expensive process. Immunization of the coronavirus is not 100% effective at present due to the reason that SARS COV-2 had undergone various mutations and showed greater variability. Alternative therapies are being explored by researcher and antiviral herbal medicines have

been found effective in many historic epidemics and have shown good results. In China, traditional herbal treatment was also adopted against COVID-19 and was proved effective against corona disease. As compared to chemical drug plant products and especially those mentioned in the Holy Quran and Hadith are safe and free from side effects. Due to their safety, these products can be used as the first line of defense and the people of our country can be protected from current and future pandemics. Further research is needed to find out the proper dose and appropriate duration of treatment that will make it safe and effective. The biologically active compounds can be optimized *in vitro* experiment, then after clinical trial can be used for treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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