International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1191-1204 www.ijprajournal.com ISSN: 2456-4494

# Natural Agents Used In the Treatment of Corona Virus (Covid -2019)

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Submitted: 01-08-2022 Accepted: 07-08-2022

**ABSTRACT**
Covid-19 is an infectious pandemic that recently infected more than two hundred countries in the world. Covid-19 has become a global pandemic in a shortperiod, which is spreading quickly among the world wide with large variety of genetical transformation. Many potential treatments have been introduced, which include different types of Vaccines, antiviral drugs and herbal compounds. Large number of vaccines has been developed by many countries but it has a major disadvantage that the mutant forms of Covid-19 viruses are less susceptible and also reported many ADRs like pain at the injection site, fever, fatigue, headache, muscle pain, chills and diarrhea. A variety of bioactive compounds from natural agents are shown to be effective against Covid-19 and the usage of natural remedies may increase the patient compliance with low sideeffects among the people. Food and Drug Administration (FDA) has approved numerous natural agents which are commercially available. In this study, a comparisive review is done on the potential effect of various natural compounds used against Covid-19 virus.

**KEYWORDS:** Corona virus, natural agents, antiviral, SARS-CoV-2

## I. INTRODUCTION

On 31 December 2019, several cases of pneumonia were re-ported in Wuhan the epicenter of the outbreak in Hubei provine of China. The novel coronavirus was identified as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) which causes Covid-19 pandemic [1,2]. From the time of emergence until, present, Covid-19 has spread worldwide in which a total of over 71 million confirmed cases with over 1.6 million death tolls has been reported by the World Health Organisation (WHO). Asymptomatic patients and patients with mild symptoms can be recovered under home care and isolation while patients with severe complications including acute respiratory distress syndrome (ARDS) require intensive care unit (ICU) which involves oxygen therapy [3]. Currently, there is scant evidence from clinical trials for WHOto approve any standard drugs or vaccines as several trials have failed due to efficacy and safety concerns [4]. Natural compounds from plant and fungi sources have been recognized in their antiviral properties with numerous mechanisms to prevent infection and strengthen host immunity [5,6]. Herein, we reviewed potential anti-viral compounds with multiple targets of action relating to coronaviruses including inhibiting of viral entry, replication and release, and compounds targeting renin angiotensin aldosterone system (RAAS) which exhibit promising effects against the disease.

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Coronaviruses are the infectious agents of respiratory tract infections but can also affect the digestive tract and systemically infect both humans and animals. Coronaviruses are singlestranded RNA viruses, which are highly diverse and first reported in 1960. Primarily, Coronavirus strains reside in bats and wild birds and can spread to other living beings. The virus that causes COVID-19 is believed to have originated in bats and then spread to humans, possibly through snakes and pangolins, perhaps by contamination of meat from wild animals and seafood, in meat and seafood markets in China. At present, about 210 countries and territories around the world are affected by COVID-19. Notably, China, the USA, the UK, Spain, France, and Italy are the most severed because of COVID-19. Common symptoms of COVID-19 include fever, cough, shortness of breath, and diarrhea, but in severe cases, it may cause pneumonia and/or even death. The incubation period may be 14 days or even longer; the disease may still be infectious up to this latent period and can spread from one person to another via respiratory droplets, close contact, and also via the fomites.

**SARS – CoV - 2**

SARS-CoV-2 is a positive-sense, single-stranded RNA beta coronavirus with 28,882 base pairs genome that encodes viral proteins in up to 14 open reading frames . There are four major viral structural proteins: Spike (S), Envelope (E), Membrane (M), and Nucleocapsid (N). Structural proteins of SARS-CoV-2 form the viral capsid that encapsulates the genome and also facilitates the entry process to human cells through the ACE-2 receptor. Usually, viral diseases are difficult to control and have a more comprehensive public health impact, so viral pathogens like HIV, human influenza, SARS, chikungunya, Ebola, Zika have received more attention and have threatened modern healthcare and pharmaceutical sectors. Till now, there are no absolute therapies for COVID-19, but preventive and supportive therapies are employed to control further complications and organ damage. Based on the information available key regions of new drug targets are RNA-dependent RNA polymerase (RdRP) of the virus, cell membrane receptors of SARSCoV-2 (ACE-2), and spike proteins (S protein). The antiviral mechanism of plant extracts varies as per the structure and replication process of the viruses. Some plants help to increase the inherent antiviral immunity of our body. It is believed that medicinal plants are the primary source of healthcare for nearly 85% of the global population and more than 40% of synthetic drugs available in pharmaceutical markets are derived from plants and microbial-based natural products. Thus, this review is focused on summarizing medicinal plants and/or herbs showing antiviral properties, which could be useful in drug discovery programs.

**NATURAL AGENTS USED IN THE TREATMENT OF CORONA VIRUS DISEASE**

The natural remedy is a naturally occurring secondary metabolite extracted from living organisms such as plants, animals, fungi and bacteria having potential antiviral agents [7] . The natural remedies are remarked as virtuous sources for the development and production of antiviral agents [8,9]. Several metabolites derived from plants and animals have been recounted with antitumor, antifungal, antiinflammatory and antiviral properties [10]. In Asian countries, herbal plant treatment has been conventionally used for many pharmaceutical purposes[11].

Many studies reported on plants based natural products as alleged remedies for viral infection [12] .

In Asia, conventional remedies based upon natural resources namely garlic, cardamom, liquorice, pepper, turmeric and tragacanth have been alleged for an effective cure against coronavirus diseases. Among these conventional remedies, curcumin, a secondary metabolite derived from turmeric, is more conspicuous and widely reported for potential COVID-19 treatment due to stronger interaction with protease enzyme as compared to other naturalcompounds (i.e. pepper, tragacanth).

❖ **LEAF USED IN THE TREATMENT OF CORONA VIRUS DISEASE**

**1. Acacia arabica (Leguminoseae)**

Acacia arabica is also known as gum arabic tree. It has many medicinal roles in Ayurvedaand is used in the management of several health diseases, for instance, asthma, inflammation, cough and flu. Ghoke et al. (2018) evaluated the antiviral activity of the leaves extract of Acacia arabica against the Influenza A virus subtype H9N2 (H9N2) using in ovo model in three different experimental procedures that is, virucidal, prophylactic, and therapeutic [13] . The most suitable nontoxic dose of each extract of this compound was evaluated using viral load along with haemagglutination level and real-time PCR (polymerase chain reaction). The study reportedthat

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its polyphenolic content and crude extract expressed promising antiviral activities against viral infections.

## 2. Ocimum tenuiflorum (Lamiaceae)

Ocimum tenuiflorum is widely distributed in India and its medicinal roles have been mentioned in Indian Ayurveda (Wealth of India, 1991). There are different parts of Ocimum tenuiflorum used for the treatment of several ailments like asthma, bronchitis, cough, cold, and digestive disorders (Ghosh, 1995) [14]. An in silico study concluded the potential role of Ocimum tenuiflorum extracts in inhibition of ACE-2 (angiotensin-converting enzyme -2) receptor of SARS-CoV-2. Out of different extracts, crude extract and terpenoid extract of Ocimum tenuiflorum exhibited a significant reduction in copy numbers of viruses genome at the lowest dose tested. The crude and terpenoid extract prepared from the Ocimum tenuiflorum leaves had strong antiviral potency against the H9N2 virus [15]. Alhazmi (2015) evaluated the antiviral properties of all phytocompounds isolated from Ocimum tenuiflorum plant using a protein of H1N1 strain under in silico study. The study reported that Apigenin has good binding properties in comparison to Oseltamivir and Zanamivir. Therefore, this compound needs further investigation under in vitro as well as in vivo conditions.

Intraperitoneal administration of seed oil extract from Ocimum tenuiflorum at the dose of 3ml/kg in sensitized rats exhibited significant augmentation of antibody titer and reduction in the release of histamines from peritoneal mast cells and also inhibited the migration of leukocyte Aqueous extract of Ocimum tenuiflorum showed significant immunomodulatory potential by increasing the lymphocytes and neutrophils population. It also augmented the phagocytic index as well as phagocytic activity .

## 3. Aloe vera (Xanthorrhoeaceae)

Traditionally, Aloe vera acts as an antioxidant, antibacterial [16] and antiviral. The activity of ethanol extract of Aloe vera was evaluated against influenza A virus in Madin Darby canine kidney (MDCK) cells. The extract significantly inhibited autophagy induced by the viral strain [17]. C. T. Huang et al. (2019) assessed the antiviral efficacy of Aloin (Aloe vera derivative) against Influenza A virus subtype H1N1 (H1N1) in MDCK cells. Aloin significantly decreased viral infections. Also, when H1N1 induced mice were treated with Aloin, the viral load and mortality significantly decreased. These results supported the application of the derivative in clinical use.

Neuraminidase (NA) is an enzyme that hydrolyses sialic acid residue of viruses and receptors of the host. It also helps in virus movement and plays an important role in escaping viruses from the host cell after replication. Aloin inhibited the NA, which further leads to immune suppression, and inhibition of virus replication. Aloin increased the immunity along with an increased hemagglutinin specific T-cell response to the infection . Aloe vera aqueous gel extract from leaves showed a significant immunomodulatory effect by increasing the cell viability of infected macrophages [18].

## 4. Azadirachta indica (Meliaceae)

The neem tree botanically referred to as Azadirachta indica is a fast-growing evergreen herb belonging to the family Meliaceae. The Indian origin traditional medicinal plant neem has been used to treat several acute and chronic diseases in different parts of Asia and Africa from the ancient period. All parts of the neem tree such as seeds, roots, leaves, flowers, and bark have been used in traditional medicine as household remedies against various human ailments. They exhibit insecticidal, antimicrobial, larvicidal, antimalarial, antibacterial, antiviral, and spermicidal effects [19] .

Different terpenoids isolated from the bark of this herb include nimbin, nimbidin, nimbolide, limonoids, β-sistosterol, 6-desacetylnimbinene, nimbione, margocin, quercetin, and so on. A compound from the extract of neem leaves called “hyperoside” possesses showed potential as a universal drug against influenza strains due to its free radical scavenging property. Hyperoside compound from neem leaf extract along with the chemical drugs LGH, Naproxen, BMS-885838, and BMS-883559 showed best results with conserved residues of nucleoprotein of influenza virus. The neem is an extraordinary plant and United Nations has declared neem as the “tree of the 21st century” (United Nations Environment Programme, 2012).

Due to its already proven antiviral properties and effectiveness, many scientists have started research on neem for discovering drugs against SARS-COV-2. Natural bioactive compounds, namely, methyl eugenol, oleanolic acid, and ursolic acid extracted from tulsi and neem act as inhibitors against SARS-CoV-2. These

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bioactive compounds function as effective inhibitors of SARS-CoV-2 by binding to the spike glycoprotein, RNA polymerase, and/or its protease which results in the prevention of both viral attachment and replication. Approximately 20 compounds isolated from neem leaves extract showed high binding affinity against COVID-19 main protease protein which is the key protein for viral replication . Muralikumar, Ramakrishnamacharya, and Seshachalam (2020) screened ligands from Nimba and Amrita (A. indica and T. cordifolia) known as Nimbamritam in silico to evaluate anti-SARS-CoV-2 activity. They found that the ligand interacted and inhibited the residues of spike protease or Mpro protease of SARS-CoV-2.

## ❖ BARK USED IN THE TREATMENT OF CORONA VIRUS DISEASE

### 1. Cinnamomum cassia (Lauraceae)

Traditionally, Cinnamon is used as a healthy herbal spice. It is extracted from the inner bark of a tree that belongs to Cinnamomum [20]. Fatima et al. (2016) determined the antiviral properties and characteristics of Cinnamon silver (Ag) nanoparticles against influenza virus infection in Vero cells [21]. The nanoparticles illustrated significant antiviral properties in treated groups along with a significant safety profile. This possible strategy of synthesized nanoparticles may be an option for the effective treatment of virus infections. Koh et al. (1998) determined two cinnamaldehyde derivatives that is, 20-hydroxycinnamaldehyde (HCA) and 20- benzoxy-cinnamaldehyde (BCA) from Cinnamomum cassia and evaluated their immunomodulatory effects. The study concluded that these derivatives have the potency to block the proliferation of lymphocytes and T-cells differentiation by inhibiting the signaling pathway of cell growth. Thirteen compounds were extracted from Cinnamomum cassia out of which hydroxycinnamaldehyde, methoxycinnamaldehyde, amygdalactone, eugenol, coniferaldehyde, and cinnamic alcohol were active compounds that significantly inhibited arachidonic acid-induced platelets aggregation and a thromboxane A2 induced aggregation in the preliminary testing [22].

### 2. Cinchona officinalis (Rubiaceae)

Cinchona trees from the Andean mountain forests have valuable benefits as a particular component of the trees contains bioactive compounds that can heal fever. This beneficial effect was first discovered by Jesuit missionaries and gradually expanded throughout the world . The bark of the trees produces quinine alkaloids,which were also an effective treatment of malaria for more than several centuries. Quinine has a mode of action that is similar to that of chloroquine, a synthetic antimalaria agent to treat malaria. Thus, it is known as a chloroquine analogue . Nowadays, quininesulphate has become one of the most wanted drugs in the society for COVID- 19 treatment. The behaviour of the people was triggered by a spontaneous reaction because of the high incidence and mortality rate of COVID-19 worldwide. This section will explain the potential of quinine to act as an antiviral agent and function as an immunomodulator in a disease caused by a virus. Further explanation will also discuss the potentially harmful effects of quinine in individuals with or without COVID-19.Quinine became popular because its effect was similar to chloroquine, an antimalarial drug. Eventually, there were shifts from malarial drug use as antimalarial drugs to their use as potent inhibitors for viral infection.A large amount of data suggested that several antimalarial drugs had been investigated and then concluded that they had some advantages against viral infection. For example, chloroquine showed an antiviral effect against the SARS-CoV infection . A clinical trial proved that hydroxychloroquine improves the SARS-CoV-2 viral load in COVID-19 patients when combined with azithromycin.

From this evidence, quinine as a chloroquine analogue might be predicted to have beneficial effects in eliminating the COVID-19 . The first investigation of the quinine effect as an antiinfluenza virus infection was conducted by Seeleretal. A recent study invariably mentioned that the proposed antiviral mechanism of quinine is indirectly killing off viruses. Previous research investigated the effect of quinine sulphate on dengue virus-infected cells. As the relative similarity of dengue virus and SARS-CoV-2 structures, it may be possible that SARS-CoV-2 uses some relative methods to infect the cell and trigger cytokines to combating the virus . The host cells infected by viruses will initiate the release of viral RNA and interfere with normal protein synthesis. However, an expression of a pathogen recognition receptor(PRR) known as RIG-I in the infected host cell increases minimally to promote the IFN-I signalling pathway rather than to elevate gene expression of IFN-stimulated genes (RNase L, PKR) that inhibit the synthesis of the

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Volume 7, Issue 4 July-Aug 2022, pp: 1191-1204 www.ijprajournal.com ISSN: 2456-4494

protein, thereby blocking viral replication . The RNase L pathway can eliminate ssRNA in virus infected cells, while PKR blocks the translation and aff ect signal transduction . The target of quinine action is the inhibition of genome replication and translation of infected host cells and increased expression of RIG-I and IFN-α. It has been proven that IFN-α is the cytokine secreted by host cells to fight the viruses . CSS mentioned earlier does not seem to appear after quinine administration in COVID-19 since the available data show that the release of TNF-α, the most important cytokine in determining the severity of COVID-19 symptoms, is inhibited by quinine. Because quinine blocks the expression of TNF-α at the mRNA transcription level, analysed by northern blot, it will alleviate an inflammatory reaction in microbe-infected individuals rather than promoting the process of inflammation . Although the extract of the cinchona tree might not directly lead to CSS, a systematic review reported by Liles et al. showed that there is a couple of general adverse reactions caused by quinine, such as immune-mediated reactions and toxic reactions. The documented damage involves organ systems including haematologic manifestations: thrombocytopenia and haemolytic anaemia; dermatologic manifestations: photosensitive eczema; systemic reactions: hypotension and anaphylaxis; cardiac manifestations: chest pain and pericarditis; liver toxicity: elevated serum transaminase; kidney manifestations: thrombotic microangiopathy, nephritis, and acute kidney injury. Quinine is rarely categorised as an immunomodulatory agent, but it has immunostimulant and immunosuppressant activities against viral infections. When quinine eff ectively intensifies the production of the well-known cytokine IFNα, it functions as an immunostimulator to inhibit viruses. Otherwise, quinine inhibits the release of TNF-α and has an immunosuppressant eff ect. These two diff erent activities may have a beneficial eff ect on people who are infectedwith COVID-19. However, routine consumption of this herbal medicine by healthy people to prevent COVID-19 is not recommended because of the possibility that it may lead to various harmful events.

### ❖ ROOT USED IN THE TREATMENT OF CORONA VIRUS DISEASE

#### 1. Glycyrrhiza glabra (Leguminosae)

Glycyrrhiza glabra, locally known as “liquorice” and “mulaithi,” is found mainly in the Punjab and Sub-Himalayan regions of India[23]. This herb is employed abundantly in traditional Indian medicine as antiinflammatory and antiviral agents[24]. Glycyrrhizin extracted from Glycyrrhiza glabra showed potency in inhibiting adsorption, penetration, and replication of SARS-CoV in Vero cell lines. The extract exhibited the virucidal property by inhibiting the cellular signaling pathways of the virus. Moreover, glycyrrhizin and glycyrrhetinic acid, an aglycone metabolite, increased nitrous oxide expression[25]. Grienke et al. (2014) determined the antiviral efficacy of Glycyrrhiza glabra roots extract. The study used NA inhibition in chemiluminescence (CL)-based assay along with additional tests. Liang et al. (2019) evaluated 18 water-soluble β-cyclodextrin (CD)-G (Glycyrrhiza glabra conjugates) for antiviral activities in A/WSN/33 (H1N1) virus. A total of six conjugates showed potential antiviral activity when evaluated in a cytopathic effect assay. The aqueous root extract of Glycyrrhiza glabra is a potent immunomodulator.

#### 2. Withania somnifera (Solanaceae)

Withania somnifera (Ashwagandha) has several medicinal roles like antiinflammatory, antioxidant, and immunomodulatory [26].

It has an active component Withaferin A (WA) that acts as an antiviral agent. Withaferin A decreased activity of NA in H1N1 influenza. The docking and molecular dynamics simulation studies found that Withaferin A has a high binding affinity toward NA and showed several important molecular relationships with the residues that are important in the course of simulations [27]. Withania somnifera extract and Withaferin A significantly decreased the toxicity mediated by zinc oxide nanoparticles under in vivo conditions. The extracts also restored TLR6 and phagocytic activities [28]. Administration of Withania somnifera extract in mice increased the number of plaque-forming cells, circulation of antibody titer in mice spleen, and phagocytosis activity of macrophages. As a thrombolytic agent, Withaferin A increased bleeding time and inhibited aggregation of platelets, the formation of thrombus, and fibrin polymerization [29].

### ❖ RHIZOMES USED IN THE TREATMENT OF CORONA VIRUS DISEASE

#### 1. Curcuma longa (Zingeberaceae)

Turmeric is an herbal plant called rhizomatous and is also known as Curcumalonga (C.longa). It is a plant that has received much interest in the medical and scientific fields.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1191-1204 www.ijprajournal.com ISSN: 2456-4494

Turmeric also belongs to the ginger (Zingiberaceae) family and the Curcumagenus . Turmeric is mostly used as an important spice, a natural food colouring, and as food flavour. For many years, turmeric has been widely known as a medicinal plant to treat various diseases and conditions. The treatment with turmeric has been investigated in preclinical and clinical studies.

Curcumalonga has been used traditionally in Asian countries as a medicine or supplement. This medicine serves as an antioxidant, anti-inflammatory, anticancer agent and isused in the treatment for many other diseases, such as diabetes mellitus, cardiovascular disease, obesity, neurodegenerative disease, inflammatory bowel disease, allergy or asthma, and psoriasis. Curcumalonga contains carbohydrate (96.4%), protein (6.3%), fat (5.1%), mineral (3.5%), and moisture (13.1%). On the other hand, its extracts contain curcuminoids, which are curcumin (77%), demethoxycurcumin (DMC;17%) and bisdemethoxycurcumin (BDMC;3%). All these curcuminoids act medicines or supplements, especially curcumin. The most common kind of curcuminoid that is used as a medication is curcumin.

Turmeric (Curcuma longa L.) belongs to the family of ginger (Zingiberaceae) and natively grows in India and Southeast Asia. Rhizomes of this plant contain several secondary metabolites including curcuminoids, sesquiterpenes, steroids, and polyphenol as major bioactive substances [30]. Curcumin is a natural polyphenol that is isolated for turmeric (Curcuma longa) and has been used from centuries as a traditional medicine in Asian countries to treat various disorders. Several studies have shown that the curcumin possesses some pharmacological properties such as anti-inflammatory, anti-angiogenic, and anti-neoplastic, without toxicity. Food Drug Administration (FDA) categorized it as "Generally Recognized as Safe." A dose of up to 12 g/day of curcumin was known to be safe for human consumption during the clinical trials without showing any side effects [31]. Shrivastava (2020) reported that the dose of curcumin from 2,500 to 8,000 mg per day for 3 months showed no toxicity from curcumin. Curcumin is a dynamic antiviral that reduces the replication of viruses.

Antiviral activity of curcumin was observed against different viruses including hepatitis viruses, SARS coronavirus, influenza viruses, human immunodeficiency virus (HIV), herpes simplex virus, dengue virus, chikungunya virus, and so on. Curcumin's antiviral activities can also be evidenced by its ability to regulate various molecular targets that contribute to various cellular events, such as transcription regulation, and the activation of cellular signaling pathways [32]. Curcumin's role in targeting various cellular pathways, further inhibiting the growth, and replication of viruses makes it an ideal candidate as an anti-viral drug. Utomo, Ikawati, and Meiyanto (2020), based on their molecular docking study, reported that the curcumin binds and inhibits the target receptors including SARS-CoV-2 protease, spike glycoprotein-RBD, and PD-ACE2, which are involved in virus infection.

**2. Zingiber officinale (Zingiberaceae)**

Ginger is one of the important medicinal plants which naturally occur in various countries. Ginger, Zingiber officinale, belongs to family Zingiberaceae and the other famous members of this plant family are turmeric, cardamom, and galangal. The plant is indigenous to Southeast Asia and is cultivated in several countries including India. Ginger (Zingiberofficinale) is known as Sunthi in Ayurveda and the description of the plant appears in the old text like Charaka, Sushruta, Vagbhatta, and Chakra-dutta [33]. Zanjabeel (Zingiberofficinale) is a famous herbal drug in the conventional Unani system of medicine [34].

Ginger is a rich source of bioactive compounds such as phenolic groups, alkaloids, and steroids, which have medicinal effect. The chief aromatic agent of the rhizome is the zingiberol with analogues such as the shogoals, paradol, and zingerone. In addition to the main bioactive compounds, ginger also contains other sub-compounds such as 4-gingerol, 6-gingerol, 8-gingerol, 10-gingerols, 6-shogaols, and 14-shogaols [35]. They are reported to demonstrate antiemetic, antipyretic, analgesic, antiarthritic, and anti-inflammatory activities.

It has been proven by many studies that the ginger and its bioactive compounds showed effective antiviral activity against SARS-CoV-2, Influenza virus, Herpes simplex virus, Human respiratory syncytial virus, Chikungunya virus, and so on . Antiviral activity of lyophilized juice extracted from Zingiber officinale has been studied on the hepatitis C virus at varying concentrations from 5–200 μg/mL. They found that 100 μg/mL dose was effective, which inhibits virus replication that was monitored by amplification of viral RNA segments.

Ahkam et al. (2020) studied the potential

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Volume 7, Issue 4 July-Aug 2022, pp: 1191-1204 www.ijprajournal.com ISSN: 2456-4494

of a few bioactive compounds, namely, gingerenone A, gingerol, geraniol, shogaol, zingiberene, zingiberenol, and zingerone from Ginger as anti-SARS-CoV-2 for their interaction to spike and main protease (Mpro) protein based on molecular docking study. They found that the bioactive compounds of ginger block the spike (S) protein from binding to the ACE2 receptor or act as an inhibitor for MPro. The S protein is responsible for SARS-CoV-2 entry during the infection which binds with angiotensin-converting enzyme 2 (ACE2) receptor from the host cell to generate an appropriate environment for viral replication [36]. Main Protease (MPro) is accountable for processing the poly-proteins pp1a and pp1ab during viral replication [37].

## ❖ SEEDS USED IN THE TREATMENT OF CORONA VIRUS DISEASE

### 1. Syzygium aromaticum ( Myrtaceae )

Clove (Syzygiumaromaticum), belonging to the family Myrtaceae, is globally used in medicine as an antiseptic against contagious diseases due to the antimicrobial activities against oral bacteria. Clove is also used in the food industry due to its antimicrobial activities for increasing shelf-life. FDA has confirmed the safety of clove buds, clove oil, eugenol, and oleoresins as a food supplement [38]. The WHO has given the acceptable daily uptake of clove in humans is 2.5 mg/kg body weight [39].

Clove has main phenolic compounds such as flavonoids, hidroxicinamic acids, hidroxibenzoic acids, and hidroxiphenylpropens. The main bioactive component of clove is eugenol. Eugenol exhibits broad antimicrobial activities against both Gram-positive, Gram-negative, and acid-fact bacteria, as well as fungi. Cloves are well known also for their antiemetic (relieves nausea and vomiting) and carminative properties. Eugeniin, a compound isolated from the herbal extracts of S. aromaticum, and Geum japonicum, was identified as anti-Herpes Simplex Virus compound at 5 µg/mL concentration. The inhibitory action of eugeniin is on the viral DNA synthesis by acting as a selective inhibitor of the HSV-1 DNA polymerase and eugenol on viral replication and reducing infection [40].

### 2. Piper nigrum (Piperaceae)

Piper is a member of family Piperaceae and famous as the king of spices due to its pungent smell. Black pepper is grown in many tropical regions like Brazil, Indonesia, and India. Piper nigrum has significant biological properties and its bioactive compounds are used medicine, preservative, and perfumery. Piperine, a dynamic alkaloid of black pepper, is widely used in the as conventional system of medicine (Ayurveda, Siddha, Unani, and Tibetan). It contains major pungent alkaloid piperine (1-peperoyl piperidine) which is known to possess many interesting pharmacological properties such as antihypertensive, anti-Alzheimer's, antidepressant, antiplatelets, anti-inflammatory, antioxidant, antipyretic, antitumor, antiasthmatic, analgesic, antimicrobial, and so on.

Priya and Saravana (2017) evaluated the antiviral activity of Piper nigrumin chloroform and methanolic extracts against vesicular stomatitis virus (an enteric virus) and human parainfluenza virus on human cell lines. They found that the anti-viral activity of Piper nigrum is higher in chloroform extract due to the presence of higher content of alkaloids. According to molecular docking based study, it has been found that piperine could inhibit methyltransferase of Dengue virus and VP35 interferon inhibitory domain of Ebola virus comparative to commercial antiviral Ribavirin [41]. Rajagopal, Byran, Jupudi, and Vadivelan (2020) in a docking based study reported that the bioactive compounds from black pepper such as piperdardiine and piperanine are considerably active against COVID-19, which can be further used for its treatment.

## ❖ BULBS USED IN THE TREATMENT OF CORONA VIRUS DISEASE

### 1. Allium sativum L. (Liliaceae)

Allium sativum L. (Garlic) family Liliaceae is originally from Asia but it is also cultivated in other countries, namely, China, North Africa (Egypt), Europe, and Mexico. It has been used as a medicinal agent from thousands of years. This plant is a bulb growing to 25– 70 cm with flowers used as a spice and flavoring agent for foods. Garlic is having high nutritive value, improves taste of food, and also helps indigestion. Garlic is having a wide range of pharmacological effects with low toxicity such as anthelmintics, anti-inflammatory, antioxidant, antifungal, and so on [42].

Allicin (diallyl-dithiosulfinate), which is produced by the garlic enzyme alliinase from the alliin, has been known for wide-antifungal and antiviral activities. The decreasing order of the compounds having virucidal activity in garlic was ajoene, allicin, allyl methyl thiosulfanate, and methyl allyl thiosulfanate [43]. Antiviral activity of

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Volume 7, Issue 4 July-Aug 2022, pp: 1191-1204 www.ijprajournal.com ISSN: 2456-4494

garlic extract has been studied against influenza virus A/H1N1 in cell culture and it was found that it inhibits the virus penetration and proliferation in cell culture [44]. The garlic extract showed inhibitory activity on infectious bronchitis virus (IBV-a coronavirus) in the chicken embryo [45].

The various parts of the plants used in the treatment of corona virus disease is listed in table 1.

| SL NO | INDIAN MEDICINAL PLANT | SOURCE | PARTSUSED | PICTURE |
|---|---|---|---|---|
| 1 | Acacia | It consist of dried gummy exudation obtained from the stem and branches of Acacia arabica wild belonging to the family leguminoseae | Leaf |  |
| 2 | Tulsi | It consist of the fresh and dried leaves of Ocimum tenuifloram belonging to the family lamiaceae | Leaf |  |
| 3 | Aloe vera | It is obtained from the dried juice of the leaves of Aloe barbadensis belonging to the family Xanthorrhoeceae | Leaf |  |

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|---|---|---|---|---|
| 4 | Neem | It consist of fresh or dried leaves and seed oil of Azadirachata indica belonging to the family Meliaceae | Leaf |  |
| 5 | Cassia | It is the dried stem bark of Cinnamomum cassia belonging to the family Lauraceae | Bark |  |
| 6 | Cinchona | It consist of the dried bark of the stem or root of Cinchona officinalis belonging to the family Rubiaceae | Bark |  |
| 7 | Liquorice | It consists of peeled and unpeeled roots,stolons,stem of Glycyrrhiza glabra belonging to the family Leguminoseae | Root |  |
| 8 | Ashwagandha | It consists of the dried roots and stem bases of Withania somnifera belonging to the family Solanaceae | Root |  |

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|---|---|---|---|---|
| 9 | Turmeric | It consists of the dried rhizome of Curcuma longa Linn. Belonging to the family Zingiberaceae | Rhizome |  |
| 10 | Ginger | It consists of the rhizomes of Zingiber officinale belonging to the family Zingeberaceae | Rhizome |  |
| 11 | Clove | It consists of the dried flower buds of Eugenia caryophyllus belongingto the family Myrtaceae | Seed |  |

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| | | | | |
|---|---|---|---|---|
| 12 | Pepper | It consists of dried unripe fruits of Pipper nigrum Linn. Belonging to the family Piperaceae | Seed |  |
| 13 | Garlic | It consists of the fresh compound bulb of Allium sativum Linn. Belonging to the family Liliaceae | Bulb |  |

## II. DISCUSSION

The coronavirus disease is highly transmittable with no effective antiviral therapy to combat the infection [46]. However, in our study, we highlighted the role of natural agents in the treatment of COVID-19. The survey has been conducted to identify the various home remedies used during COVID-19, which include many spices and herbs.

We have analyzed that cinnamon, black pepper, tulsi, and turmeric play vital role against SARS-CoV-2 (COVID-19) as well as other viral infections, which was also supported by some other recent studies. Shrivastava reported that tulsi leaves increase the level of helper T cells as well as natural killer cells, which helps fight against viral infection. Tulsi is being used for curing pain, pneumonia, diarrhea, cough, and fever of ancient times, which are the common symptoms of COVID-19 [47]. Black pepper provides relaxation from sinusitis and nasal congestion, which are the most common symptoms of COVID-19 [48]. Quercetin, a flavonoid present in black pepper, improves the body's immunity constantly due to its antiviral properties.

An important strategy could be the use of natural agents that shows potential pharmacological activity against the acute viral infections that mainly persist in the lower respiratory tract. Correspondingly, the Indian subcontinent is a huge repository of medicinal herbs that have been in use to counteract numerous virus related infections of the respiratory tract for ages. There is an unmet need for antiviral agents against COVID-19 that must be effective, safe, and cost-effective. The current review puts light on some of the important traditional Indian medicinal herbs that can be a potential antiviral agent against SARS-CoV-2.

Apart from preclinical studies, numerous traditional Indian natural agents are considered to be evaluated under clinical trials. These studies attempt to establish the safety and efficacy of traditional Indian natural agents. The potential use of these traditional Indian medicinal plants cannot be proposed for the management of mild or moderate or in critical conditions but these plant products can be used as an add-on therapy. More mechanism-based studies are required to identify the effective components of these plants that could be effective against SARS-CoV-2.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1191-1204 www.ijprajournal.com ISSN: 2456-4494

## III. CONCLUSION

In the current pandemic scenario, precautions and boosting immunity are one of the best choices to get away from COVID-19 infection. As per our study, we conclude that the uses of natural agents that may play a significant role against viral infections. We have analyzed that cinnamon, black pepper, basil, and turmeric play a vital role against SARS-CoV-2 (COVID-19) as well as other viral infections, which was also supported by some other recent studies. In India, people are using spices as well as herbs from ancient times due to their taste, antiviral, antimicrobial, antioxidant, and immunity-boosting properties. Since ages Indians are habitual of taking these natural products that have conferred immunity in the Indian population, which probably is the major cause for low mortality in India. However, the excessive use of natural agents like spices and herbs may cause various side effects, namely, acidity in the stomach, heartburn, constipation, diarrhea, ulcers in the mouth, high blood pressure, and so on. Therefore, detailed studies about the bioactive compounds present in common Indian natural agents and their effectiveness and mode of action against lethal viruses need to be explored.

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