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THE ROLE OF PROPHETIC MEDICINE IN MANAGEMENT OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-COV-2)

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ABSTRACT

Current trials to the treatment of coronavirus disease 2019 should open new prospects in the search for novel drugs from medicinal plants and other natural products. This paper provides details of some nutraceuticals that inhibit human coronavirus entry into cells, general replication, and specific chymotrypsin-like protease (3CLpro)-mediated replication. Many non-pharmaceutical interventions were approved by countries worldwide in the fight against the COVID-19 pandemic with adverse socioeconomic side effects, which raises the question about their differential effectiveness. We estimate the effect of each intervention on the incidence of COVID-19. In recent years, there has been a growing interest in nutraceuticals, which are those nutrients in foods that have beneficial effects on health. There has been extensive interest in the antiviral properties of nutraceuticals, which are especially topical in the context of the ongoing COVID-19 pandemic. The Prophet Mohamed may God's prayers and peace be upon him, came with the religion and assistance to the world as he urged what is in the benefit of the bodies and prohibited everything that spoils them, so he commanded and desired medication. Many quranic verses in the Book of God Almighty talk about the bliss of paradise and what God has prepared for his pious servants. Therefore, the aim of this review is to evaluate the main nutraceuticals to which antiviral roles have been attributed (either by direct action on viruses or by modulating the immune system), with a focus on what was mentioned in the Holy Quran and Sunnah. Furthermore, the possible use of these substances against SARS-CoV-2.

KEYWORDS

COVID-19, Nutraceuticals, Chymotrypsin-like protease and ACE-2.

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INTRODUCTION

COVID-19, a disease induced by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2), has been the reason of a global pandemic.

The coronaviruses (CoVs) are large enveloped viruses, contain positive (+) sense single strand

ribonucleic acid as genetic material and the genome size differs from 26- 32kb¹. The coronaviruses belong to the Coronaviridae family, and are grouped into Alpha (α), Beta (β), Gamma (γ), and Delta (δ) genera classified according to their serological and genetic characteristics²⁻³.

Human beings were affected and influenced by many viral diseases. The COVID-19 is a lower respiratory tract disease and it is characterized by flu-like symptoms, which occurs after 5-6 days of virus infection. Symptoms include sore throat, cough, fever, muscle or body aches and even loss of taste or smell was also observed. These symptoms are identical to the SARS and MERS diseases⁴. Old people and people with poor immunity were found more vulnerable to the disease⁵.

Some individuals (asymptomatic individuals) act as potential source of SARS-CoV-2 infection. The disease transmitted through respiratory droplets, close contact with the infected person and exposures to the aerosols generated by the infected individuals. For these reasons COVID19 disease is spreading rapidly and is responsible for death of millions of people across the world⁶.

The effective treatment against SARS-CoV-2 is very essential to rescue the world from COVID-19 pandemic. However, there is a critical requirement to develop antiviral agents which are effective to control the infections. According to WHO 80% of the people in developing countries depends on plant sources for several disease⁷⁻⁸. Various natural plant products have been explored as antiviral agents^{7,9-10}. Many researchers have focused on drugs which can affect replication or protease activity of coronavirus. The clinical testing and regulatory approvals for these drugs will take time. However, there is a requirement of treatments which are safe, effective and can be implemented through readily available products in market.

The occurrence of spike (S) protein is characteristic for all SARS related coronaviruses. The variable receptor binding domain (RBD) present in S protein of SARSCoV-2 recognizes and binds to the receptor angiotensin converting enzyme-2 (ACE-2). ACE-2 which, is a transmembrane protein present

in lungs, heart, gastrointestinal tract and kidney, facilitates the entry of the virus to target cells¹¹. As the virus binds to the ACE-2 receptors in the type II pneumocytes in the lungs, ACE-2 cleaves by type 2 transmembrane protease (TMPRSS-2) complex and activates the S protein of the virus^{12,13}. The mechanism viral entry and infection detected in cells which have both ACE2 and TMPRSS-2¹⁴. Entry and infection in to the cell triggers the host immune response and cascade of inflammation in the lower respiratory tract¹⁵. Therapeutically targeting these proteins can stop progression of the infection at an early stage.

The coronavirus main protease, chymotrypsin-like protease, 3CLpro also referred to as Mpro is found to be integral to the expression of viral gene and replication and is being encoded by the nsp5 in the viral genome¹⁶. Functional proteins as RNA-dependent RNA polymerase (RdRp) and Helicase (Hel) are generated when 3CLpro cleaves the polyproteins. Furthermore, the papain-like protease (PLpro) cleaves polyproteins generating proteins essential for virus replication. Also, it helps to strip ubiquitin making coronaviruses evade the innate immune responses of the host¹⁷.

The virus enter the host cell via transmembrane spike (S) made up of glycoproteins which form homotrimers protruding from its surfaces¹⁸. Spike S consist of of two functional subunits (S1 and S2) which permit its efficient binding to surface receptor and also, helps in viral and cellular membranes fusion. The Receptor Binding Domain (RBD) of spike S proteins induces conformational alterations in ACE2 receptors, which dissociates the S1 subunit of the spike S and therefore initiates host cell membrane fusion¹⁹.

An elevated level of inflammatory cytokines observed in infected patients^{20,21}. The inflammatory cascade is triggered by antigen presenting cells (APC). The APC performs two functions; firstly it presents the virus, to CD4+ T-helper (Th1) cells and secondly releases interleukin (IL)-12 to further stimulate Th1 cells. The stimulated Th1 cells activate CD8+ -T-killer (Tk) cells that will target and attack any cells containing foreign antigen and

triggers B-cells to produce the specific antibodies against the antigen. Therefore, to fight with the antigens immune cells respond by releases of many inflammatory cytokines which leads to formation of cytokine storms. The cytokines storms consist of, tumor necrosis factor- α (TNF α), interleukins (IL)-1, 6 and interferon- γ (IFN- γ). Pain, redness and swelling represent the signs of inflammation. The TNF- α production triggers many signaling events in the cells, resulting in necrosis or cell death as a mechanism to control the spread of infection. TNF- α and IL1 β are responsible of vascular permeability, inflammatory cells, induction of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2)^{22,23}. The iNOs is the enzyme that produces nitric oxide (NO), a free radical gas molecule which has a crucial role in secondary inflammatory response and cell apoptosis²⁴. As a consequence of these reasons patients are susceptible to acute respiratory distress syndrome (ADR) and multiple organ failure^{21,23}. Usually, the viral infections are associated with coagulation disorders or thrombotic complications. Inflammation impacts initiation, propagation and inhibitory phases of blood coagulation²⁵. Xu *et al*, 2020, when examined various blood samples of SARS-CoV-2 patients, found that SARS-CoV-2 virus instantly activates pathogenic T cells and induces numerous cytokines such as, IL-1, IL-6, granulocyte-macrophage colony stimulating factor (GM-CSF), and IFN- γ ²⁶. GM-CSF further activates CD14+ cells, CD16+ cells and monocytes, resulting in further release of inflammatory cytokines such as IL-6. This progression continues to strengthen the inflammatory cascade and intense immune response leading to damage to the vital organs. Li *et al*, (2020) found that SARSCoV-2 systemic cytokine storm and the microcirculation dysfunctions leads to viral sepsis and multiple organ failures²⁷. Hence, effective antiviral agents that controls innate immune response and stabilizes the adaptive immune response are important for effective treatment of COVID-19. The Prophet Mohamed may God's prayers and peace be upon him, came with the goodness of the religion and the world, and

from that he urged what is in the benefit of the bodies and forbade everything that spoils them, so he commanded and desired medication. And after I was keen to adhere to the scientific method based on experience and to prove what is mentioned in the Prophet Sunnah, peace be upon him, in the topics of medication, to see the extent of compatibility between the correct hadith and what science has proven by experience and proof.

Self-hygiene (Ablution)

The oral cavity, is believed to play an important role in the pathogenicity and transmission of SARS-CoV-2²⁸. Recently, research in Hong Kong has shown that patients infected with SARS-CoV-2 had high viral load in the oropharyngeal saliva swab sample in the first week, especially on day4²⁹. The viruses in the oropharynx and throat were the ones that most actively replicated within the first week in infection. Wearing masks was important, which could reduce the inhaled virus quantity, thereby reducing the initial viral load. The most suggested personal protection habits include wearing masks, washing hands frequently, and maintaining social distance³⁰. In quranic verses in the Book of God, the Almighty said: O you who believe! When you intend to offer Aş-Şalāt, wash your faces and your hands (forearms) up to the elbows, rub your heads, and your feet up to the ankles. If you are in a state of Janāba, purify yourselves. But if you are ill or on a journey, or any of you comes from the Ghait, or you have been in contact with women, and you find no water, then perform Tayammum with clean earth and rub therewith your faces and hands. Allāh does not want to place you in difficulty, but He wants to purify you, and to complete His Favour to you that you may be thankful.

Considering mouth rinses as agents that can reduce the salivary viral load of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in the fight against the COVID-19 pandemic is an extremely attractive concept²⁸.

COVID-19 enters from nose and the mouth because the infection is mainly transmitted by contact with infected droplets or inhalation of droplets. The implement of quickly and effectively non-

pharmaceutical interventions including nasal irrigation and oral rinse to reduce the burden of COVID-19 is needed³¹.

Nasal mucosa considered a vulnerable area for coronavirus to colonize for its abundant blood vessels, mucinous glands and serous glands which create a humid environment. In addition, ACE2 expression was found in the basal layer of the nonkeratinizing squamous epithelium in nasal mucosa, indicating that coronavirus may infect nasal mucosa cells if basal layer is exposed due to nasal mucosa barrier breakdown³². Slapak *et al*³³ showed that the use of seawater SNIs, three times daily for 8 weeks, reduced URTI episodes.

In Japan, a randomized trial study showed that throat gargling with tap water 3 times a day significantly reduced the incidence of upper respiratory tract infection by 36%. The probable mechanism for effectiveness of throat gargling could be that the washing agent used in throat gargling causes detaching of the virus and infected cells or causes chemical inactivation of the virus. The concentration of chlorine in tap water in Japan reaches >0.1mg/L and up to 0.5e0.8mg/L in some areas, which is enough to ensure inactivation of the virus. In hypertonic saline chloride ions used by cells to produce hypochlorous acid to exert antiviral effects³⁴.

Nasal cavity irrigation and throat gargling with hypersonic saline during 48 h after the symptom onset reduced the period of illness by 1.9 days³⁵.

The use of a face mask and nasal rinsing can be included as part of intervention methods that include vaccination as it reduced the symptoms of rhinorrhea, cough, and nasal blockage. Nasal rinsing during ablution reduce symptoms of ARI. As nasal rinsing can be easily practiced, which is an integral element of Muslims' daily life since it is a Sunnah act in ablution³⁶.

Hand washing has received widespread attention during the COVID-19 pandemic. Washing with soap and water for at least 20 s represent a primary preventive measure. Also, the use of alcohol-based sanitizers when soap and water are not accessible is

the first line defense in preventing the spread of infection³⁷.

The ablution to maintain individual's hygiene is the best cleaning the nasal-cavity well during the day. In addition, ablution five times as requested Islam protect against bacterial infectious diseases³⁸.

Miswak (*Salvadora persica*)

Miswak (*Salvadora persica*), as a cultural and scientific heritage oral hygiene tool, it has been used as a natural method for tooth cleaning in many parts of the world for thousands of years. The Islamic followers have emphasized to practice the use of Miswak as a Sunnah by the Prophet for maintaining the oral hygiene³⁹ as the preaching says "The implementation of the cleaning the mouth with Miswak pleases Allah". The miswak possesses antibacterial, anti-fungal, anti-viral, anti-cariogenic, and antiplaque properties. It was reported that miswak has anti-oxidant, analgesic, and anti-inflammatory effects. The use of a miswak has direct effect on the composition of saliva. It was confirmed that the mechanical and chemical cleansing efficacy of miswak chewing sticks are equal and at times greater than that of the toothbrush⁴⁰⁻⁴².

The chemical substances present in miswak are as follows: chloride, fluoride, saponins, salvadorine, silica, sulfur, sterols, trimethylamine, and vitamin C, b-sitostrol, m-anisic acid, salvadorea, and gypsum; organic compounds, including pyrrolidine, pyrrole, and piperidine derivatives; glycosides, such as salvadoside and salvadoraside; and flavonoids, including karpferol, querceting rutin, and a quercetin glucoside while, the main constituent of the *Salvadora persica* root oil is Benzyl-isothiocyanate³⁹.

Miswak contains substances that possess plaque inhibition and antibacterial properties against several types of oral aerobic and anaerobic bacteria^{39,43}. Topical application of miswak on the skin of mice infected with Herpes simplex virus (HSV-1) inhibited the replication of HSV-1 and also reduced the development of cutaneous lesions and the viral titers in the skin and ganglia⁴⁴.

Flavonoids content of miswak exhibited significant binding stability at the N3 binding site of COVID-19 main protease, when compared with the currently used inhibitor, darunavir using molecular docking. The identified flavonoids and the receptor in the N3 binding site of the COVID-19 main protease were Structural similar in the structure. The basic flavonol nucleus possesses the same activity⁴⁵.

More than 80% of the participants of the Jamaat Tablighi conference who tested positive showed no symptoms. On analysis, the crude death rate was found to be 6.29 units per 1000 persons per time period. The percentage of death rate was evaluated to be 0.62% which is less than 1%. The Sunnah practice of majority people of the conference were Miswak users who have regularly undertaken the pharmacological benefits of the arak tree and as per the analysis 99% of them were found to be asymptomatic. Also they were the first forefront plasma volunteer donors who were negative for symptomatic COVID-19 to carry out the plasma therapy in affected Covid patients. Therefore regular use of miswak in tooth brushing may be the main scenario behind their asymptomatic⁴⁶.

Olive oil

Olive oil is rich source of plant secondary metabolites. In quranic verses in the Book of God, the Almighty said: With it He causes to grow for you the crops, the olives, the date-palms, the grapes, and every kind of fruit. Verily, in this indeed an evident proof and a manifest sign for a people who give thought.

The oleuropein, hydroxy tyrosol, oleanolic acid and maslinic acid from olives have been used as an effective antiviral agent and for treating other diseases as well⁴⁷⁻⁵⁴. In molecular docking studies it was found that, the oleuropein, oleanolic acid and maslinic acid have shown highest affinity to Mpro and 3CL pro part of SARS-CoV-2 which are essentially required for virus replication and found promising future drugs against COVID-19^{55,56}. In addition, olive oil content possess ACE2 inhibitory activity and inhibit entrance of the virus to the living cell^{57,58,56,59-61}. Apart from antiviral properties

these bioactive compounds found to interfere and modulate various signalling pathways and possess various properties such anti-inflammatory, anti-modulatory, antithrombotic and anti-oxidant properties⁶²⁻⁷¹. These compounds were known to control the cytokine storms which is observed during various viral infection and other diseases. Furthermore, the olive oil can also be applied all over the body as a preventive measure to avoid the virus infection. The oleanane a triterpenoid extracted from olive plant was reported as safe and effective fumigant and was used to prevent the spread of infectious biological agents^{72,73}.

Fig (Ficus carica)

The fig tree belongs to the Moraceae family and the fig fruit (Ficus carica) has been shown to be beneficial in some diseases. In quranic verses in the Book of God, the Almighty said: By the fig, and the olive.

The fig latex has been included in traditional herbal medicines to treat warts, skin ulcers and sores; it has also been shown to exert antiviral activity against some human viruses; other researchers have also investigated the antitumour effects of figure⁷⁴. Patil *et al*⁷⁵, found that oral administration of ethanolic leaves extracts of the common fig ameliorated humoral and cell-mediated immune responses. Traditionally, this plant has also been used against several respiratory, gastrointestinal, inflammatory and cardiovascular problems⁷⁶.

Figure constituents include, cerin, sugar, caoutchouc, resin, malic acid, rennin, proteolytic enzymes, diastase, esterase, lipase, catalase and peroxidase⁷⁷.

Figure is able to interfere with the replication of CpHV-1 *in vitro* and to reduce the viral titres produced by CpHV-1-infected MDBK cells. CpHV-1 is responsible for genital herpesvirus infection in goats but it shares several features with HHV-2, the aetiological agent of human genital herpesvirus infection⁷⁸. In addition figure possess antiviral activity against HSV-1, HSV-1, ECV-11, and ADV, influenza virus⁷⁹.

Figure was screened to find out active phytochemicals against SARS-CoV-2 main

protease through molecular docking, molecular dynamics simulation, and ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiling. Screening of the binding affinity with SARS-CoV-2 main protease revealed that lupeol, α -myrin, and luteolin show the highest binding affinity. These compounds also interact with hydrogen bonds, van der Waals bonds, and alkyl bonds. Amyrin was the most stable, inhibitor SARS-CoV-2 main protease. The binding free energy analysis revealed that amyrin and lupeol have higher binding free energy compared to the known SARS-CoV-2 Mpro inhibitor α -ketoamide⁷⁹. N-arginine, luteolin, caffeic acid content in fig prevents covid-19 infection as luteolin inhibits spike protein and caffeic acid prevents the viral attachment. Furthermore, lupeol, α -amyrin, and luteolin inhibit COVID-19 main protease (Mpro) enzyme⁸⁰.

Date palm (Phoenix dactylifera)

Date palm (*Phoenix dactylifera*)⁸¹ is edible sweet fruit. Date consumption has been recommended in hadith for Muslims by Prophet Muhammad. Date fruits are a good source of low cost food and are an integral part of Arabian diet. Muslims all over the world considered eating dates for religious importance as dates are mentioned in many places in the Quran. In quranic verses in the Book of God, the Almighty said: And from the fruits of date-palms and grapes, you derive strong drink and a goodly provision. Verily, therein is indeed a sign for a people who have wisdom. Date consumption has been recommended in hadith for Muslims by Prophet Muhammad. Date is customarily used to break the day long fast during the holy month of Ramadan. The Messenger of God, may God's prayers and peace be upon him, said: "Whoever eats seven Ajwa dates in the morning will not be affected by poison or magic on this day"⁸².

This plant has a great medicinal value as it has been reported to have versatile phytochemicals including phenolics, sterols, carotenoids, anthocyanins, procyanidins, flavonoids, different minerals and vitamins. These phytochemicals have been responsible for the different pharmacological effects

like antibacterial, antidiabetic, antiasthmatic, antifungal, anti-inflammatory, anticancer, antioxidant, hepatoprotective, nephroprotective, gastrointestinal protective, antihyperlipidemic, immunostimulatory, gonadotropic, and antitussive⁸³. Anti-myocardial Infarction Activity also was reported⁸⁴. In traditional medicine date was used for the treatment of various disorders which include memory disturbances, fever, inflammation, paralysis, loss of consciousness, nervous disorders⁸⁵.

There was a positive relationship between consumption rate of dates and decrease rate of COVID-19 cases as observed in a study to investigate the relation between trends of information about dates in Indonesia and Saudi Arabia, the result showed that COVID-19 cases in Saudi Arabia are decreased more than Indonesia as a result of date consumption⁸⁶.

The antiviral activity of date was evaluated against lytic *Pseudomonas* phage ATCC 14209-B1, using *Pseudomonas aeruginosa* ATCC 25668 as the host cell. The antiviral activity of *Phoenix dactylifera* was found to be mediated by binding to the phage⁸⁷. Different fractions of date showed antihypertensive activity which was mediated through ACE inhibition and was higher than lisinopril⁸⁸.

Black seed (Nigella sativa)

Nigella sativa belongs to the family Ranunculaceae. The herb is available in households by the name of black seed. It is considered as a curative herb and in Islam it is one of the miracle plants which is described as a universal healer. The hadith about the black seed is very interesting, for it has been authenticated from the Prophet, peace be upon him, with his call for treatment with it and that it is a cure for every disease. And we stop at the words of the Prophet, may God bless him and grant him peace, "a cure for every disease". Abu Hurairah narrated that the Messenger of Allah (s.a.w) said: "Use this black seed. For indeed it contains a cure for every disease except As-Sam" And As-Sam is death⁸⁹. *Nigella sativa* has proven antiviral, antihypertensive, liver tonics, diuretics, digestive, anti-Diarrhoeal, appetite stimulant, analgesics, anti-

bacterial properties⁹⁰⁻⁹⁵. The more attributed role of black seed includes antidiabetic, anticancer, immunomodulator, analgesic, antimicrobial, anti-inflammatory, spasmolytic, bronchodilator, hepato-protective, renal protective, gastro-protective, cardioprotective, antihypertensive, and antioxidant nature. The main constituents include thymoquinone, thymol, carvacrol, c-terpinene and p-cymene etc⁹⁶⁻⁹⁸.

Thymoquinone (2-methyl-5-propan-2-ylcyclohexa-2, 5-diene-1, 4-dione) is a major bioactive constituent of *Nigella sativa*. It has anti-inflammatory effects besides providing protection against gastrointestinal problems, bronchial headache, asthma, and dysentery⁹⁹. It possesses anti-inflammatory properties as it inhibits thromboxane B2 and leukotriene, the oxidative products of arachidonic acid by blocking the activity of cyclooxygenase and lipoxygenase enzymes^{100,101}. Thus, controlling the over expression of cytokines may help in management of SARS-CoV-2 infection. *Nigella sativa* seed oil was found to suppress viral load caused by cytomegalovirus in mice to untraceable levels in the liver and spleen within a span of 10 days of intraperitoneal administration¹⁰². This may be attributed to the increase in expression of CD-T cells and interferon-gamma (INF- γ). Mu *et al*, 2015¹⁰³, reported that Thymoquinone acts as a potent chemosensitizer and apoptotic agent via down regulation of the PI3K/Akt/mTOR activation. An over expression of PI3K/Akt/mTOR signaling is reported in SARS-CoV-2 infection therefore intervention of *Nigella sativa* may prove useful against SARS-CoV-2. A human system molecular docking analysis was performed to determine the predominant binding mode(s) of different *Nigella sativa* constituents as ligand with a purposed protein (ACE2). The most suitable binding ligand to ACE2 was found to be a-hederin (-6.265kcal/mol), Thymohydroquinone (-5.466kcal/mol) and Thymoquinone (-5.048kcal/mol). Since ACE2 is the entry site of virus in the human system, the *Nigella sativa* bioactive constituents were taken further for a docking study. ACE2 was found to

bind to the components- a-hederin and Thymohydroquinone with good binding energies. Hence, these 2 components of *Nigella* can be exploited therapeutically¹⁰⁴.

Ginger (*Zingiber officinale*)

Ginger contains volatile and non-volatile compounds with important pharmacological properties as antioxidant, anti-inflammatory, antiemetic and antiviral. Phenolic compounds in ginger oil possess synergistic effect when acting as an antioxidant and anti-inflammatory, among these compounds stand out gingerol, shogaol, zingerone and gingerdiols. Its anti-inflammatory activity is associated with reduction of mRNA expression of biomarkers such as interleukine (IL-6) and could act similarly as Tocilizumab, a medicine used to treat patients with COVID-19. It also has antiviral activity by inhibiting SARS-CoV-2 proteins by binding with ACE-2, 3CLpro and PLpro, and an antiemetic activity by which it will decrease the patient's symptoms. Many quranic verses in the Book of God Almighty talking about the bliss of Paradise and what God has prepared for His pious servants, the Almighty said: (And they give them drink in it a cup that was made of ginger)¹⁰⁵.

Gingerone one of ginger constituent showed *in vitro* and *in vivo* antiviral activity on Influenza A virus¹⁰⁶. Chang *et al*¹⁰⁷ have shown that only fresh ginger inhibited human respiratory syncytial virus-induced. They have shown that fresh ginger inhibited viral attachment and internalisation dose dependently. Fresh ginger of high concentration could stimulate mucosal cells to secrete interferon- β that possibly contributed to counteracting viral infection. Fresh ginger stimulates secretions more effectively compared to dry ginger¹⁰⁸.

Ginger interacts at the active sites of the RBD of COVID-19 spike protein and human ACE-2, to elicit antiviral property and inhibit spreading of COVID-19 disease¹⁰⁹. Ginger was evaluated to find their binding with these proteins by conducting ligand-receptor binding docking study with Auto Dock Vina. It was revealed that Gingerone (-5.87kcal/mol) and Zingiberene (-5.77kcal/mol) have shown effective binding affinity towards

ACE2. Shoagol (-5.72kcal/mol), Zingerone (-5.79kcal/mol) and Zingiberene (-5.52kcal/mol) have shown higher binding with extracellular domain of serine protease TMPRSS2 in the docking study. Zingiberene scored significant binding energy of -6.23kcal/mol with Spike protein of SARS-CoV-2¹¹⁰.

The molecular docking between ligands and ACE2 revealed that Gingerenoneone and Zingiberene phytoconstituent of ginger has the binding energy value -5.87kcal/mol and -5.77kcal/mol that lies between the binding energy values of Chloroquine (-5.52kcal/mol) and Hydroxychloroquine (-6.95kcal/mol). Both the chemotherapeutic marker drugs also have *in vitro* activity against SARS-CoV-2 and may possess immunomodulating properties. ACE2 cellular receptor inhibition, acidification at the surface of the cell membrane inhibiting fusion of the virus, and immunomodulation of cytokine release may be the mechanism. Other mechanisms may contain inhibition of viral enzymes such as viral DNA and RNA polymerase, viral protein glycosylation, virus assembly, and new virus particle transport and virus release^{111,112}.

The binding of ligands with the extracellular domain of serine protease/hepsin/TMPRSS2 by considering the fact that these host cellular protease prime Spike protein of SARS-CoV-2 after viral-host cell attachment to facilitate the viral infection were explored. Finding a serine protease inhibitor may block the SARS-CoV-2 Zingerone (-5.79kcal/mol), Shoagol (-5.72kcal/mol) and Zingiberene (-5.52kcal/mol) have shown significantly higher binding score as compared to chemotherapeutic counterpart, Camostat mesylate (-5.24kcal/mol). The docking results revealed that binding energy value of phytochemicals with Spike protein have shown a significant range from -3.93kcal/mol to -6.23kcal/mol¹¹⁰.

Nine compounds in ginger displayed a higher binding affinity with least binding energy with the main protease enzyme which include [6]-Paradol, [6]-Shogaol, Cedr-8-ene, Copaene, Gingerenone A, Isogingerenone B, Shogasulfonic acid A and

Zonarenebe made use of as potential inhibitors of COVID-19 Main Proteases¹¹³. Finally, 6-gingerol proves anti-viral efficiency against SARS CoV-2 by showing the highest binding affinity and interaction with multiple targets of COVID-19 including viral proteases, RNA binding protein, Spike protein¹¹⁴.

Fenugreek (*Trigonella foenum-graecum*)

Another important medicinal plant commonly used in traditional medicine is Fenugreek (*Trigonella foenum-graecum*). Fenugreek seed and leaves are used in food and traditional medicine all over the world. The hadith about the fenugreek is very interesting, for it has been authenticated from the Prophet, peace be upon him, with his call for treatment with it, and that it is a cure for many disease. And we stop at the words of the Prophet about fenugreek, may God bless him and grant him peace, "If the people knew of its benefits, they would buy it for its weight in gold".

Fenugreek biological actions include antiviral, hypoglycaemic and antidiabetic, antiulcerogenic, hypocholesterolaemic, antinociceptive and also possess immunostimulatory effects. It has also proven to be antioxidative, antihypertensive, hepatoprotective, and chemoprotective^{115,116}.

The aqueous extract of fenugreek seeds seems to be effective and safe treatment of mild asthma, lung tonic, and can facilitate lung secretions. The aqueous extract of fenugreek seeds improved the lung function tests and quality of life in patients with mild asthma significantly in compare with honey and placebo syrup. The use of fenugreek seed extract led to a 10% increase in FEV1 and FEV1/FVC levels, in addition to a significant decrease in serum cytokine IL-4 levels. Along with the antioxidant effect of fenugreek, and its quercetin content can inhibit Charcot-Leyden crystals and eosinophil cationic proteins, which are involved in asthma pathogenesis¹¹⁷.

The quercetin content of fenugreek makes a stable link with the site of entry of the virus into the cell Spike-ACE2 protein. Thus, these natural compounds can compete with the ACE2 binding site for the COVID-19 virus consequently, preventing the virus from entering the host

cells^{118,119}. Furthermore, fenugreek seeds reduce the level of ACE2¹²⁰. This may be due to the fact that the fenugreek contains 4-Hydroxyisoleucine, a compound derived from fenugreek seeds and reduces the level of angiotensin converting enzyme^{121,122}.

The fenugreek also prevents the reproduction of the virus through its inhibitory effect on main protease, 3CLpro, which is the part required for viral gene expression and viral replication. The antiviral properties reported in a molecular docking protocol on 3CLpro which was more significant than the antiviral drugs ritonavir, indinavir, and remdesiver. The docking results revealed that phytochemicals from fenugreek showed higher 3CLpro inhibitory potential when compared to those from *N. sativa*. Among the most important compounds in the fenugreek, which showed a strong inhibition of the enzyme, Apigenin, Kaempferol, Luteolin, Naringenin and Quercetin?¹²³.

Grape (*Vitis vinifera*)

Grape is a plant rich in bioactive compounds, known for its therapeutic effects. In quranic verses in the Book of God, the Almighty said: And from the fruits of date-palms and grapes, you derive strong drink and a goodly provision. Verily, therein is indeed a sign for a people who have wisdom. Flavonoids, most of which were derivatives of quercetin were isolated from grape. Others included derivatives of luteolin, kaempferol, apigenin, isorhamnetin, myricetin, chrysoeriol, biochanin, isookanin, and scutellarein. The grape extract was studied for a long time for its hepatoprotective, hypoglycemic, cardio-protective, hypotensive, antioxidant, antibacterial, and antiviral activity which are due to the high levels of polyphenolic compounds found in grapes skin, seeds, and stem. The anti-cancer effect is attributable to the consistent antioxidant activity of these molecules. Resveratrol, one of the most abundant molecules in the extracts, acts at various levels of carcinogenesis. Grapeleaf extract inhibit SARS-CoV-2 replication in the initial stages of infection through direct blocking the proteins on the viral surface, at low concentration of 10µg/mL¹²⁴.

Delta δ-Viniferin content of grape which was reported as antitussive and anti-viral identified as potent SARS-CoV-2 MPro inhibitor. The selected molecule along with myricitrin also, displayed a high binding affinity to SARS-CoV-2 RdRp and hACE-2.δ-viniferin, chrysanthem, myricitrin and myricitrin are present in the extract of black grapes¹²⁵.

Dietary intake of resveratrol could modulate SARS-CoV-2 disease severity through regulating ACE2 function and expression. Rodents fed a high-fat diet supplemented with resveratrol have shown upregulated ACE2 expression and increased ACE2 protein levels compared to rodents fed a high-fat diet alone. Quercetin inhibited SARS-CoV infection by preventing virus entry into the cell. Hence, polyphenols might (i) reduce SARS-CoV-2 viral infection by binding to the ACE2 receptor, preventing the viral entry, and (ii) modulate the severity of lung injury associated with COVID-19 by regulating ACE2 expression. In addition flavonoids such as kaempferol inhibited 3CLpro and PLpro *in vitro*¹²⁶⁻¹³⁵.

S. costus (*Saussurea lappa*)

S. Costus, belongs to family Asteraceae, widely distributed in different regions in the world. *S. costus* is Familiar in Islamic medicine. The Prophet Muhammad may God's prayers upon him, said: "Why do you cover your children with this stick? You have to use this Indian stick, for it has seven cures, including those with pleurisy¹³⁶.

The biological activities of the roots of *S. costus* are widely investigated¹³⁷. Various compounds isolated from the plant have medicinal properties including terpenes, alkaloids, anthraquinones, and flavonoids. *S. costus* by its myrcene content that acts on ACE receptors¹³⁸ may interfere with viral entry into the cells. *S. costus* is used to treat fever, headache, cough, and bronchial asthma and is traditionally used as a bronchodilator¹³⁹. Oleic acid acts as antileukotriene-D415 therefore acts as a bronchodilator. Camphene, caryophyllene, inulin, alpha-phellandrene, hexanoic acid act as expectorant¹⁴⁰. *S. costus* has antimicrobial and

antibacterial properties against many Gram-positive and Gram-negative pathogenic bacteria¹⁴¹.

Also, it has antifungal activity due to presence of (caryophyllene oxide, myrcene, octanoic acid, p-cymene¹³⁸. The decoction of the plant increases the endogenous motilin release and accelerates gastric emptying, and improves gastric cytoprotection. It amplified the mucus discharge and was proved to be an antiulcer agent^{141,142}. Caryophyllene and increased intracellular glutathione are responsible for protection against gastric cell injury¹⁴³. *S. costus* has significant antidiarrheal activity¹⁴⁴.

The studies that demonstrated its antiviral activity were done on the hepatitis B virus (HBV) and showed its considerable activity against the virus and its ability to inhibit hepatitis B surface antigen (HBsAg) expression. Costunolide and dehydrocostus lactone showed an inhibitory effect on the expression of HBsAg by Hep3B cells. They suppressed HBsAg gene expression at the mRNA level. Costunolide and dehydrocostus lactone are candidates to be developed as potent anti HBV drugs. P-cymene, stigmasterol, tannin, lupeol, and botulin have antiviral effects^{145,146}.

It is frequently used for inflammatory diseases. It inhibited the cytokine-induced neutrophil chemotactic factor induction. Costunolide has anti-inflammatory activity. *S. costus* decreases pain and inflammation by inhibition of cyclooxygenase (COX) enzyme. *S. costus* is used for management of chest congestion, lung inflammation, and respiratory distress. Also, *S. costus* considered immunostimulant. It increased the leukocytic count, phagocytosis and antibody-secreting cells¹⁴⁷⁻¹⁵⁰.

S. costus roots have immunomodulator activity. Cynaropicrin has immunomodulatory effects on cytokine release. *S. costus* has complement inhibitor substances helpful in the treatment of some diseases related to marked activation of the complement system, respiratory distress¹⁵¹⁻¹⁵³.

Omega-3

Omega-3 fatty acids are polyunsaturated fatty acids that are abundantly available in nature. Many Quranic verses in the Book of God Almighty talking about the bliss of Paradise and what God has

prepared for his pious servants, God, the most merciful said: (It is He who has subjected the sea to you, so that you eat of its soft flesh and bring up from it ornaments which you wear. And you see the ships plowing their course through it in order that you seek His bounty and give thanks). On the authority of Ibn Omar (may God be pleased with him) that the Prophet may God's prayers and peace be upon him, said: "Two dead bodies and two bloods are permitted for us. As for the two dead bodies, they are whales and locusts, and as for the two bloods, they are the liver and the spleen." And in the answer of the Prophet, peace be upon him, to the questions of one of the Jewish rabbis, as narrated by Anas (may God be pleased with him) on the authority of the prophet, may God's prayers and peace be upon him, he said: (As for the first food that the people of Paradise will eat, it is an increase in the liver of a whale).

Omega-3 FA has a role in host cellular membrane as it regulates membrane fluidity and lipid raft assembling in the cell membrane¹⁵⁴. Gutierrez and colleagues showed that omega-3 FA is incorporated into the bi-phospholipid layer of the cell membrane of neutrophils and produces different mediators such as prostaglandins, leukotrienes, and maresins¹⁵⁵. So, if the injury occurs byproducts of those cell membranes may produce less inflammatory mediators compared to omega-6¹⁵⁶.

Omega-3 FA promotes the ability of phagocytosis, activate macrophages, and induce secretion of cytokines and chemokines¹⁵⁷. Omega-3 FAs also down-regulate Nuclear Factor- κ Beta (NF κ B). NF- κ B is a transcription factor involved in cell signaling to initiate an inflammatory response by the innate immune system. Fish oil improves antiviral response by inducing interferon (IFN) which inhibits viral replication¹⁵⁸.

Omega-3 FA intake in the diet could promote better immune function, and decrease the severity of infection¹⁵⁹.

Omega-3 FA decline the antiviral response induced by CD8 T cells which lead to the surge of cytokines and could modulate cytokine response¹⁶⁰.

Omega-3 index test represent a measure of the amount of Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) in the blood, especially in the red blood cell membranes. This index shows the ratio of omega-3 FAs to all other fatty acids which, was inversely associated with risk for death from COVID-19¹⁶¹.

Omega-3 supplementation by the i.v. route is a possible treatment option in COVID-19, as proven in a trial "Resolving Inflammatory Storm in COVID19. Importantly, the simultaneous monitoring of pro-inflammatory and pro resolving mediators facilitated the understanding of a possible failure of the resolution of inflammation in COVID-19. The lipid mediators detected include resolvins of the E and D series, lipoxins, leukotrienes, and prostanoids, as well as their intermediates, of which 18-HEPE has been previously established as a robust marker for pro-resolving mediator formation from omega-3¹⁶².

In addition, omega-3 also reduces angiotensin-converting enzyme (ACE) activity, angiotensin II formation¹⁶³. Polyunsaturated fatty acids effectively interfere with binding to hACE2. Linolenic acid and eicosapentaenoic acid significantly block the entry of SARS-CoV-2. Furthermore, eicosapentaenoic acid and linolenic acid reduce activity of TMPRSS2 and cathepsin L proteases¹⁶³.

Pomegranate (*Punica granatum*)

Pomegranate has been traditionally used in the folk medicine in treatment of different chronic diseases like diabetes type 2, atherosclerosis, cardiovascular diseases, inflammatory diseases or cancer. Pomegranate peel extracts are rich with hydrolysable tannins (ellagitannin, punicalagin, punicalin, gallic and ellagic acid), favonoids, anthocyanins and other phenols. These polyphenols possess a wide range of biologic properties including anti-inflammatory, antioxidant, hypoglycemic, lipid-lowering, antihypertensive or antimicrobial effects¹⁶⁴. In quranic verses God, the almighty said: And it is he who produces gardens trellised and untrellised, and date-palms, and crops of different shape and taste (their fruits and their seeds) and olives, and pomegranates, similar and

different. Eat of their fruit when they ripen, but pay the due thereof on the day of its harvest, and waste not by extravagance. Verily, He likes not Al-Musrifūn.

Several studies have reported the inhibitory effect of pomegranate extracts on the influenza virus, herpes virus, poxviruses and human immuno deficiency virus^{165,166}. The pomegranate ligand molecules, namely the punicalagin, punicalin and ellagic acid, showed a strong interaction with the catalytic and substrate binding residues of the hepatitis C virus (HCV) NS3/4A protease. In an additional experiment, these polyphenols specifically blocked the NS3/4A protease *in vitro*¹⁶⁷.

Recent *in vitro* studies have shown that the antiviral effect of pomegranate peel extracts on influenza virus is associated with the inhibition of viral absorption and RNA transcription^{168,169,166}.

pomegranate peel extracts content ellagic acid, gallic acid, punicalagin and punicalin inhibit the process of the entry of virus into a host cell, inhibit also SARS-CoV-2 spike glycoprotein, angiotensin converting enzyme 2, and the two proteases with a crucial role in the process of S glycoprotein cleavage in two biologically active subunits (furin and transmembrane serine protease 2 (TMPRSS2)). The results showed that the constituents of pomegranate peel extracts, namely punicalagin and punicalin had very promising potential for significant interactions with the selected protein targets¹⁷⁰⁻¹⁷³.

Ellagic acid, one of pomegranate components, interact with important proteins involved in Sars-CoV-2 as angiotensin-converting enzyme 2 (ACE2), RNA-dependent RNA polymerase, spike glycoprotein, and main protease (3CLpro) in docking study^{174,175}. Furthermore, hydrolysable tannins present in pomegranate, punicalin seems to establish H-bonds with the catalytic residues of the viral main protease enzyme¹⁷⁶.

Pomegranate juice extract decreased the serum levels of ACE¹⁷⁷. Quercetin its metabolites present in juice, seed, and peel of pomegranate inhibit

recombinant human angiotensin-converting enzyme 2¹⁷⁸.

Milk

Milk, not only provides necessary energy and nutrients but also plays an important role in regulating homeostasis related to the immune system, gut microecology and nutrition balance¹⁷⁹. Milk peptides possess many therapeutic properties such as antihypertensive, antiviral, antimicrobial, antioxidant, immunomodulatory, analgesic, antithrombotic and other bioactivities¹⁸⁰. In quranic verses in the Book of God, the Almighty said: And verily, in the cattle, there is a lesson for you. We give you to drink of that which is in their bellies, from between excretions and blood, pure milk; palatable to the drinkers.

Lactoferrin is the main whey protein in human milk, and it possesses a wide array of antimicrobial and immunomodulatory functions. Also, it plays a critical role in protecting newborn infants from infection¹⁸¹. In addition, milk contains a wide range of bioactive proteins, growth factors, cells, and other constituents that modulate the development of a competent immune system and intestinal microecology. Furthermore, milk stimulates the proliferation of a well-balanced and diverse microbiota, which activate of T-regulatory cells by specific breast milk-stimulated organisms (Bifidobacterium, Lactobacillus, and Bacteroides)¹⁸².

SARS-CoV-2 RNA did not detected in milk collected from women with mild-to-moderate COVID-19 infection. In contrast, SARS-CoV-2 RNA was detected on several breast swabs. However, we demonstrated that milk contains anti-SARS-CoV-2 antibodies (SARS-CoV-2-specific IgA and IgG, and levels of anti-RBD IgA) and that their concentrations are correlated with milk's ability to effectively neutralize SARS-CoV-2 infectivity¹⁸³. In addition, the use of cow's milk immune to Bovine Corona virus would cause a total or partial inactivation of SARS-COV-2 (acting as a particular vaccine)¹⁸⁴.

Milk-derived peptides can reduce blood pressure through ACE 2 inhibition^{185,186}. ACE-inhibitory

peptides from fermented milk were reported. Fermentation of bovine milk using Lactobacillus helveticus KLDS.31 and Lactobacillus casei KLDS.105 yields fermented milk that is rich in peptides with ACE-inhibitory activity. Moreover, after ACE-inhibitory peptides derived from the fermented milk were digested with pepsin and trypsin, almost 94% of its initial activity remained¹⁸⁷.

Digestion of isolated caseins and whey proteins of goat milk by gastric pepsin generated soluble hydrolysates exhibiting significant inhibition of ACE compared to undigested proteins. The peptides from whey and caseins exert significant ACE inhibitory activities comparable to that of captopril, an antihypertensive drug¹⁸⁸.

Milk proteins are composed of approximately 80% caseins and 20% whey proteins. The hydrolysis of these fractions yields various peptides. Whey bioactive peptides possess *in vitro* ACE-inhibitory activity and *in vivo* antihypertensive effects. Peptides derived from betalactoglobulin, which inactivates both the virus and its receptors in the host cell. The beta-lactoglobulin derived peptides were obtained by the treatment of goat milk whey fraction with trypsin. Beta-lactoglobulin derived peptides inhibit the ACE, DPP-4, and furin enzymes in the host cell and SARSCoV-2 main protease and that bind to the spike protein of SARS-CoV2¹⁸⁹.

The target of milk peptides are entry points like ACE2, Spike, TMPRSS2, Cathepsin-L and Furin. Also, several milk peptides were found to interact with different protease targets as well with the Spike protein¹⁹⁰.

Honey

Honey contains several compounds including sugars, organic acids, amino acids, phenolic compounds, vitamins, and minerals¹⁹¹. In quranic verses in the Book of God, the Almighty said: "Then, eat of all fruits, and follow the ways of your Lord made easy (for you)." There comes forth from their bellies, a drink of varying colours wherein is healing for men. Verily, in this is indeed a sign for a people who think.

Honey possess several therapeutic properties including immunostimulatory, antibacterial, anti-inflammatory, wound healing, antiulcer, antidiabetic, anticancer, antiviral, and antifungal¹⁹²⁻¹⁹⁴. It reduce hyperlipidemia, and systolic blood pressure in experimental animals¹⁹⁵. In addition, honey alleviates acute respiratory distress symptoms when ingested daily¹⁹⁶. Honey may inhibit SARS-CoV2 proteases as some compounds of honey may be able to bind SARSCoV-2 protease¹⁹⁷. Methylglyoxal (MGO) modification might be involved in SARS-CoV-2 replication¹⁹⁸. MGO is a component of manuka honey that can inhibit enveloped virus growth, viral transcription, and translation¹⁹⁹.

Honey and its compounds attenuate acute inflammation through enhancing immune response. Several studies have proved its potential healing capability against pulmonary disorders, cardiac disorders, diabetes, hypertension, bacterial, and fungal infections. Furthermore, honey has been proved to be virucidal on several enveloped viruses such as HIV, influenza virus, herpes simplex, and varicella-zoster virus. Therefore honey may be beneficial for patients with COVID-19 by boosting the host immune system, improving comorbid conditions, and antiviral activities²⁰⁰. Besides, honey may act as a preventive agent against hyperinflammation caused by SARS-CoV-2²⁰¹.

The anti-viral activity of honey and its main constituents is also related to their modulatory effects on various molecular targets involved in cellular signaling pathways such as apoptosis and inflammation. In addition, honey and its main constituents can modulate signaling cascades which are necessary for virus replication and attachment²⁰². Honey and its main constituents can alter the viral surface protein and membrane proteins, which leads to an inhibition of virus entry into the cell²⁰³.

Honey and its main components could combat against Herpes zoster, rubella, influenza, herpes disease, respiratory syncytial virus, AIDS, immunodeficiency virus, viral hepatitis,

gingivostomatitis, rabies, rhino conjunctivitis and COVID-19²⁰⁴.

The anti-viral activity of honey and its main components is usually associated with anti-oxidant, anti-inflammatory, anti-resistance and anti-apoptotic effects by modulating cellular signaling pathways such as MAPK, NF-kB and Nrf2²⁰⁵⁻²⁰⁹.

Quercetin and kaempferol and quercetin content of honey showed a high affinity to SARS-CoV-2 3CL hydrolase²¹⁰. Kaempferol and quercetin were able to attach to ACE2 and modulate signal pathways. In addition, chrysin inhibites viral replication by blocking viral RNA replication and viral capsid protein formation. In addition, it was observed that kaempferol and quercetin can inhibit the replication of SARS-CoV-2 by targeting on phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit gamma (PIK3CG) and E2F1 (E2F Transcription Factor 1) through modulating Phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathway. Also, quercetin and kaempferol inhibited SARS-CoV-2 replication by modulation of kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway^{211,212}.

Further, quercetin has been found to have protective effects against murine coronavirus by inhibiting H_p-ATPase of the lysosomal membrane and preventing removal of the virus coating. In addition, quercetin inhibited the ATPase of multidrug resistance-associated proteins, thereby increasing the bioavailability of anti-viral drugs²¹³.

Compounds present in honeybee and propolis have anti-viral activity against COVID-19 through strong binding affinity to main protease (Mpro). It has been shown that chrysin, Galangine, and caffeic acid could interact with the main protease of COVID-19¹⁹⁷.

Nuclear factor erythroid 2-related factor 2 (Nrf2) dependent antioxidant genes expression is markedly reduced in COVID-19 patients. Nrf2 stimulators may inhibit the replication of SARS-CoV2 and also related inflammatory genes expression²¹⁴. In this regard, it was found that honey significantly improved hypertension via stimulation of Nrf2 in

the kidney of hypertensive rats²¹⁵. Chrysin ameliorated the neutrophils infiltration and other lung pathological damages through modulation of oxidative stress dependent Nrf2 pathway in lungs of rats exposed to carrageenan²¹⁶. Chrysin, luteolin and apigenin protected rat primary hepatocytes against oxidative stress through modulating Nrf2 signaling pathway²¹⁷. Regarding to stimulatory effects of honey on the Nrf2 signaling, this natural agent can potential effect to combat against SARS-CoV2.

A recent study measured and checked the binding constants of 10 flavonoids, including caffeic acid, caffeic acid phenethyl ester, galangin, chrysin, rutin, hesperetin, myricetin, pinocembrin, quercetin, and luteolin, using the AutoDock 4.2 molecular arrival program and compared to a reference substance of MLN-4760 which is known as ACE2 inhibitor²¹⁸.

Interestingly, twelve completely different flavonoids were detected in propolis extracts namely, pinocembrin, acacetin, chrysin, rutin, luteolin, kaempferol, apigenin, myricetin, catechin, naringenin, galangin, and quercetin; 2 synthetic resin acids, caffeic acid and cinnamic acid (Volpi, 2004). Among others, myricetin has high binding affinity toward the RdRp of each SARS-CoV and SARS-CoV-2²¹⁹.

Six compounds present in honey act as antiviral components against the COVID-19 main protease. The 6 compound (3-phenyllactic acid, Caffeic acid phenylethyl ester, Caffeic acid, Chrysin, Galangin, and Lumichrome) give high affinity in binding the enzyme in the molecular docking²¹⁹.

Flavonoids in propolis and honey (e.g., rutin, naringin, caffeic acid phenyl ester, luteolin, and artemillin C) may inhibit viral S spike fusion in host cells, ACE 2, viral-host interactions that trigger the cytokine storm, and viral replication. Equivalent to the potent antiviral drug remdesivir, rutin, propolis ethanolic extract, and propolis liposomes inhibited non-structural proteins of SARS-CoV-2 *in vitro* and these compounds along with naringin inhibited SARS-CoV-2 infection in Vero E6 cells.

Nanocarriers delivered Propolis extracts exhibit better antiviral effects against SARS-CoV-2 than ethanolic extracts. Also, luteolin inhibitory effect against Mpro/3CLpro, PLpro, and ACE-II was comparable to Camostat mesylate and remdesivir. In addition, Caffeic acid phenethyl ester inhibited TMPRSS2, ACE-II, and Mpro²¹⁹.

Earlier viral clearance, symptom recovery, discharge from the hospital as well as less decreased mortality was observed in hospitalized COVID-19 patients receiving green Brazilian propolis or a combination of honey and *Nigella sativa*, than counterparts receiving standard care alone¹⁹⁷.

Onion (*Allium Cepa*)

Onion extracts were effective in decreasing infection of the New Castle Disease virus by blocking the attachment of the virus with the cell²²⁰. In Quranic verses in the Book of God, the Almighty said: And (remember) when you said, "O Musa (Moses)! We cannot endure one kind of food. So invoke your Lord for us to bring forth for us of what the earth grows, its herbs, its cucumbers, its Fum (wheat or garlic), its lentils and its onions".

Onion and garlic are, therefore, important plants which could be used as an alternative treatment for viral infection and for the prevention of severe disease development²²¹.

Molecular docking study of inhibition of the main protease of COVID-19 by natural compounds found in *Allium sativum* and *Allium cepa* was used to propose that natural compounds from garlic and onion can be used as potent inhibitors against the main protease of COVID-19, which could be helpful in combating the COVID-19 pandemic²²².

Molecular docking was used to evaluate phytoconstituents from *Allium cepa* as COVID-19 M-pro inhibitor, compared to remdesivir (standard drug). The most potential compound was oleanolic acid. Oleanolic acid with a docking score of -9.20kcal/mol was reported as anti-COVID-19 activity. This docking score was higher than remdesivir. Oleanolic acid interacted with GLU166, CYS44, HIS41, and THR25 via the hydrogen bond. Oleanolic acid interact with CASP-9, XIAP, CASP-

3 signalling pathway. This docking score was higher than remdesivir. Oleanolic acid interacted with GLU166, CYS44, HIS41 and THR25 via the hydrogen bond²²³.

The American Academy of Allergology on inhibitory effects of onions on human allergen-induced late phase inflammatory reactions and bronchial asthma: In double blind studies it was observed a marked reduction inflammatory response to intradermal injection of anti-human IgE-antibodies by 45% ethanolic onion extracts. The extract and control solutions have been applied topically one hour prior to the injection under occlusion. In addition, in an open study with two patients suffering from allergic bronchial asthma the inhibitory effects was pronounced after oral ingestion of 200ml 5% ethanolic extract of 200g raw onions²²⁴.

The beneficial effect of onion active ingredients may be mediated through impairment of mediator systems such as corticosteroids, as well as through their pronounced antithrombotic and platelet activation hindering properties, which was found in numerous *in vivo* and *in vitro* models²²⁵.

The components of *Allium cepa* include Quercetin 3-glucoside, Quercetin 7, 4-diglucoside, Kaempferol-3-O-rutinside, Quercetin 3, 7, 4-triglucoside, Quercetin, Quercetin 3, 4- diglucoside, Isorhamnetin 4-glucoside, Isohamnetin 3, 4- diglucoside, Quercetin-4-glucoside. Rutin, Luteolin, Isorhamnetin, Apigenin are *Allium cepa* isolates inhibit SAR-CoV-2 viral replicating protease; Chymotrypsin-like main protease (3CLpro) together with PLpro. In addition, to the inhibition of RNA-dependent RNA polymerase (RdRp). Onion constituents target all the viral proteins by exhibiting good binding affinity and thus could serve as ideal inhibitors for SARS-CoV-2²²⁶. Twelve compounds of *Allium cepa* screened *in silico* for their binding affinities to 3C-like protease of SARS and SARS-CoV-2, and the human receptor for SARS and SARSCoV-2, the angiotensin converting enzyme-2 or ACE-2, the compounds showed in molecular docking studies high predicted binding energies for all three

proteins compared to the rest of the phytochemicals. Furthermore, the same compounds showed similar binding affinities to the 3C-like proteases of SARS and SARSCoV-2. In addition, the high binding energies of these twelve phytochemicals to ACE-2 were proven. Binding of these phytochemicals (Cyanidin, Leucocyanidin, Leucodelphinidin, (2S)-Dihydrotricetin, Ampelopsin A, Aromadendrin, Oleanolic acid, Pelargonidin, Quercetin 3 ,4'-diglucoside, Quercetin 4-O-beta-glucoside, Taxifolin, and Tricetin) to ACE-2 blocks the viral entry into the cell and also has the advantage of stopping the formation of non-structural proteins even if the virus has entered the cell²²⁷.

Garlic (*Allium sativum*)

Garlic (*Allium sativum*) is an aromatic herbaceous annual spice with several therapeutic activities. Garlic considered one of the efficient antibiotics against wide spectrum of viruses and bacteria. Organosulfur (e.g. allicin and alliin) and flavonoid (e.g. quercetin) compounds are responsible for immunomodulatory effects of garlic. Phytochemicals present in garlic provides substantial immunomodulatory, anti-inflammatory, anticancer, antitumor, antidiabetic, antiatherosclerotic, and cardioprotective properties²²⁸.

Garlic extracts has antiviral effect against influenza A and B, rhinovirus, HIV, herpes simplex virus 1, human cytomegalovirus (HCMV), herpes simplex type 1 and 2 herpes simplex virus 2, parainfluenza virus type 3, viral pneumonia, rotavirus, vaccinia virus, and vesicular stomatitis virus²²⁹⁻²³⁴. Garlic antiviral activity may be due to allicin, organosulfur compound. Allicin shows antiviral activity through prevention of several thiol enzymes. Diallyl trisulfide and ajoene have also been shown to be active. Ajoene inhibit the integrin dependent processes in HIV infection. Allyl alcohol and diallyl disulfide have also been shown to be effective against HIV-infection^{235,236}.

The potential of effective natural compounds from garlic against the main protease of COVID-19 in comparison to proposed drug hydroxychloroquine was estimated. It has been observed that alliin

showed the best binding efficacy against COVID-19 main proteases²³⁷.

Garlic constituents have been observed to block the formation of protein and genetic material in the virus²³⁸. Garlic possesses high anti-viral properties against influenza A and B viral infections²³⁹. Likewise, garlic is effective against cytomegalovirus, rhinovirus, HIV, herpes simplex virus 1, herpes simplex virus 2, viral pneumonia, and rotavirus. Also, it significantly minimizes the occurrence of the common cold virus²⁴⁰. Allicin, diallyl trisulfide, and ajoene are the main chemicals that impart anti-viral properties to garlic^{241,234}. It was observed that these chemicals affected the oxidative stress response mechanism²³⁵.

Out of 7 best compounds, S-Allylcysteine sulfoxide (Alliin) has shown the lowest compound binding energy (-5.24Kcal/mole) and two hydrogen bond interactions with GLU290 and LYS5 residues. Furthermore, we have also compared our natural compounds with proposed drug molecule hydroxychloroquine and found that it shows lower binding efficacy in comparison to our best-selected compound alliin with a binding energy of -3.61Kcal/mole. Therefore, we suggested that alliin alone or in combination with a currently used therapeutic drug could be considered as a potential anti-viral agent with minimal side effects in the prevention of COVID-19. These findings are in support of previously reported studies that suggested the inhibitory role of natural compounds against major protease of COVID-19 via in silico based methods.

Garlic compounds mediated virucidal effects through disruption of the viral envelope and inhibition of viral replication^{242,243}. Additionally, experiments in pigs showed an immune-enhancing effect of garlic to prevent viral infections by increasing CD8+ T- and B-cells, antiinflammatory cytokines and antibody titres²³⁴. The various anti-inflammatory and immunomodulatory effects of garlic compounds to improve innate and adaptive immunity are summarized in a recent review²⁴⁴.

The antiviral activity of allicin against SARS-CoV-2 in infected lung cells (Vero E6 and Calu-3) were

proven. Allicin efficiently inhibited viral replication and infectivity in both cell lines. By determining decreased levels of viral RNA and infectious viral particles, the antiviral effect of allicin against SARS-CoV-2 was demonstrated in both cell lines²⁴⁵.

The organosulfur compounds represent 99.4% contents of the garlic essential oil; have strong interactions with the amino acids of the ACE2 protein and the main protease PDB6LU7 of SARS-CoV2. Allyl disulfide and allyl trisulfide, which account for the highest content in the garlic essential oil (51.3%) showed the strongest anti-coronavirus activity. Interestingly, docking results indicate the synergistic interactions of the organosulfur substances, which exhibit good inhibition of the ACE2 and PDB6LU7 proteins²⁴⁶.

Allicin suppresses the inflammation via inhibiting the TNF- α induced expression levels of IL-1 β , IL-8, IP-10, and IFN- γ and also through suppression of degradation of NF- κ B inhibitory protein I κ B in intestinal epithelial cells. Some of the garlic compounds that show viricidal activity are ajoene, allicin, allyl, methyl thiosulfinate and methyl allyl thiosulfinate^{247,248}.

The antiviral effects of Allicin may have an impact on COVID19 through two mechanisms indirect and direct one. The indirect one is through Angiotensin-converting enzyme-2 (ACE2) protein inhibition as SARS-CoV-2 encodes spike S protein containing receptor binding domain (RBD) that binds to the human angiotensin-converting enzyme-2 (ACE2), and promotes membrane fusion and uptakes of the virus into human cells such as the lung by endocytosis²⁴⁵.

Lipid bilayers do not constitute a barrier for allicin penetration and its diffusion through the lipid bilayer does not cause membrane leakage, fusion or aggregation²⁴⁹. As Allicin vapors naturally from the crushed garlic into surrounding air. Allicin vapors inhaled into lungs' alveoli pass alveoli membranes and exert its biological activities intracellularly. Allicin affects the processing of DNA, RNA synthesis, signal transduction and apoptosis²⁵⁰. The inhibitory effect of garlic extract on Infectious

bronchitis virus (IBV) which is a coronavirus in the chicken's embryo was reported by²⁵¹. This research adds to expected anti-coronavirus activity of allicin. The antiviral effect of garlic is explained by in part to direct antiviral effects and in part to immune system stimulation as it enhanced NK-cell (Natural killer-cell) activity that destroys virus-infected cells²⁵². Also it was reported that garlic extract exhibited in vitro activity against influenza A and B²⁵³, cytomegalo virus^{240,231}, rhinovirus, HIV, herpes simplex virus 1²⁵⁴, herpes simplex virus 2²³², viral pneumonia, and rotavirus. Allicin and its secondary products; diallyl trisulfide and ajoene all have been

Shown to have biological activities^{255,234}, Allicin is thought to be the major compounds responsible for the antimicrobial effect of garlic as it inhibit RNA polymerase which is necessary for viral replication²⁴². Ajoene one of the secondary compounds of Allicin has a direct antiviral activity²³³. Allicin can kill bacteria²⁵⁴. This adds to the benefits of Allicin to prevent secondary bacterial infection associated with COVID-19 patients.

Inhalation of raw freshly crushed garlic give virucidal activity and can reduce infection load, prevent infection and or may be of a value for significant treatment²⁵⁵.

Some researchers revealed that the preventive action of *Allium sativum* against various viruses like influenza B, human rhinovirus type 2, human cytomegalovirus (HCMV), Parainfluenza virus type 3, herpes simplex type 1 and 2, vaccinia virus, and vesicular stomatitis virus²⁵⁶. Chemical constituents isolated from *Allium sativum* can inhibit adhesive interaction and fusion of leukocytes which leads by enhancement of natural killer cell (NK cell) activity which destroys the infected virus cells²³³. Many reviews suggested that allicin and S-allylcystein were found in *Allium sativum* inhibit the ACE receptor through the production of Hydrogen Sulfide (H₂S) and stimulation of Nitric Oxide (NO), with blockage of α adrenergic receptors and calcium channels²⁵⁷. Some studies suggested that extracts of *Allium sativum* can prevent from influenza A

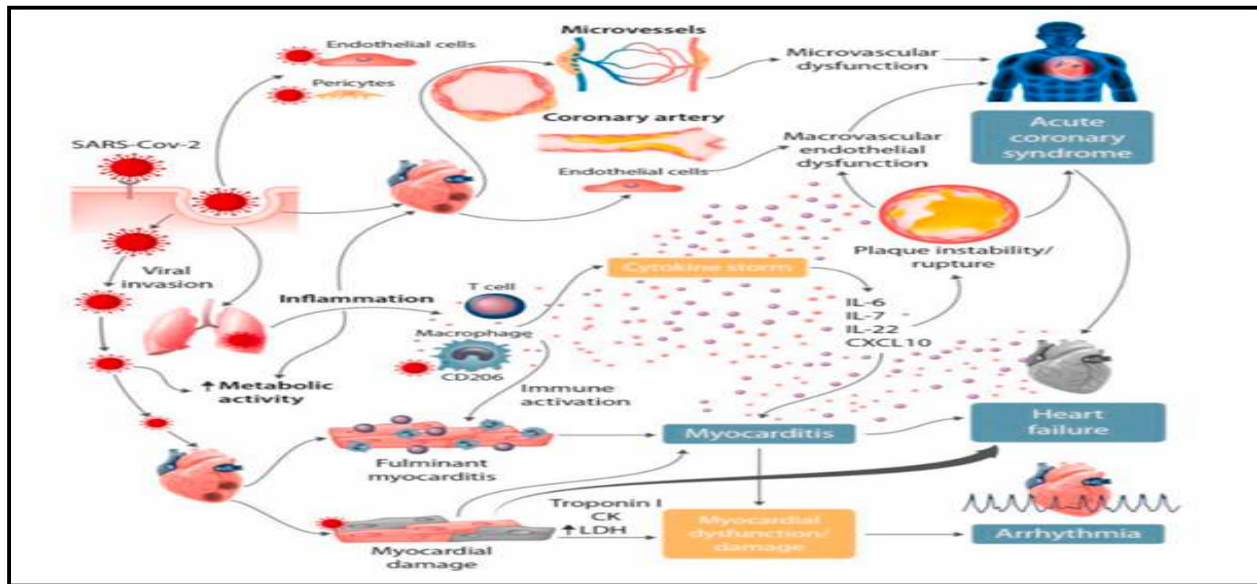
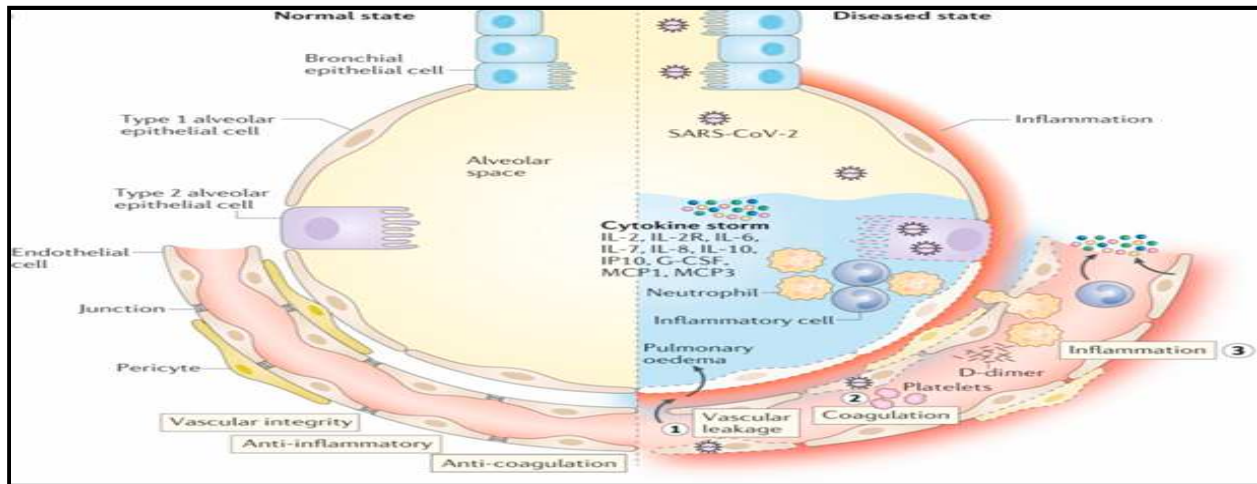
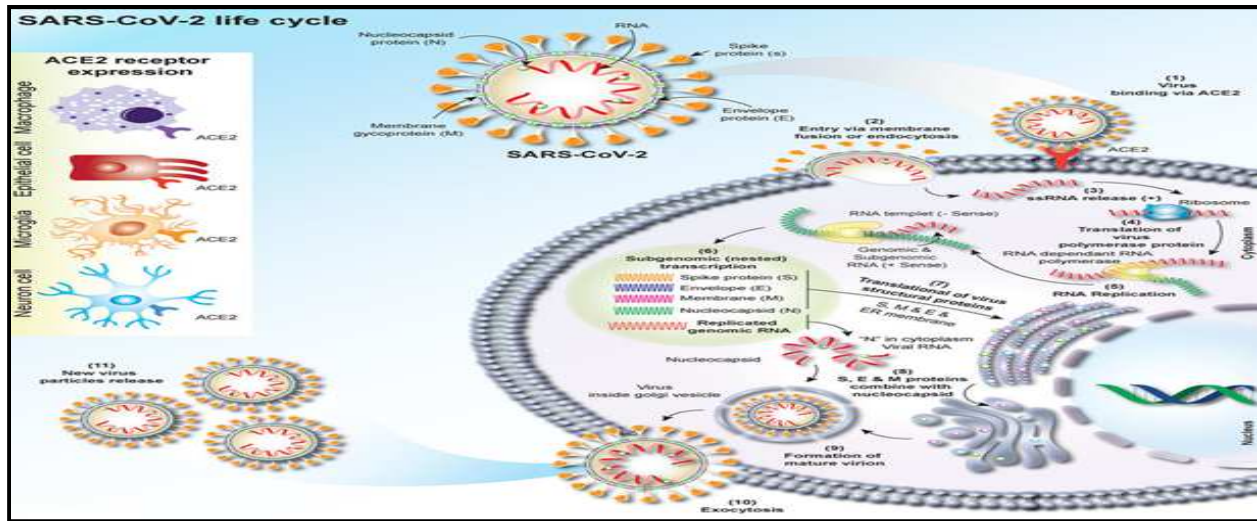
(H1N1) virus by inhibiting the nucleoprotein synthesis of virus and polymerase Activity²⁵⁸.

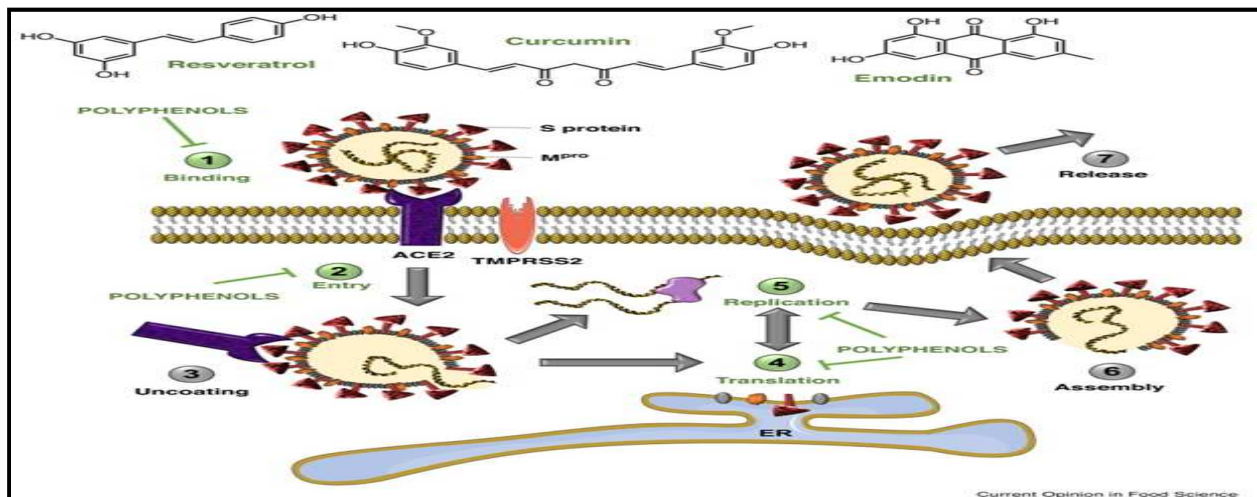
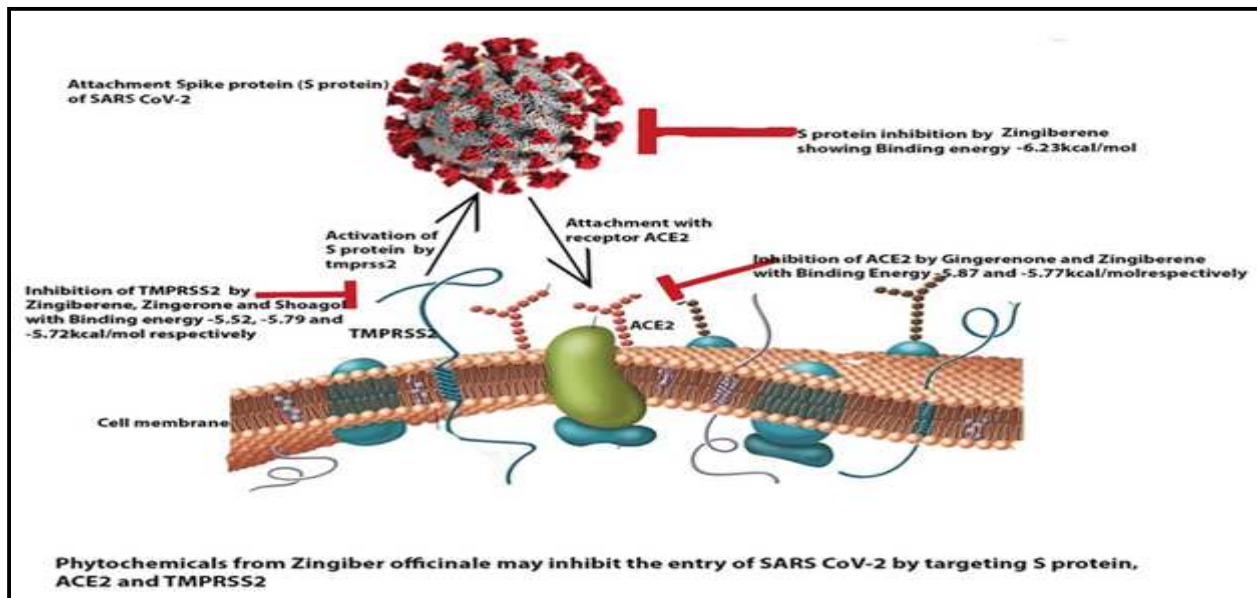
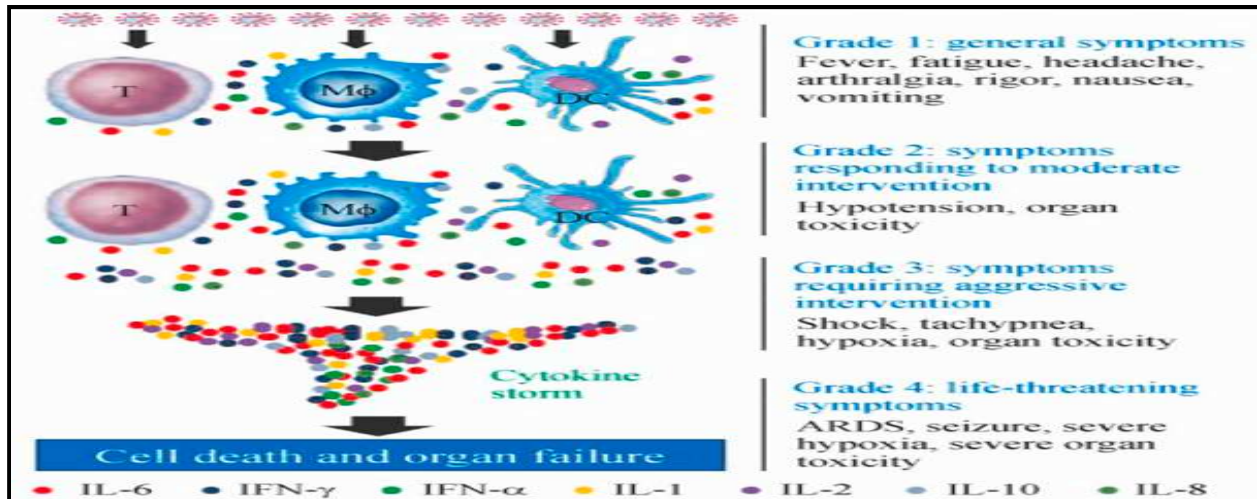
In silico approach on the inhibitory effect of garlic against SARS-CoV-2, seven products of alliin, S-(allyl/ methyl/ ethyl/propyl)-cysteine, S-propyl L-cysteine, and S-allylmercapto-cysteine were considered as possible constitutes to inhibit the Mpro of SARS-CoV-2 through H-bonds with this protease enzyme. Molecular docking analysis showed that alliin among the other seven compounds has higher antiviral potential to prevent COVID-19. This bioactive component alone or in combination with the main therapeutic drug would be an efficient therapy to eradicate SARS-CoV-2 with the lowest side effects and toxicity^{259,260}.

Lentil Lens culinaris

Lentil lectin consequent from *Lens culinaris* showed the most potent and broad antiviral activity with very weak haemagglutination activity and no cytotoxicity. Lentil lectin possess anti-SARS-CoV-2 activity against a panel of SARS-CoV-2 mutant strains and epidemic variants. The lentil lectin also exhibit antiviral activity against SARS-CoV and MERS-CoV. In addition it was found that lentil lectin inhibits SARS-CoV-2 in the early steps of infection, and could efficiently block the ACE2-S trimer binding²⁶¹.

Lentil contains a large number of phytochemicals (primarily belonging to the flavonoid group of compounds but also phytosterols), which show high binding affinities to the SARS-CoV-2 3C-like protease²⁶².





CONCLUSION

Plants and food products are rich sources of various content and secondary metabolites. These substances have been used as an effective antiviral agent and for treating other diseases as well. In molecular docking studies was found that, some nutraceuticals have shown highest affinity to Mpro and 3CLpro part of SARS-CoV-2 which are essentially required for virus replication and found promising future drugs against COVID-19. Apart from antiviral properties these bioactive compounds found to interfere and modulate various signalling pathways and possess various properties such anti-inflammatory, anti-modulatory, antithrombotic and anti-oxidant properties. These compounds were known to control the cytokine storm which is observed during various viral infection and other diseases. Hence Plants and food products should be a part of our daily diet to harness the potential health benefits and to boost the immunity against COVID-19. With all these proven scientific evidences of antiviral, potential health benefits and their general safety, these compounds can be considered for future pharmaceutical developments against SARS-CoV-2 or other viral diseases.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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