# Role of herbal medicine for controlling coronavirus (SARS-CoV-2) disease (COVID-19)

Ravindra B. Malabadi[*1], Neelambika T. Meti[2], Raju K. Chalannavar[3]

[1*, 3]*Department of Applied Botany, Mangalore University, Mangalagangotri-574199, Mangalore, Karnataka State, India*

[2]*Plant Biotechnology Laboratory, Rajiv Gandhi Institute of IT and Biotechnology, Bharati Vidyapeeth University, Pune-Satara Road, Katraj, Pune - 411046, Maharashtra State, India*

**Corresponding author*

***Abstract:*** **This review paper highlights the use of herbal medicine in the management of the coronavirus disease COVID-19 (SARS-CoV-2) pandemic, which has caused a worldwide outbreak of respiratory illness. This is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which is zoonotic infecting both animal and human. Vaccines are the most promising solution to mitigate new viral strains. The Indian system of holistic medicine known as "*Ayurveda*" plays an important role in controling the viral disease SARS-CoV-2 and other health disorders. Dietary therapy and herbal medicine could be a complementary preventive therapy for COVID-19 (SARS-CoV-2). Plants have been used as a expression systems for the production of diagnostic reagents and pharmaceutical proteins often described as 'molecular farming. On the basis of literature survy presented, some of the plant secondary metabolites that showed prominent antiviral activity against coronaviruses SARS-CoV-2 through impeding the main machinery used in their pathogenesis and replication cycle. The *in vitro, in vivo,* and in silico investigations revealed numerous plant-derived compounds with promising anti- SARS-CoV and anti- SARS CoV-2 activity. Therefore, this review gathered all antiviral plants in a single platform to facilitate the laboratory-based research for the development of novel drug/molecular therapeutics to overcome the SARS-CoV-2 and future pandemic situations. Further detailed clinical trial experiments should be conducted for the scientific validation.**

***Keywords:*** **Coronavirus, covid-19, antiviral, herbal medicine, social distancing, vaccine'**

## I. INTRODUCTION

The SARS-CoV-2 pandemic has swept the world and poses a significant global threat to lives and livelihoods (Wu et al., 2020a, 2020b; Shi et al., 2020; V'kovski et al., 2020; Hoffmann et al., 2020; Lima et al., 2020; Yang, 2021; Shin et al., 2020). The coronavirus outbreak has been declared as a global health emergency and represents one of the greatest risks to global health, as the coronavirus has a tendency to infect a large number of human populations (Wu et al., 2020a, 2020b; Zhou et al., 2020a, 2020b; Shanmugaraj et al., 2020). Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel coronavirus responsible for an ongoing human pandemic (COVID-19) (Wu et al., 2020a, 2020b;V'kovski et al.m 2020; Hoffmann et al., 2020; Perlman and Netland, 2009; Shang et al., 2020; Masters, 2006; Li et al., 2003; Guan et al.m 2003; Dinka and Milkesa, 2020). A novel severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) causing COVID-19 pandemic in humans, recently emerged and has exported in more than 200 countries as a result of rapid spread (Shereen et al., 2020; Khan et al., 2020; V'kovski et al., 2020; Hoffmann et al., 2020; Perlman and Netland, 2009; Shang et al., 2020; Masters, 2006; Li et al., 2003; Pardi et al., 2015, 2018). The virus can infect cells of the lungs, kidneys, heart and intestine, resulting in the organ damage leading to the multiple organ dysfunction syndrome (Wu et al., 2020a, 2020b; Zhou et al., 2020a, 2020b;Cheng et al., 2007; Yang, 2021; Pardi et al., 2018). This has provoked governments across the world to introduce emergency containment and control measures (Kirkcaldy et al., 2020). During the late December of 2019, many people were diagnosed with severe pneumonia of unknown etiology and was epidemiologically linked to a local seafood market in Wuhan, Hubei Province, People's Republic of China (Wu et al., 2020a, 2020b ; Zhou et al., 2020a, 2020b;Shereen et al., 2020; Zhu et al., 2020; Lu et al., 2020;Cheng et al., 2007; Zhang et al., 2020b). These patients were found to be infected with the novel coronavirus strain, severe acute respiratory syndrome coronavirus-2 (SARSCoV- 2)(Wu et al., 2020a, 2020b). Therefore, supportive care and prevention of complications is an important management strategy to minimize the harm (Zhang et al., 2020c).

Airborne transmission, particularly *via* nascent aerosols from human atomization, is highly virulent and represents the dominant route for the transmission of covid-19 disease (Zhang et al., 2020c). Wearing of face masks in public corresponds to the most effective means to prevent inter human transmission, and this inexpensive practice, in conjunction with simultaneous social distancing, frequent hand wash with soap and hand sanitizers, extensive testing, quarantine, and contact tracing, poses the most probable fighting opportunity to stop the SARS-CoV-2 (covid-19) pandemic, prior to the development of a vaccine (Zhang et al., 2020c; Chin et al., 2020). Another problem is asymptomatic infections cannot be recognized if they are not confirmed by RT-PCR or other laboratory testing, and symptomatic cases may not be detected if they do not seek medical attention (Nishiura et al., 2020).

Coronavirus (SARS-CoV-2) outbreak has also sparked fears of affecting socio economic development leading to the worldwide financial crises and recession (Nicolaa et al., 2020; Kirkcaldy et al., 2020). Due to coronavirus (SARS-CoV-2) pandemic, social distancing, self-isolation and travel restrictions have lead to a reduced workforce across all the economic sectors and caused many jobs to be lost (Nicolaa et al., 2020). Furthermore, lockdown and social distancing measures to prevent spread of COVID-19 (SARS-CoV-2) have heightened the fears of increasing levels of domestic violence, which includes physical, emotional and sexual abuse (Nicolaa et al., 2020; Kirkcaldy et al., 2020). The impact of COVID-19 has led to the forced closing of supermarkets, street vendors, bar and restaurants and cafes resulted in the loss of jobs and financial income. In addition, the demand for respiratory ventilators has skyrocketed due to the outbreak of COVID-19 (SARS-CoV-2) (Nicolaa et al., 2020; Coronavirus, 2020a, 2020b; Kirkcaldy et al., 2020). World economy has been collapsed due to covid-19 (SARS-CoV-2) outbreak and the year 2020 is one of the worst year in the history of mankind.

*1). Coronavirus: Herbal medicine*

Herbal medicine is the use of medicinal plants for the prevention and treatment of diseases (Singh et al., 2021; Parida et al., 2020; Thota et al., 2020; Masiello et al., 2020; Weng, 2020; Malabadi and Chalannavar, 2020; Firenzuoli and Gori, 2007; Brendler et al., 2020; Nugraha et al., 2020; Dave et al., 2020). Plants have been used as a platform for the production of diagnostic reagents and pharmaceutical proteins often described as 'molecular farming (Singh et al., 2021; Islam et al., 2020; Lima et al., 2020; Chrzanowski et al., 2020; Goswami et al., 2020; Huang et al., 2020; Kumar et al., 2020; Farooq and Ngaini, 2020; Xu and Zhang, 2020; Li et al., 2020; Tutunchi et al., 2020). India is endowed with innumerable medicinal plants. India predominantly relied on plant-based medications under different domain names like Ayurveda, Siddha, Unani, etc (Parida et al., 2020; Malabadi et al., 2018; Malabadi and Chalannavar, 2020; Adhikari et al., 2020; Dave et al., 2020; Antonelli et al., 2020). Traditional medicines involving plant-based formulations have been proven successful in boosting immunity and providing tolerance to the virus infections (Fakhri et al., 2020; Malabadi et al., 2017a, 2017b, 2018; Bouchentouf and Missoum, 2020; Ganguly and Bakhshi, 2020; Derosa et al., 2020; Habtemariam et al., 2020; Dave et al., 2020).

Plant derived medicines have played a pivotal role in the health care (Zhang et al., 2020; Huang et al., 2020; Xu and Zhang, 2020; Li et al., 2020; Fakhri et al., 2020). Many of these natural products have the pharmacological or biological activity that can be exploited in pharmaceutical drug discovery and drug design (Masiello et al., 2020; Malabadi and Chalannavar, 2020; Zhang et al., 2020; Huang et al., 2020; Xu and Zhang, 2020; Li et al., 2020; Malabadi, 2008; Malabadi and Vijayakumar, 2008; Malabadi et al., 2009, 2010a, 2010b, 2011a, 2011b; Malabadi et al., 2012a, 2012b, 2012c, 2012d; Malabadi et al., 2016a, 2016c, 2016d; Malabadi et al., 2017a, 2017b; Malabadi et al.. 2018). Herbal medicines of antiviral activity are of great interest and have been widely explored (Chrzanowski et al., 2020). Plant based antiviral compounds can block or inhibit the virus replication cycle by interfering with virus attachment to cells, interfering with viral enzymes or suspending the viral genome replication (Parida et al., 2020; Adhikari et al., 2020; Islam et al., 2020b; Zhang et al., 2020; Huang et al., 2020; Xu and Zhang, 2020; Li et al., 2020 ;Malabadi et al., 2018; Islam et al., 2020; Thota et al., 2020). Plants have been used as a platform for the production of diagnostic reagents and pharmaceutical proteins for more than 30 years, an approach often described as 'molecular farming (Parida et al., 2020; Tutunchi et al., 2020; Islam et al., 2020b; Capell et al., 2020; Chrzanowski et al., 2020). Plants are also considered as natural bioreactors for pharmaceutical protein due to their safety, low cost, high output, simple storage requirement, and benefits of eukaryotic posttranslational modifications (Mahmood et al., 2021; Malabadi, 2008; Malabadi et al., 2010b, 2011a; Malabadi et al., 2016a, 2017a, 2017b, 2018).

Antigen preparation also plays a crucial role in the development of a diagnostic test, and plants represent an ideal biofactory system (Malabadi, 2008; Malabadi et al., 2010b, 2011a; Malabadi et al., 2016a, 2017a, 2017b, 2018). Plant production platforms are being used to generate the vaccines and antiviral proteins inexpensively at mass scale. Phytodrugs also played an important role as antiviral compounds and inhibited SARS-Cov-2 activity (Thota et al., 2020; Chrzanowski et al., 2020; Ahmad et al., 2020; Upadhyay et al., 2020; Bahrami et al., 2020; Oladele et al., 2020; Weng, 2020; Kanjanasirirat et al., 2020; Alrasheid et al., 2021; Mahmood et al., 2021; Hossain et al., 2020; Machado-de-Abreu et al., 2020; Akindele et al., 2020; Yonesi and Rezazadeh, 2020; Khan et al., 2020; Khan and Al-Balushi, 2020; Zaman et al., 2020; Antonelli et al., 2020; Islam et al., 2020b; Brendler et al., 2020; Singh et al., 2021). Plant-based vaccines are safe, economical, exhibited immunogenicity, and protection against different viral infectious diseases (Malabadi, 2008; Malabadi et al., 2010b; Malabadi et al., 2011a, 2016a, 2017a, 2017b, 2018; Mahmood et al., 2021; Singh et al., 2021).

This review paper highlights the list of potential medicinal plants used as immunity booster, antiviral plant extracts, and as a viral growth inhibitors during current outbreak of coronavirus (SARS-CoV-2) disease (covid-19) based on the ethnobotanical studies, animal studies, *in vitro* experiments and animal clinical trial experiments. *Ayurveda* has enough potential and possibilities to be employed both for prevention and treatment of COVID-19 (SARS-CoV-2). On the basis of this preliminary literature survey reported, there is a ray of hope for the potential development of a new herbal medicine drugs against coronavirus (SARS-CoV-2) could be developed. However, further large scale clinical trials are warranted to understand the usefulness of medicinal plants for the

pharmacological application against coronavirus (SARS-CoV-2) disease (covid-19) outbreak.

*2). Coronavirus: Classification*

Coronaviruses belong to the family *Coronaviridae* in the order *Nidovirales* have the largest genomes (30 Kb) of all RNA viruses. *Coronaviruses are actually a family of hundreds of viruses*. Corona represents crown-like spikes on the outer surface of the virus therefore, named as a coronavirus. (Wu et al., 2020a, 2020b; Shereen et al., 2020; Zhou et al., 2020a, 2020b; Zhu et al., 2020; Lu et al., 2020; Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, 2020). The family *Coronaviridae* is divided into the subfamilies *Coronavirinae* and *Torovirinae* (Irigoyen et al., 2016;Cui et al., 2019; Lai et al., 2020). *Torovirinae* includes the genera Bafinivirus and Torovirus, infecting fish and mammals (Han et al., 2015; Chan et al., 2015; Corman et al., 2015; Irigoyen et al., 2016; Singhal et al., 2020). *Coronavirinae* includes the genera Alphacoronavirus, Betacoronavirus (originated from Bats and rodents), Gammacoronavirus and Deltacoronavirus (originated from avian hosts) commonly infecting mammals and birds (Wu et al., 2020a, 2020b; Irigoyen et al., 2016). Coronaviruses have been identified in human and several avian hosts as well as in various mammals, including pigs, chicken, camels, bats, Himalayan palm civets, mice, dogs, and cats (Dinka and Milkesa, 2020;Ksiazek et al., 2003; Kuiken et al., 2003; Zhou et al., 2020a, 2020b). Severe Acute Respiratory Syndrome associated coronaviruses (SARS-CoV-2) could spread throughout the population of domestic and wild animals that come to market (Wu et al., 2020a, 2020b ; Zhou et al., 2020a, 2020b; Guan et al., 2003; Dinka and Milkesa, 2020). The global pandemic coronavirus (SARS-CoV-2) was circulating in bat populations and its cross-species transmission events leading to outbreaks in humans (Wu et al., 2020a, 2020b ; Dinka and Milkesa 2020; Zhou et al., 2020a, 2020b). Phylogenetic analysis of the complete viral genome (29,903 nucleotides) revealed that the coronavirus (SARS-CoV-2) was the most closely related (89.1% nucleotide similarity) to a group of SARS-like coronaviruses (genus Betacoronavirus, subgenus Sarbecovirus) that had previously been found in bats in China (Wu et al., 2020a, 2020b). Even though the global outbreak was contained, there are concerns that the coronavirus (SARS-CoV-2) will reemerge or that it could potentially be used as a bioterrorist agent, thus it is important to develop safe effective vaccines (Zhou et al., 2020a, 2020b; Zhang et al., 2020; Huang et al., 2020; Xu and Zhang, 2020; Li et al., 2020).

*3). Human coronaviruses*

*The first coronavirus was discovered in chickens in the 1930s.* Human coronaviruses were first identified in the mid-1960s (Hamre and Procknow, 1966; Tyrrell and Bynoe, 1965; Shanmugaraj et al., 2020). The evolution of human coronaviruses (HCoVs) has been reported due to the mutation, high nucleotide substitution rates, its ability to establish infection in a new host, and cross-species transmission (Zhou et al., 2020a, 2020b; Hamre and Procknow, 1966; Tyrrell and Bynoe, 1965; Shanmugaraj et al., 2020). Human coronaviruses (HCoVs) are a major group of coronaviruses associated with respiratory and intestinal infections, common cold, pneumonia, and bronchiolitis (Wu et al., 2020a, 2020b; Hamre and Procknow, 1966; Tyrrell and Bynoe, 1965; Shanmugaraj et al. 2020; Zhou et al., 2020a, 2020b).

*Seven coronaviruses that can infect humans* are **1**) HCoV-229E (alpha coronavirus), **2**) HCoV-NL63 (alpha coronavirus), **3**) HCoV-OC43 (beta coronavirus), **4**) HCoV-HKU1 (beta coronavirus), **5**) SARS-CoV (the beta coronavirus that causes severe acute respiratory syndrome, or SARS), **6**) MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome, or MERS), **7**) SARS-CoV-2 (the 2019 novel coronavirus that causes coronavirus disease or COVID-19). Human coronaviruses such as HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1 usually cause mild infections in humans (Wu et al., 2020a, 2020b; Hamre and Procknow, 1966; Tyrrell and Bynoe, 1965; Shanmugaraj et al. 2020; Zhou et al., 2020a, 2020b).

Among these 7 human coronaviruses, four (HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1) are endemic (regularly found among particular people or in a certain area) and usually cause mild disease (Woo et al., 2005; Hoek et al., 2004; Pyrc et al., 2007). On the other hand, the rest of three coronaviruses (SARS-CoV, MERS- CoV, and SARS-CoV-2) can cause much more serious and even fatal disease (Shereen et al., 2020; Zhu et al. 2020; Lu et al. 2020). Furthermore, people around the world commonly get infected with the human coronaviruses are HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1 (Hamre and Procknow, 1966; Tyrrell and Bynoe, 1965; Hoek et al., 2004; Pyrc et al. 2007). Sometimes coronaviruses that infect animals can evolve and make people sick and become a new human coronavirus (Wu et al., 2020a, 2020b; Zhou et al., 2020a, 2020b). Three recent examples of this are SARS-CoV, and MERS-CoV and SARS-CoV-2 (Wu et al., 2020a, 2020b; Shanmugaraj et al., 2020; Zhu et al., 2020; Lu et al., 2020; Zhou et al., 2020a, 2020b).

*The first coronaviruses discovered in mid-sixties were able to infect humans are 229E and OC43* (Hamre and Procknow, 1966; Tyrrell and Bynoe, 1965; Pyrc et al., 2007). Both of these coronaviruses usually resulted in the common cold and rarely cause the severe disease on their own (Pyrc et al., 2007). They are often detected at the same time as other respiratory infections. When several viruses, or bacteria, are found in patients this is called co-infection and can result in the more severe disease (Pyrc et al., 2007). These two human coronaviruses were studied extensively from approximately 1965 to the mid- 1980s (Pyrc et al., 2007).

In 2004, the human coronavirus NL63 was detected for the first time in a baby suffering from bronchiolitis (a lower respiratory tract infection) in the Netherlands (Hoek et al., 2004; Pyrc et al., 2007). This virus has probably been around

for hundreds of years, we just hadn't found it until then (Hoek et al., 2004; Pyrc et al., 2007). A year later, in Hong Kong, another coronavirus was found – this time in an elderly patient with pneumonia (Woo et al., 2005; Lau et al., 2006). It was later named HKU1 and has been found to be present in populations around the world (Woo et al., 2005; Pyrc et al., 2007; Lau et al., 2006). The virus particle is enveloped and carries extended spike proteins on the membrane surface, providing the typical crown-like structure seen by electron microscopy (Woo et al., 2005; Pyrc et al., 2007; Lau et al., 2006; Zhou et al., 2020a, 2020b).

*4). Coronavirus: Recent Outbreak*

In 2002-2003, the Chinese population was infected with a virus causing Severe Acute Respiratory Syndrome (SARS) in Guangdong province, China and was named as SARS-CoV (9% mortality) (Wu et al., 2020a, 2020b; Zhou et al., 2020a, 2020b). As a result of this outbreak, large Chinese population were suffering from high fever, dry cough, tiredness, sneezing, throat infections, pnemonia and respiratiory illness leading to the death (Wu et al., 2020a, 2020b; Zhou et al., 2020a, 2020b). SARS-CoV is a Biodefense Category C priority pathogen (Wu et al., 2020a, 2020b). Most of these infect animals such as bats, chickens, camels and cats. Occasionally, cornaviruses that infect one species can mutate in such a way that allows them to start infecting another species. This is called "cross-species transmission" or "spillover" (Wu et al., 2020a, 2020b; Shereen et al., 2020; Zhu et al., 2020; Lu et al., 2020). Therefore, SARS-CoV infecting animals to human population is one of the best example since virus is zoonotic in origin (Wu et al., 2020a, 2020b; Zhou et al., 2020a, 2020b).

A decade later in 2012, coronavirus was reported in Middle East. As a result of outbreak, couple of Saudi Arabian nationals were diagnosed to be infected with another coronavirus and named as the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (40-50% mortality) (Shereen et al., 2020; Zhu et al., 2020; Lu et al., 2020; Zhou et al., 2020a, 2020b). The primary host for MERS-CoV was bats and secondary host was camel leading to the human infections in the Middle East. There were two further MERS-CoV outbreaks: South Korea in 2015 and Saudi Arabia in 2018. There are a handful of MERS-CoV cases every year, but the outbreaks are usually well contained. MERS-CoV cases have been linked to the close contact with the infected camels or very close contact with an already infected person. Both SARS-CoV and MERS-CoV are the members of the genus Betacoronavirus.

At the end of December 2019, the outbreak of coronavirus caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) occurred in Wuhan, Hubei, China (Wu et al., 2020a, 2020b; Zhou et al., 2020a, 2020b). The novel virus was named as Wuhan coronavirus or 2019 novel coronavirus (2019-nCov) by the Chinese researchers (Wu et al., 2020a, 2020b; Zhou et al., 2020a, 2020b). The International Committee on Taxonomy of Viruses (ICTV) named the virus as SARS-CoV-2 and the disease as COVID-19 (Wu et al., 2020a, 2020b; Cui et al., 2019; Lai et al., 2020; Shereen et al., 2020; Zhou et al., 2020a, 2020b). World Health Organization (WHO) declared the outbreak of coronavirus disease-2019 (COVID-19) is a viral infectious disease caused by SARS-CoV-2 is a global pandemic similar to 1918 influenza outbreak (Wu et al., 2020a, 2020b; Kwon et al., 2020; Dong et al., 2020; Wang et al., 2020; Zhou et al., 2020a, 2020b). The outbreak was declared as Public Health Emergency of International Concern by the WHO on 30 January 2020 (Zhou et al., 2020a, 2020b). SARS-CoV-2 is a betacoronavirus responsible for the COVID-19 pandemic. Furthermore, SARS-CoV-2 compared to 1918 influenza pandemic is also a seasonal disease with a very high infection rate, and long incubation period (14 days) with mild to moderate symptoms leading to the most dangerous viral disease. SARS-CoV-2 is a zoonotic virus that can infect humans and animals (Wu et al., 2020a, 2020b; Shin et al., 2020; Wang et al., 2020). Therefore, SARS-CoV-2 is an international outbreak of acute respiratory illness (Wu et al., 2020a, 2020b; Ang et al., 2020; Zhou et al., 2020a, 2020b). Coronaviruses are believed to be originated from bats and subsequently transmitted to the humans. The higher pathogenicity of coronavirus in humans has been observed when they cross the species barrier from animals to humans (Wu et al., 2020a, 2020b; Zhu et al., 2020; Lu et al., 2020; Zhou et al., 2020a, 2020b).

*5). Coronavirus: Outbreak of mutants (SARS-Cov-2)*

SARS-CoV-2 has been continually changing its genetics through the course of the pandemic. Mutation is very high in RNA-based viruses like SARS-CoV-2 (Pachetti et al., 2020; Khan et al., 2020; Grubaugh et al., 2020; Zhou et al., 2020a, 2020b). Viruses mutate because they're constantly making the copies of themselves in an enormous numbers. Within a human body, a virus can replicate itself millions or billions of times (Grubaugh et al., 2020). Viruses that use RNA as their genetic material, like SARS-CoV-2, are particularly vulnerable to mutations since the RNA molecule itself is more unstable than DNA (Pachetti et al., 2020; Khan et al., 2020; Grubaugh et al., 2020). The process of copying RNA is also more prone to error. But in rare instances, some mutations can give a virus an advantage, like allowing it to infect cells more readily or spread among people faster. Those mutant strains can then become dominant within a population (Pachetti et al., 2020; Khan et al., 2020; Grubaugh et al., 2020). Individually, many of these mutations have already been seen in other strains of the virus around the world (Wise et al., 2020). But the combination of these changes in a single virus could be making the new variant more likely to spread (Wise et al., 2020; Davies et al., 2020). However, some mutations may be more important than others, and there are several mechanisms by which mutations could make the virus more infectious (Wise et al., 2020; Davies et al., 2020).

SARS-CoV-2 is a RNA coronavirus responsible for the pandemic of the Severe Acute Respiratory Syndrome

(COVID-19) (Pachetti et al., 2020; Khan et al., 2020). RNA viruses are characterized by a high mutation rate, up to a million times higher than that of their hosts (Pachetti et al., 2020; Khan et al., 2020; Grubaugh et al., 2020). Virus mutagenic capability depends upon several factors, including the fidelity of viral enzymes that replicate nucleic acids, as SARS-CoV-2 RNA dependent RNA polymerase (RdRp) (Pachetti et al., 2020; Khan et al., 2020; Grubaugh et al., 2020).

Biological characterization of viral mutations can provide precious insights for assessing the viral drug resistance, immune escape and pathogenesis related mechanisms (Pachetti et al., 2020). Additionally, viral mutation studies can be crucial for designing the new vaccines, antiviral drugs and diagnostic assays (Pachetti et al., 2020; Grubaugh et al., 2020). The viral genome mutagenic process depends on the viral enzymes that replicate the nucleic acids, influenced by few or no proofreading capability and/or post-replicative nucleic acid repair (Pachetti et al., 2020; Khan et al., 2020; Grubaugh et al., 2020).

Mutations arise as a natural by-product of viral replication (Grubaugh et al., 2020). RNA viruses typically have the higher mutation rates than DNA viruses (Grubaugh et al., 2020). Corona viruses, however, make fewer mutations than the most RNA viruses because they encode an enzyme that corrects some of the errors made during replication (Grubaugh et al., 2020). In most cases, the fate of a newly arising mutation is determined by natural selection (Grubaugh et al., 2020; Duffy, 2018; Khan et al., 2020; Salemi et al., 2004). The rate of SARS-CoV-2 mediated disease spread and the mortality varies from country to country (Khan et al., 2020).

Khan et al., (2020) investigated the SARS-CoV-2 genome reported from 13 different countries, identification of mutations in major corona virus proteins of these different SARS-CoV-2 genomes and compared with SARS-CoV (Khan et al., 2020). These thirteen complete genome sequences of SARS-CoV-2 showed high identity (>99%) to each other, while they shared 82% identity with SARS-CoV (Khan et al., 2020). This includes several important country-specific unique mutations in the major proteins of SARS-CoV-2 namely, replicase polyprotein, spike glycoprotein, envelope protein and nucleocapsid protein (Khan et al., 2020). Indian strain showed mutation in spike glycoprotein at R408I and in replicase polyprotein at I671T, P2144S and A2798V (Khan et al., 2020). Mutation R408I in spike protein of Indian strain has a significant influence on receptor-binding domain (RBD) of spike protein and this point mutation has a stabilization effect on the spike protein (Khan et al., 2020). Further, molecular dynamics and other *in silico* studies revealed that mutations decrease the stability of protein and also hinders the binding of inhibitor (Khan et al., 2020). The findings of the this study could help for the design of potential vaccine candidates/small molecular inhibitor against COVID-19 (SARS-CoV-2) (Khan et al., 2020).

The coronavirus spreads fast enough and the *UK variant* (Lineage B.1.1.7 (also called 501Y.V1) where a strain called 501.V2 has become the dominant version among new cases of the virus (Wise et al., 2020; Davies et al., 2020; Lauring and Hodcroft, 2021). This is strongly suggestive of natural selection of a virus that is more transmissible at a population level (Wise et al,. 2020; Davies et al., 2020; Lauring and Hodcroft, 2021). The UK variant of SARS-CoV-2 (Lineage B.1.1.7 (also called 501Y.V1) actually contains 23 mutations in the genome of the virus (Wise et al. 2020; Davies et al. 2020) (Wise et al., 2020; Davies et al., 2020; Lauring and Hodcroft, 2021). As of December 28, 2020, this variant accounted for approximately 28% of cases of SARS-CoV-2 infection in England, and population genetic models suggest that it is spreading 56% more quickly than other lineages (Wise et al., 2020; Davies et al., 2020; Lauring and Hodcroft, 2021).

Concerning outbreaks of SARS-CoV-2 began to emerge on *mink farms* in the Netherlands and Denmark in late spring and early summer 2020 (Spike N453Y and Mink) (Oude Munnink et al., 2020; Lauring and Hodcroft, 2021). Many SARS-CoV-2 sequences from the Netherlands and Danish outbreaks had a Y453F mutation in the receptor binding domain of spike, which might mediate the increased binding affinity for mink ACE2 (angiotensin-converting enzyme 2) (Oude Munnink et al., 2020; Lauring and Hodcroft, 2021). The apparent adaptation of SARS-CoV-2 to mink was nevertheless concerning because continued evolution of the coronavirus in an animal reservoir could potentially lead to recurrent spill over events of novel SARS-CoV-2 from mink to humans and other mammals (Oude Munnink et al., 2020; Lauring and Hodcroft, 2021).

The *South African* mutant strain of SARS-CoV-2 is named as *N501Y*. South Africa named the variant "501Y.V2" because of the N501Y mutation they found in the spike protein that the coronavirus uses to gain entry into cells within the body. The variant in South Africa carries two other mutations in the spike protein (E484K and K417N, among others) which are not present in the U.K. strain, named "VOC-202012/01," with VOC standing for "Variant of Concern. The same mutation has been found in the *South African* variant of SARS-CoV-2 named as N501Y (Wise et al., 2020; Davies et al., 2020; Tegally et al., 2020). One mutation, called N501Y, makes the virus binding more tightly to human cells (Wise et al., 2020; Davies et al., 2020; Tegally et al., 2020).

Recent analyses of the fine-scale sequence variation of SARS-CoV- 2 isolates identified several genomic regions of the increased genetic variation (Korber et al., 2020). Another mutation, called D614G, makes the virus more transmissible (Korber et al., 2020). The S-protein mutation, D614G, that appears to promote SARS-CoV-2 transmission in humans also enhances the functional S-protein incorporation into SARS-CoV-2 VLP and retroviral PV and increases the PV infectivity (Korber et al., 2020).

*6). Coronavirus symptoms*

The human to human spreading of the coranavirus (SARS-CoV-2) occurs due to the close contact with an infected person, exposed to coughing, sneezing, respiratory droplets or aerosols and fecal to oral transmission. These aerosols can penetrate the human body (lungs) via inhalation through the nose or mouth (Shereen et al., 2020; Zhu et al., 2020; Lu et al., 2020). The coronavirus (SARS-CoV-2) designated as COVID-19 prominently affect the respiratory tract (both lower and upper respiratory tract), with the initial symptoms of common cold, fever, dry cough, fatigue, general feeling of being unwell, runny nose, aches and pains, nasal congestion, loss of taste or smell, loss of speech or movement, headache, sore throat, a rash on skin, or discolouration of fingers or toes, conjunctivitis, shortness of breath, chest pain or pressure, and diarrhea to severe pneumonia, difficulty in breathing and ends with the patient death (Wu et al., 2020a, 2020b; Zhou et al., 2020a, 2020b;Wang *et al*. 2020; Pandey *et al*. 2020; Paules *et al*. 2020; Saif , 2004; Fisher and Heymann, 2020). Infection with these highly pathogenic coronaviruses (SARS-CoV-2) could result in the acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) followed by the failure of the lung function and death (Wu et al., 2020a, 2020b). The incubation period of the coronavirus disease is 14 days and the time from onset of symptom to developing pneumonia is 4 days (Pandey et al., 2020; Paules et al., 2020; Saif , 2004; Fisher and Heymann, 2020). Therefore, interaction between virus SARS-CoV-2 and host may be responsible for its unusual high morbidity and mortality (Wu et al., 2020a; Blanco-Melo et al., 2020; Wu et al., 2020a, 2020b; Zhou et al., 2020a, 2020b). Therefore, COVID-19 (SARS-CoV-2) is a serious threat to human health (Wang et al., 2020). Several coronaviruses, such as Severe acute respiratory syndrome-related coronavirus (SARS-CoV) and Middle East respiratory syndrome-related coronavirus (MERS-CoV) are virus pandemics. SARS-CoV-2, is the novel coronovirus responsible for the ongoing COVID-19 (SARS-CoV-2) human pandemic leading to the global outbreak of respiratory illness (Ang et al., 2020; Wu et al., 2020a, 2020b; Kwon et al., 2020; Dong et al., 2020). There is also the potential for laboratory acquired infections. Therefore, the development of effective vaccines is still of significant importance (Wu et al., 2020a, 2020b).

*7). Coronavirus (SARS-CoV-2): Detection methods*

*1) Swab Test:* Nasopharyngeal (NP) and oropharyngeal (OP) swabs are the most common upper respiratory tract specimen utilized for SARS-CoV-2 diagnostic testing (Paz et al., 2020; Xu et al., 2020; Wyllie et al., 2020a, 2020b). The bio-sample needs to be eluted in viral or universal transport medium (VTM, UTM), stored and transported to a testing facility (Paz et al., 2020; Xu et al., 2020; Wyllie et al., 2020a, 2020b). Saliva samples have become an increasingly attractive specimen alternative being as- or more sensitive and reliable than NP swabs (Paz et al., 2020; Xu et al., 2020; Wyllie et al., 2020a, 2020b).

This testing protocol for the detection of minimal quantities of SARS-CoV-2 that can be utilized by the most laboratories equipped with standard molecular biology equipment without the need of higher biosafety facilities is known as swab test where saliva is collected as sample source for the detection of coronavirus (Paz et al., 2020; Xu et al., 2020; Wyllie et al., 2020a, 2020b). The coronavirus has been shown to be present at high titer in saliva. In addition, observed a recovery of viral RNA between 50 and 90% with the TRIzol method and the RT-qPCR assay can amplify as little as 6 copies of viral RNA. The high sensitivity of this protocol might be useful in testing the patients with low viral titers such as asymptomatic patients (Paz et al., 2020; Xu et al., 2020; Wyllie et al., 2020a, 2020b).

Quantitative PCR (qPCR) based molecular tests that detect the presence of the viral nucleic acid offer the most sensitive and reliable method for the detection of SARS-COV-2 in patients' samples (Paz et al., 2020; Xu et al., 2020; Wyllie et al., 2020a, 2020b).

*2) The rapid identification and sequencing* of SARS-CoV-2 has enabled the rapid development of *nucleic acid and protein tests.* These approaches have provided a first line of defense against an coronavirus outbreak (Udugama et al., 2020).

*3) Serological test:* Currently, serological tests (i.e., blood tests for specific antibodies) are in development (Udugama et al., 2020). Detection of immunoglobulin G and M (IgG and IgM) from human serum of COVID-19 (SARS-CoV-2) patients using an enzyme-linked immunosorbent assay (ELISA) (Udugama et al., 2020).

*4) Point-of -care testing:* Point-of-care tests are used to diagnose the patients without sending samples to centralized facilities, thereby enabling communities without laboratory infrastructure to detect infected patients (Udugama et al., 2020). Lateral flow antigen detection for SARS-CoV-2 is one of the point-of-care approach under the development for diagnosing COVID-19 (SARS-CoV-2) (Udugama et al., 2020). In commercial lateral flow assays, a paper-like membrane strip is coated with two lines: gold nanoparticle-antibody conjugates are present in one line and capture the antibodies in the other (Udugama et al., 2020). The patient's sample (e.g., blood and urine) is deposited on the membrane, and the proteins are drawn across the strip by capillary action (Udugama et al., 2020).

As it passes the first line, the antigens bind to the gold nanoparticle-antibody conjugates, and the complex flows together through the membrane (Udugama et al., 2020). As they reach the second line, the complex is immobilized by the capture antibodies, and a red or blue line becomes visible (Udugama et al., 2020). Individual gold nanoparticles are red in color, but a solution containing clustered gold nanoparticles is blue due to the coupling of the plasmon band (Udugama et al., 2020). Another approach for use at the point-of-care is microfluidic devices. However, these tests are single use and

suffer from poor analytical sensitivity in comparison to RT-PCR (Udugama et al., 2020).

*5) Sandwich-ELISA-Test:* Sensitive diagnosis of SARS is essential for the control of the disease in humans. Recombinant SARS-CoV S1 antigen was produced and purified for the development of monoclonal and bi-specific monoclonal antibodies (Sunwoo et al., 2013). The hybridomas secreting anti-S1 antibodies, F26G18 and P136.8D12, were fused respectively with the YP4 hybridoma to generate quadromas (Sunwoo et al.,2013). The sandwich ELISA was formed by using F26G18 as a coating antibody and biotinylated F26G18 as a detection antibody with a detection limit of 0.037 μg/ml ($p < 0.02$) (Sunwoo et al., 2013). Therefore, this method described in this study allows sensitive detection of a recombinant SARS spike protein by sandwich ELISA with bi-specific monoclonal antibody and could be used for the diagnosis of patients suspected with SARS (Sunwoo et al., 2013).

*8). Coronavirus: Size of the virus*

Electron micrographs of negative-stained 2019-nCoV particles were generally spherical with some pleomorphism (Bar-On et al., 2020). Diameter varied from about 60 to 140 nm (Bar-On et al., 2020). Viruses are often transmitted through respiratory droplets produced by coughing and sneezing (Bar-On et al., 2020). Respiratory droplets are usually divided into two size bins, large droplets (5 mm in diameter) that fall rapidly to the ground and are thus transmitted only over short distances, and small droplets (5 mm in diameter) (Bar-On et al., 2020). The characteristic diameter of large droplets produced by sneezing is 100 mm. while the diameter of droplet nuclei produced by coughing is on the order of 1 mm (Bar-On et al., 2020).

*9). Preventive Guidelines for controlling coronavirus (SARS-CoV-2) outbreak (WHO) (Kirkcaldy et al., 2020)*

1) Use of face mask (medically approved or cotton face masks) are mandatory to keep your nose and mouth covered when you are outside of your home.
2) Maintain social distancing and avoid non-essential traveling. Do not travel if you are sick.
3) Use of hand sanitizers with 70-80% ethanol will limit the spread of coronavirus.
4) Stay home as much as possible.
5) Drink enough warm water.
6) Gargle with warm water with a pinch of salt and turmeric.
7) Gargle with warm water added with a pinch of turmeric and salt, Triphala, and Yashtimadhu. ShuddhaTankana (2% aqueous solution), Madhoodaka (5% aqeuous solution) also can be used for Kavala graha.
8) Regularly and thoroughly wash hands with soap or any other detergent. Avoid touching one's eyes, nose and mouth (Chin et al., 2020; Kampf et al., 2020; Kampf, 2020).
9) Washing hands with soap or any other detergent will easily destroy the coronavirus (SARS-CoV-2) within 20 seconds outside the host since soap or detergent acts as a lipid solvents which break or dissolve the outside coated fatty layer of the coronavirus (Chin et al., 2020; Kampf et al., 2020; Kampf, 2020)
10) Avoid touching your face with unwashed hands. Frequent touching of eyes, nose and mouth that can pick up coronaviruses is to be avoided. Once contaminated, hands can transfer the coronavirus to your eyes, nose or mouth. From there, the virus can enter your body and can cause sever lung infections.
11) Avoiding greetings that include physical contact, such as handshakes.
12) Usage of gloves can be encouraged whenever possible.
13) If anyone has fever, cough and difficulty breathing, please consult a physician immediately and all instructions are to be followed meticulously.
14) To help to limit the spread of COVID-19 (SARS-CoV-2), the WHO also recommends people cover their mouth and nose when they cough or sneeze and clean commonly used surfaces frequently with an alcohol-based disinfectant (Chin et al., 2020; Kampf et al., 2020; Kampf, 2020).
15) Avoid cultural and religious gatherings, community gatherings and large group events.
16) Avoid being around people at higher risk for severe illness from COVID-19 (SARS-CoV-2).
17) Consider getting tested for COVID-19(SARS-CoV-2).
18) Consume warm food or drink rich in iron and vitamin C which is essential for keeping good health in terms of boosted immunity.
19) Drink lemon juice rich in vitamin C in warm water with one tea spoon of natural honey.
20) In a breakthrough discovery, the Japanese researchers have found that the SARS-CoV-2 can remain active on human skin for at least nine hours (Hirose et al., 2020). Hence, the hand washing using 80% ethanol was key to avoid contracting the COVID-19 disease."The nine-hour survival of SARS-CoV-2 (the virus strain that causes Covid-19) on human skin may increase the risk of contact transmission in comparison with IAV (influenza A virus), thus accelerating the pandemic (Hirose et al., 2020). Both the coronavirus and the flu virus were inactivated within 15 seconds by applying 80% ethanol, which is commonly found in hand sanitizers (Hirose et al., 2020; Kampf et al.,

2020; Kampf, 2020). However, this time frame, compared to other objects showed that the coronavirus was inactivated more rapidly on skin surfaces as compared to stainless steel, glass objects, or plastic, where virus remained alive significantly longer period between 58 and 85 hours (Hirose et al.,2020; Kampf et al., 2020; Kampf, 2020).

21) Viruses have been shown to be readily transferred between contaminated skin and a fomite surface with high contact surfaces such as touch screens on mobile phones, bank ATMs, airport check-in kiosks and supermarket self-serve kiosks all acting as fomites for the transmission of coronaviruses (Riddell et al., 2020; Kampf et al., 2020; Kampf, 2020). Recent study demonstrated that infectious coronavirus (SARS-CoV-2) can be recovered from the nonporous surfaces for at least 28 days at ambient temperature and humidity (20 °C and 50% RH) (Riddell et al., 2020; Kampf et al., 2020; Kampf, 2020). Viable virus was isolated for up to 28 days at 20 °C from the common surfaces such as glass, stainless steel and both paper and polymer banknotes (Riddell et al., 2020). Conversely, infectious coronavirus survived less than 24 h at 40 °C on some surfaces (Riddell et al., 2020). The persistence of SARS-CoV-2 demonstrated in this study is pertinent to the public health and transport sectors (Riddell et al., 2020). This data should be considered in strategies designed to mitigate the risk of fomite transmission during the current coronavirus pandemic response (Riddell et al., 2020).

*10). Ministry of AYUSH, Government of India, general guidelines for controlling covid-19 outbreak*

Ministry of AYUSH, Government of India, recommends the following self-care guidelines for the preventive health measures and boosting immunity with special reference to respiratory health based on Ayurvedic literature and scientific publications. (https://www.ayush.gov.in/docs/ayurved-guidlines.pdf).

a. Drink warm water throughout the day.
b. *Drink herbal tea / decoction (Kadha*) made from Tulsi (Basil), Dalchini (Cinnamon), Kalimirch (Black pepper), Shunthi (Dry Ginger) and Munakka (Raisin) - once or twice a day. Add jaggery (natural sugar) and / or fresh lemon juice to your taste, if needed.
c. *Daily practice of Yogasana*, Pranayama and meditation for at least 30 minutes as advised by Ministry of AYUSH (#YOGA at Home #Stay Home #Stay Safe).
d. *Spices like Haldi* (Turmeric), Jeera (Cumin), Dhaniya (Coriander) and Lahsun (Garlic) are recommended in cooking.
e. *Take Chyavanprash* 10gm (1tea sfoon) in the morning. Diabetics should take sugar free Chyavanprash.
f. *Golden Milk*- Half tea spoon Haldi (turmeric) powder in 150 ml hot milk - once or twice a day.
g. *Nasal application* - Apply sesame oil / coconut oil or Ghee in both the nostrils (Pratimarsh Nasya) in morning and evening.
h. *Oil pulling therapy*- Take 1 table spoon sesame or coconut oil in mouth. Do not drink, Swish in the mouth for 2 to 3 minutes and spit it off followed by warm water rinse. This can be done once or twice a day.
i. Steam inhalation with fresh Pudina (Mint) leaves or Ajwain (Caraway seeds) can be practiced once in a day.
j. Lavang (Clove) powder mixed with natural sugar / honey can be taken 2-3 times a day in case of cough or throat irritation.
k. These measures generally treat normal dry cough and sore throat. However, it is best to consult doctors if these symptoms persist.

*11). Coronavirus: Genetic analysis*

The genetic sequence of SARS-CoV-2, the coronavirus that causes COVID-19, was published on 11 January 2020, triggering intense global R&D activity to develop a vaccine against the disease (Wu et al., 2020). The complete genome sequences of SARS-CoV-2 (29, 903 bp ss-RNA) isolate Wuhan-Hu-1(Wuhan seafood market pneumonia virus isolate) were available in a NIH website, National Library of Medicine (https://www.ncbi.nlm.nih.gov/sars-cov-2) (National Center for Biotechnology Information (NCBI) Reference Sequence: NC_045512.2) (Wu et al., 2020a; Zhou et al., 2020a, 2020b). The pathogen, severe acute respiratory syndrome coronavirus (SARS-CoV-2) shared a phylogenetic similarity to SARS-CoV (about 79%) and Middle East respiratory syndrome (MERS)-CoV (about 50%). Furthermore, the genome sequence of coronavirus (SARS-CoV-2) also showed phylogenetic similarity to one of the species of bats (80%). Therefore, coronavirus (SARS-CoV-2) is originated from bats and bats are the primary hosts for the spread of the covid-19 disease (Zhou et al. 2020a, 2020b). In one of the recent reported study, different epidemiological and clinical features of COVID-19 (SARS-CoV-2) were found to be related to the genetic changes of SARS-CoV-2 (Caccuri et al., 2020; Guo et al., 2020; Tang et al., 2020). The novel coronavirus has been found to evolve into two subtypes, L and S with the former being more aggressive and spreading more rapidly than the latter (Caccuri et al., 2020; Guo et al., 2020; Tang et al., 2020). Furthermore, the relative high number of mutations were observed in the sequences of other strains of SARS-CoV-2 collected at the early stage of China epidemic

(Zhou et al., 2020a, 2020b; Caccuri et al., 2020; Guo et al., 2020; Tang et al., 2020). Another study reported that the functional characterization of 11 patient-derived viral isolates showing significant variation in cytopathic effects and viral load, suggesting that patient-derived mutations have an impact on SARS-CoV-2 pathogenicity (Yao et al., 2020; Caccuri et al., 2020). Therefore, SARS-CoV-2 GZ69 variant displays several point mutations that may account for its unique features (Caccuri et al., 2020). This will allow to identify critical genetic mutations that might be a part of the viral adaptation process eventually leading to changes in virus pathogenicity (Caccuri et al., 2020). Therefore, investigation of genetic and phenotypic characteristics of SARS-CoV-2 strains circulating lately in the epidemic will definitely give an idea about the evolution of SARS-CoV-2 pathogenicity and its adaptation to the host (Caccuri et al., 2020; Zhou et al., 2020a, 2020b).

The novel coronavirus (SARS-CoV-2) originated from the Hunan seafood market at Wuhan, Hubei, China where bats, snakes, raccoon dogs, palm civets, and other animals are sold, and viral disease was rapidly spread up to 177 countries (Zhou et al., 2020a, 2020b; Ang et al. 2020; Shereen et al. 2020; Wang et al., 2020). The genetic material of coronavirus is highly prone to frequent recombination process that results into the formation of new strains with altered virulence (Pandey et al., 2020; Paules et al., 2020; Saif, 2004; Fisher and Heymann, 2020; Zhou et al., 2020a, 2020b). However, the strains of SARS- CoV (outbreak in 2002), MERS-CoV (outbreak in 2012) and SARS-CoV-2 (outbreak in 2019) were reported to be extremely pathogenic and highly adopted to the changing environment (Pandey et al., 2020; Zhou et al., 2020a, 2020b).

*12). Structure of coronavirus*

Coronaviruses are obligate intracellular parasites and rely on hosts for their propagation. Coronaviruses (SARS-CoV-2) are pleomorphic or spherical in shape with a diameter of 125 nm and characterized by club shaped spike projections on its surface (Pandey et al., 2020). Coronaviruses are the large family of enveloped single- stranded positive -sense RNA viruses which encode the 12 putative open reading frames responsible for the synthesis of viral structural and nonstructural proteins which are very similar to SARS-CoV and MERS-CoV proteins (Woo et al., 2004; Wu et al., 2020; Yuen et al., 2020). The coronavirus genome is surrounded by a helical capsid and an envelope; the spike protein forms large protrusions in the envelope in the shape of a crown, which gives the virus a coronal appearance. The word 'corona' in Latin means crown. The large SARS-CoV-2 genome, a polyadenylated RNA of 29,727 nucleotides, which is capped, infectious and encodes four major viral structural components, the spike glycoprotein (S), envelope (E), membrane (M), and nucleocapsid (N) proteins, and 16 non-structural proteins (Bartlam et al., 2007; Suresh et al., 2008; Shin et al., 2020). The spike glycoprotein (S) is an attractive target for the vaccine production because it facilitates viral entry into the host cell during the virus infection process (Shin et al., 2020). The spike glycoprotein (S) protein of the coronavirus is the major target for neutralizing antibodies. The two spike glycoprotein subdomains, S1 and S2, are responsible for the host cell angiotensin-converting enzyme 2 (ACE2) receptor binding and host cell membrane fusion, respectively (Shin et al., 2020). S1 contains the receptor-binding domain (RBD) and S2 the fusion machinery enabling virus entry into the host cell following coronavirus (covid-19) infection (Shin et al., 2020). The receptor-binding domain (RBD) is immunogenic and is a major neutralizing determinant. Therefore, spike glyco protein (S) antigens have become an important focus of many serological studies (Burgers et al., 2020).

*13). Life cycle of coronavirus*

In general, coronavirus life cycle is divided into 3 distinct stages; 1) Entry (attachment, penetration and uncoating), 2) Genome replication, and 3) Exit (Virion assembly and Release) (V'kovski et al., 2020; Hoffmann et al., 2020; Perlman and Netland, 2009; Shang et al., 2020; Masters, 2006; Li et al., 2003;Yamauchi and Helenius, 2013). The initial steps of coronavirus infection involve the specific binding of the coronavirus spike (S) protein to the cellular entry receptors, which have been identified for several coronaviruses and include human amino peptidase N (APN; HCoV-229E), angiotensin-converting enzyme 2 (ACE2; HCoV-NL63, SARS-CoV and SARS-CoV-2) and di-peptidyl peptidase-4 (DPP4; MERS-CoV) (V'kovski et al., 2020; Hoffmann et al., 2020; Perlman and Netland, 2009; Shang et al., 2020; Masters, 2006; Li et al., 2003).

In a fluorescent study, it was confirmed that the SARS-CoV-2 also uses the same ACE2 (angiotensin-converting enzyme 2) cell receptor and mechanism for entry to the host cell which is previously used by the SARS-CoV (V'kovski et al., 2020; Hoffmann et al., 2020; Perlman and Netland, 2009; Shang et al., 2020; Masters, 2006; Li et al., 2003; Gralinski and Menachery, 2020; Xu et al., 2020; Shereen et al., 2020). Following attachment of the virus particle on the target cells, the next step is the penetration into the cytoplasm (Yamauchi and Helenius, 2013). The mechanism for the penetration differs, whether enveloped or not. For enveloped viruses, one of the following two mechanisms is used: direct fusion and receptor-mediated endocytosis (V'kovski et al., 2020; Hoffmann et al., 2020; Perlman and Netland, 2009; Shang et al., 2020; Masters, 2006; Li et al., 2003).

During the intracellular life cycle, coronaviruses express and replicate their genomic RNA to produce full-length copies that are incorporated into newly produced viral particles (V'kovski et al., 2020; Hoffmann et al., 2020; Perlman and Netland, 2009; Shang et al., 2020; Masters, 2006; Li et al., 2003). The release of the coronavirus genome into the host cell cytoplasm upon entry marks the onset of a complex programme of viral gene expression, which is highly regulated in space and time (V'kovski et al., 2020; Hoffmann et al.

2020; Perlman and Netland, 2009; Shang et al. 2020; Masters, 2006; Li et al., 2003; Singhal et al., 2020).

For non enveloped naked viruses, receptor mediated endocytosis is used for penetration. Following successful penetration inside cells, the coronavirus particles need to get to an appropriate site in the cell for genome replication (V'kovski et al., 2020; Hoffmann et al., 2020; Perlman and Netland, 2009; Shang et al., 2020; Masters, 2006; Li et al., 2003). This process is termed intracellular trafficking. In fact, the biological importance of the cytoplasmic trafficking was not realized until the invention of live cell imaging technology (V'kovski et al., 2020; Hoffmann et al., 2020; Perlman and Netland, 2009; Shang et al., 2020; Masters, 2006; Li et al., 2003). As the coronavirus particles approach to the site of replication, from the cell periphery to the perinuclear space, the viral genome becomes exposed to cellular machinery for viral gene expression, a process termed uncoating (V'kovski et al., 2020; Hoffmann et al., 2020; Perlman and Netland, 2009; Shang et al., 2020; Masters, 2006; Li et al., 2003).

Uncoating is often linked with the endocytic route or cytoplasmic trafficking (Yamauchi and Helenius, 2013). The viral genome replication strategies are distinct from each other among the virus families (Yamauchi and Helenius, 2013). In fact, the genome replication mechanism is the one that defines the identity of each virus family (Yamauchi and Helenius, 2013). In general, the virus uses the host cell machinery for the replication process and replicate enormously (V'kovski et al., 2020; Hoffmann et al., 2020; Perlman and Netland, 2009; Shang et al., 2020; Masters, 2006; Li et al., 2003).

However, all viruses, without exception, entirely rely on host translation machinery, ribosomes, for their protein synthesis (Yamauchi and Helenius, 2013; Gralinski and Menachery, 2020; Xu et al., 2020; Shereen et al., 2020; Singhal et al., 2020). Exit can be divided into three steps: capsid assembly, release, and maturation. The virus particles are released *via* cell lysis of the infected cells. Thus, no specific exit mechanism is necessary, because the cell membrane that traps the assembled virus particles are dismantled (Yamauchi and Helenius, 2013; V'kovski et al., 2020; Hoffmann et al., 2020; Perlman and Netland, 2009; Shang et al., 2020; Masters, 2006; Li et al., 2003; Gralinski and Menachery, 2020; Xu et al., 2020; Shereen et al., 2020). Viruses, being intracellular parasites, rely on hosts for their propagation (Yamauchi and Helenius, 2013). Through evolution, viruses have acquired the abilities to subvert the host functions to comply with their needs (V'kovski et al., 2020; Hoffmann et al., 2020; Perlman and Netland, 2009; Shang et al., 2020; Masters, 2006; Li et al., 2003; Yamauchi and Helenius, 2013).

*14). Coronavirus: Synthetic drugs*

Synthetic drugs such as Ivermectin (potent inhibitor of SARS-CoV-2 infections with excellent ability to suppress pathogenic virus against *in vero*-hSLAM cells model) (Farooq and Ngain, 2020). Remdesivir, Chloroquine, Hydroxychloroquine, Favipiravir/Favilavir have not given satisfactory results when used as antiviral agent against SARS-Co2 (Farooq and Ngain, 2020). Camostat mesilate (CM), was developed in Japan as a a serine protease inhibitor in the 1980s (Uno, 2020; Hoffmann et al., 2020; Farooq and Ngain, 2020). Camostat mesilate (CM), an inhibitor of TMPRSS2, blocked the spread and pathogenesis of SARS-CoV in a pathogenic mouse model and would be expected to show similar effect in MERS-CoV (Uno, 2020; Hoffmann et al., 2020; Farooq and Ngain, 2020). Nafamostat mesylate inhibits TMPRSS2-dependent host cell entry of MERS-CoV (Hoffmann et al., 2020). Gabexate mesylate slightly inhibited SARS-CoV-2 S-driven host cell entry while camostat mesylate robustly suppressed entry (Hoffmann et al., 2020; Farooq and Ngain, 2020). Therefore, these compounds should be evaluated in clinical trials as a COVID-19 treatment.

*15). coronavirus: Herd Immunity*

Herd immunity, also known as indirect protection, community immunity, or community protection, refers to the protection of susceptible individuals against an infection when a sufficiently large proportion of immune individuals exist in a population (Omer et al., 2020; Anderson et al., 2020; Britton et al., 2020). In other words, herd immunity is the inability of infected individuals to propagate an epidemic outbreak due to the lack of contact with sufficient numbers of susceptible individuals (Omer et al., 2020; Anderson et al., 2020; Britton et al., 2020).

Herd immunity occurs when a large portion of a community (the herd) becomes immune to a disease, making the spread of the disease from one person to another person unlikely (Omer et al., 2020; Anderson et al., 2020; Britton et al., 2020). As a result, the whole community becomes protected not just those who are immune. A percentage of the population must be capable of getting a disease in order for it to spread (Omer et al., 2020; Anderson et al., 2020; Britton et al., 2020). This is called a threshold proportion. If the proportion of the population that is immune to the disease is greater than this threshold, the spread of the disease will decline(Omer et al., 2020; Anderson et al., 2020; Britton et al., 2020). This is known as the herd immunity threshold. There are two paths to herd immunity for COVID-19 vaccines and infection (Omer et al., 2020; Anderson et al., 2020; Britton et al.. 2020). A vaccine for the virus that causes COVID-19 (SARS-CoV-2) would be an ideal approach to achieving herd immunity (Omer et al., 2020; Anderson et al., 2020; Britton et al., 2020). Using the concept of herd immunity, vaccines have successfully controlled deadly contagious diseases such as smallpox, polio, diphtheria, rubella and many others (Omer et al., 2020; Anderson et al., 2020; Britton et al., 2020). Herd immunity can also be reached when a sufficient number of people in the population have recovered from a disease and have developed antibodies against future infection (natural infection) (Omer et al., 2020; Anderson et al., 2020; Britton et al., 2020).

*16) Coronavirus vaccine*

Following is the list of available vaccines for SARS-CoV-2 and approved for the immunization programme to combat the viral disease covid-19.

1. The ChAdOx1 nCoV-19 vaccine (AZD1222) was developed at Oxford University(UK) -AstraZeneca, and consists of a replication-deficient chimpanzee adenoviral vector ChAdOx1, containing the SARS-CoV-2 structural surface glycoprotein antigen (spike protein; nCoV-19) gene (Voysey et al., 2021; Folegatti et al., 2020; Barrett et al., 2020; Ewer et al., 2020; Ramasamy and Minassian, 2020). Oxford University. London, UK has entered into a partnership with AstraZeneca for further development of ChAdOx1 nCoV-19 (Voysey et al. , 2021; Barrett et al., 2020; Ewer et al., 2020).
2. COVISHIELD: SII's Recombinant Chimpanzee Adenovirus vector vaccine, Covishield, encodes the SARS-CoV-2 Spike (S) glycoprotein with technology transfer from AstraZeneca-Oxford University for the first made-in-India vaccine, COVISHIELD, Serum Institute of India, Pune, Maharashtra, India.
3. Covaxin (inactivated whole virus vaccine), Bharath Biotech, Hyderabad, Telangana, India. COVAXIN$^{TM}$, India's indigenous COVID-19 vaccine by Bharat Biotech is developed in collaboration with the Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV). The indigenous, inactivated vaccine is developed and manufactured in Bharat Biotech's BSL-3 (Bio-Safety Level 3) high containment facility.
4. Pfizer-BioNTech COVID-19 (mRNA vaccine) (Tozinameran or BNT162b2) is used to prevent COVID-19. The Pfizer-BioNTech COVID-19 vaccine is manufactured by Pfizer Inc, USA and BioNTech Inc., Manufacturing GmbH, Germany. initial efficacy results of 95% in their primary analysis (Pfizer/BioNTech) (Pfizer. Pfizer and BioNTech, 2020).
5. Moderna COVID-19 vaccine (mRNA-1273) is used to prevent coronavirus SARS-CoV-2 (COVID-19). The Moderna COVID-19 mRNA vaccine is manufactured by Moderna Therapeutics Inc, Cambridge, Massachusetts, USA. (Baden et al. 2020; Moderna COVID-Vaccine (mRNA-1273) (mRNA-based vaccin), Moderna, BARDA, NIAID, USA) (Baden et al. 2020). Initial efficacy results of 94·5% (Baden et al. 2020; Moderna, 2020). The vaccine (The investigational vaccine known as mRNA-1273 was co-developed by Moderna, Inc., a biotechnology company based in Cambridge, Massachusetts, USA and the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, USA (Baden et al., 2020).
6. Sputnik V (Non-replicating viral vector), Gamaleya Research Institute, Acellena Contract Drug Research and Development, Russia (The Gamaleya National Centre, 2020)
7. EpiVacCorona (Peptide vaccine), Federal Budgetary Research Institution, State Research Center of Virology and Biotechnology, Russia.
8. BBIBP-CorV (Inactivated vaccine), Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm), China
9. Comirnaty (BNT162b2) ( mRNA-based vaccine), Pfizer, BioNTech; Fosun Pharma, Multinational.
10. Covovax- (It's a protein subunit vaccine, and uses nanoparticles): The Serum Institute of India (SII), Pune, Maharashtra, India hopes to launch Covovax — developed in partnership with American vaccine developer Novavax, Gaithersburg, Maryland, USA
11. Novavax candidate vaccine, (NVX-CoV2373) Novavax, Inc. (Nasdaq: NVAX) is a biotechnology company, Gaithersburg, Maryland, USA (Tian et al., 2021)

i. NVX-CoV2373 is a vaccine candidate engineered from the genetic sequence of SARS-CoV-2, the virus that causes COVID-19 disease. NVX-CoV2373 was created using Novavax' recombinant nanoparticle technology to generate antigen derived from the coronavirus spike (S) protein and contains Novavax' patented saponin-based Matrix-M™ adjuvant to enhance the immune response and stimulate high levels of neutralizing antibodies. NVX-CoV2373 contains purified protein antigen and cannot replicate, nor can it cause COVID-19 (Tian et al., 2021).

*17). Plants used as immunity booster*, antiviral activity and inhibited the activity of coronavirus (SARS-CoV-2) during recent (2019-2020) outbreak

*1) Turmeric* (*Curcuma longa* L.) (Haladi; *Arashina* in Kannada) is a rhizomatous herbaceous perennial plant belonging to the ginger family *Zingiberaceae*, which is native to tropical South Asia (Prasad and Aggarwal, 2011; Ammon and Wahl, 1991; Apisariyakul et al., 1995; Araujo and Leon, 2001; Arora et al., 1971; Dixit et al., 1988*). Turmeric (Curcuma longa* L.) has been widely used as a common household remedy for cough, sore throat and respiratory ailments in Asia (Gupta et al., 2020; Prasad and Aggarwal, 2011; Ammon and Wahl, 1991; Apisariyakul et al., 1995; Araujo and Leon, 2001; Arora et al., 1971; Dixit et al., 1988).

During recent covid-19 outbreak, Turmeric (*Curcuma longa* L.) in hot water or milk was given to patients everyday suffering from high fever, throat infections for preventing further infections (Singh et al., 2021; Thota et al., 2020; Zahedipour et al., 2020; Brendler et al., 2020; Manoharan et al., 2020; Jia et al ., 2005; Li et al., 2017; Rocha and Assis, 2020; Pang et al., 2015; Das et al., 2020; Praditya et al., 2019;

Roy et al., 2020). It is reported that, curcumin exerts antiviral activities against broad spectrum of viruses including HIV, HSV-2, HPV viruses, Influenza virus, Zikavirus, Hepatitis virus and Adenovirus (Gupta et al., 2020; Manoharan et al., 2020; Zahedipour et al., 2020; Thota et al., 2020; Jia et al ., 2005; Rocha and Assis, 2020; Li et al., 2017; Pang et al., 2015; Das et al., 2020; Praditya et al., 2019). Furthermore, a hypothetical treatment strategy of using curcumin as (1) potential inhibitory agent blocking the host viral interaction (viral spike protein—ACE2 receptor) at an entry site in humans and (2) as an attenuator via modulating the proinflammatory effects of Angiotensin II-AT1 receptor-signalling pathways reducing respiratory distress in the treatment of COVID19 (Singh et al., 2021; Zahedipour et al., 2020; Brendler et al., 2020; Rocha and Assis, 2020; Manoharan et al., 2020; Jia et al., 2005; Li et al., 2017; Pang et al., 2015; Das et al., 2020; Praditya et al., 2019).

Numerous curcumin derivatives have been evidenced to have antiviral properties (Singh et al., 2021; Gupta et al., 2020; Thota et al., 2020; Manoharan et al., 2020; Roy et al., 2020; Rocha and Assis, 2020; Brendler et al., 2020). A study using In silico approach involving docking and stimulation, demonstrated the dual binding affinity of polyphenolic compounds in which both the viral S protein and ACE2 binds to curcumin (Manoharan et al., 2020; Jia et al., 2005; Li et al., 2017; Pang et al., 2015; Das et al., 2020; Praditya et al., 2019). Binding of curcumin to receptor-binding domain (RBD) site of viral S protein and also to the viral attachment sites of ACE2 receptor, demonstrated that curcumin can act as a potential inhibitory agent antagonizing the entry of SARS-CoV-2 viral protein (Thota et al., 2020; Rocha and Assis, 2020; Roy et al., 2020; Zahedipour et al., 2020; Manoharan et al., 2020; Jia et al 2005; Li et al., 2017; Pang et al., 2015; Das et al., 2020; Praditya et al., 2019; Brendler et al., 2020; Singh et al., 2021).

The emulsion form of topical application of curcumin may also effectively prevent the SARS-CoV-2 infection in humans, as the viral entry site of ACE2 receptor is predominantly distributed at the nasal cells, mucosal surface of respiratory tract and eyes (Rocha and Assis, 2020; Manoharan et al., 2020; Jia et al., 2005; Li et al., 2017; Pang et al., 2015; Das et al., 2020; Praditya et al., 2019; Brendler et al., 2020). Nutritional supplements of curcumin with vitamin C and zinc have showed promising results in boosting the natural immunity and protective defense mechanism against the SARS-CoV-2 infections, which have been noted in many hospitalized patients in Indian setting (Gupta et al., 2020; Manoharan et al., 2020; Jia et al., 2005; Li et al., 2017; Pang et al., 2015; Das et al., 2020; Praditya et al., 2019). It is also noted that pharmacological formulation of curcumin in nanoemulsion system proved increased solubility and bioavailability and with enhanced antihypertensive effect (Thota et al., 2020; Manoharan et al., 2020; Jia et al., 2005; Li et al., 2017; Pang et al., 2015; Das et al., 2020; Praditya et al., 2019). Therefore, the mode of drug delivery system of curcumin could be considered while formulating the pharmaceutical products and its application as a preventive measures in the inhibition of transmission of SARS-COV-2 infection among humans (Manoharan et al., 2020; Jia et al., 2005; Li et al., 2017; Pang et al., 2015; Das et al., 2020; Praditya et al., 2019). However, further large scale clinical trials are warranted to understand the usefulness of curcumin for the pharmacological applications in nanoemulsion system. Hence curcumin as an antiviral and anti-inflammatory agent can be helpful for both prevention and treatment of new emerging coronavirus (Singh et al., 2021; Zahedipour et al., 2020; Brendler et al., 2020; Thota et al., 2020).

Studies using neuraminidase activation assay showed that five active curcumin derivatives decreased H1N1-induced neuraminidase activation in H1N1-infected lung epithelial cells (Gupta et al., 2020; Manoharan et al., 2020). Tetramethylcurcumin and curcumin even down regulates nucleoprotein expression (Gupta et al., 2020; Richart et al., 2018; Lai et al., 2020). Various researchers have found that turmeric derivatives useful in the management of influenza virus infections (Gupta et al., 2020; Richart et al., 2018; Lai et al., 2020). Richart et al., (2018) observed that monoacetylcurcumin and curcumin both inhibited influenza virus infection, but via different pathways (Manoharan et al., 2020; Gupta et al., 2020; Richart et al., 2018; Lai et al., 2020). Significant antiviral activity of turmeric against H5N1 (highly pathogenic avian influenza) virus in Madin–Darby canine kidney (MDCK) cells *in vitro* by interfering with viral haemagglutination (HA) activity has also been observed (Gupta et al., 2020; Richart et al., 2018; Lai et al., 2020). The effects of anti-H5N1 virus activity by turmeric extracts were demonstrated by the upregulation in the tested MDCK cells of the mRNA expression of the genes for tumour necrosis factor-α and interferon-β, which are potent antiviral agents (Gupta et al., 2020; Richart et al., 2018; Lai et al., 2020).

Curcumin has been found to be beneficial in other viral disorders such as AIDS due to its inhibitory activity against HIV protease along with its synergistic action on other therapeutic drugs (Singh et al., 2021; Manoharan et al., 2020; Gupta et al., 2020; Richart et al., 2018; Lai et al., 2020; Prasad and Tyagi, 2015). It has also been shown to inhibit other viruses such as hepatitis B, hepatitis C, zika, chikungunya and dengue (Gupta et al., 2020; Richart et al., 2018; Lai et al., 2020; Prasad and Tyagi, 2015). Respiratory distress syndrome with hypercytokinaemia and multi organ failure is the leading cause of mortality with COVID-19 (Gupta et al., 2020; Richart et al., 2018; Lai et al., 2020; Prasad and Tyagi, 2015). Curcumin has been found to attenuate influenza A virus-induced lung tissue injury by blocking nuclear factor κB signalling and inhibiting the production of inflammatory cytokines (Gupta et al., 2020; Richart et al., 2018; Lai et al., 2020; Prasad and Tyagi, 2015; Singh et al., 2021). Curcumin is a natural ligand of peroxisome proliferator-activated receptor-γ, which represses the inflammatory process by reducing cytokine production. Therefore, curcumin might play

a similar role of protection against lung injury associated with COVID (Gupta et al., 2020; Richart et al., 2018; Lai et al., 2020; Prasad and Tyagi, 2015; Ciavarella et al., 2020; Manoharan et al., 2020; Singh et al., 2021).

In conclusion, curcumin could be used as a supportive therapy in the treatment of COVID19 disease in any clinical settings to circumvent the lethal effects of SARS-CoV-2 (Singh et al., 2021; Zahedipour et al., 2020; Brendler et al., 2020; Manoharan et al., 2020; Jia et al., 2005; Li et al., 2017; Pang et al., 2015; Das et al., 2020; Praditya et al., 2019; Gupta et al., 2020).

*2)* In India, the combination of *Ginger-Mulethi Tea* is a soothing remedy for sore throat, cold, and cough and acts as a immunity booster. *Ginger (Aadrak or Shunti*) (*Zingiber officinale*) and Mulethi or Liquorice (***Glycyrrhiza glabra***) are two such plant spices that are being used in a number of tea-blends, and it's not just for the kick of flavours (Bhat et al., 2010).

**Ginger** (*Zingiber officinale*) belongs to family *Zingiberaceae* is a herbaceous perennial flowering plant whose rhizome, ginger root or ginger, is widely used as a spice and a folk medicine (Thota et al., 2020; Grzanna et al., 2005; Bhat et al., 2010). Ginger (*Zingiber officinale*) has a powerful antioxidant and anti-inflammatory properties that are not only averts the risk of cold and flu, but also helps to manage the symptoms (Grzanna et al., 2005; Bhat et al., 2010; Singh et al., 2021). The active constituent "Gingerol has analgesic, sedative, antipyretic and antibacterial effects; another component zingerone is an antioxidant." (Grzanna et al., 2005; Bhat et al., 2010; Thota et al., 2020; Singh et al., 2021).

***Mulethi** (liquorice) (**Glycyrrhiza glabra)*** is a flowering plant of the bean family *Fabaceae* is also called as *Yashtimadhu* in *Ayurveda*. It is an important herb used in the Indian medicines, home remedies, folk medicines and *Ayurveda* (Damle, 2014; Kataria et al., 2013; Saxena, 2005). The herb Mulethi or Liquorice (*Glycyrrhiza glabra*) is also a treasure of antioxidants that helps to combat the dangerous free radical activity that causes premature ageing of cells and takes a toll on immunity as well (Damle, 2014; Kataria et al., 2013; Saxena, 2005). Mulethi or Liquorice (*Glycyrrhiza glabra***)** helps to develop immunity naturally, and has a balmy effect on your throat and inflamed tracts (Damle, 2014; Kataria et al., 2013; Saxena, 2005).

Glycyrrhizin is the major component responsible for the sweet-tasting constituent of *Glycyrrhiza glabra* (Mulethi or Liquorice) root, has been tested against eleven flaviviruses including DENV-1, DENV-2, and DENV-3 (dengue) (Crance et al., 2003; Teixeira et al., 2014). This antiviral compound glycyrrhizin has already been used in patients in the treatment of other diseases (Crance et al., 2003; Teixeira et al., 2014). The use of Mulethi or Liquorice (*Glycyrrhiza glabra***)** is known to boost immunity, and helped the body to produce lymphocytes and macrophages that protect the body from microbes, pollutants, allergens and cells that causes the autoimmune diseases (Damle, 2014; Kataria et al., 2013; Saxena, 2005). Therefore, a well-defined randomized studies should be performed to evaluate the efficacy of Mulethi or Liquorice (*Glycyrrhiza glabra***)** derivatives against SARS-CoV-2 and to assess its value as a possible treatment for this deadly coronavirus.

*3)* Initial studies in China showed that, the alcoholic extract of sweet wormwood (***Artemisia annua***) was the second most potent herbal medicine used on the 2005, SARS-CoV outbreak (Kapepula et al., 2020; Haq et al., 2020; Thota et al., 2020). The tonic, based on the plant *Artemisia annua*, belongs to a family of *Asteraceae* which has anti-malarial properties (Kapepula et al., 2020; Haq et al., 2020; Singh et al., 2021). Antimalarial drugs led to the discovery of artemisinin, a compound which is extracted from *Artemisia annua* (Kapepula et al., 2020; Haq et al., 2020).). The plant parts have been used for the preparation of a tonic COVID-19 Organics, Malagasy Institute of Applied Research has been used as a immunity booster for the patients suffering from covid-19 (Kapepula et al., 2020; Haq et al., 2020). The clinical trials of this medicinal plant yet to be conducted. *Artemisia annua* extracts showed a very little toxicity and artemisinin-based drugs were widely used to treat malaria even in newborns (Kapepula et al., 2020; Haq et al., 2020). Further pre-clinical and clinical trials need to be done for the evaluation of safety and efficacy of this polyherbal formulation (Kapepula et al., 2020; Haq et al., 2020).

*4) Azidarachta indica* (Neem) belongs to family *Meliaceae*. Neem is a fast-growing tree with a final height in the range of 15–20 m (Malabadi et al., 2018). It is native to India and grows throughout tropical and semi-tropical regions (Malabadi et al., 2018). The aqueous extract of *Azidarachta indica* (Neem) leaves has been given to the patients suffering from coronavirus high fever since *Azidarachta indica* (Neem) has antiviral, antifungal and antibacterial properties (Thota et al., 2020; Singh et al., 2021). *In vitro* and *in vivo* inhibitory potential of crude aqueous extract of *Azidarachta indica* (neem) leaves and pure neem compound (Azadirachtin) on the replication of dengue virus type-2 has been reported (Singh et al., 2021; Parida et al., 2002; Malabadi et al., 2018). *Azidarachta indica* (Neem) is also widely used as an immunity booster (Singh et al., 2021; Thota et al., 2020). The clinical trials of *Azidarachta indica* (neem) in case of coronavirus outbreak (SARS-CoV-2) are yet to be concluded (Singh et al., 2021; Thota et al., 2020). However, well-designed clinical trials are needed to demonstrate the potential efficacy of neem against SARS-CoV-2 infection and its ensuing complications (Singh et al., 2021; Thota et al., 2020).

*5) Tulsi* (*Ocimum sanctum*) belongs to basil family *Lamiaceae* (tribe ocimeae), is an aromatic shrub originated in India (Bast et al., 2014; (Malabadi et al., 2018). Tulsi (*Ocimum sanctum*) being antiviral in nature frequently consumed as a herbal tea or chai acts as a preventive botanical medicine against dengue fever (DF) (Tang et al., 2012; Mondal et al., 2009, 2011; Malabadi et al., 2018). The aromatic leaf of Tulsi (*Ocimum*

*sanctum*) can be a primary line of defence preventing the infection of COVID-19 (Singh et al., 2021; Thota et al., 2020; Malabadi et al., 2018).

Natural products have the potential to serve as prophylactic agents in populations that are at risk to develop COVID-19 infection (Singh et al., 2021; Thota et al., 2020). Natural products like ginger, turmeric, garlic, onion, cinnamon, lemon, neem basil and black pepper have been scientifically proven to have therapeutic benefits against acute respiratory tract infections including pulmonary fibrosis, diffuse alveolar damage, pneumonia, and acute respiratory distress syndrome, as well as associated septic shock, lung and kidney injury, all of which are symptoms associated with COVID-19 infection (Singh et al., 2021; Thota et al., 2020).

*6) Guduchi* or Giloy (*Tinospora cordifolia*) **(***Amruthballi in* Kannada) belonging to family *Menispermaceae* is a genetically diverse, large, deciduous climbing shrub with greenish yellow typical flowers, found at higher altitude (Kumar et al., 2017; Dhama et al., 2017; Saha and Ghosh, 2012; Rana et al., 2012; Parthipan et al., 2011; Rastogi et al., 2020; Sharma et al., 2012). Guduchi or Giloy (*Tinospora Cordifolia*) is a very important medicinal plant found in the Western Ghat Forest, Karnataka (Kumar et al., 2017; Dhama et al., 2017; Saha and Ghosh, 2012; Rana et al., 2012; Parthipan et al., 2011; Rastogi et al., 2020; Sharma et al., 2012).

The climber growing over walls, hedges and trees is a familiar sight in Mysuru city, Karnataka (Kumar et al., 2017; Saha and Ghosh, 2012). Consuming Guduchi or Giloy (*Tinospora Cordifolia*) juice can help you to get rid of fever, which is one of the signs of COVID-19. Its anti-inflammatory properties helped in tackling respiratory problems like cough, cold, and breathing problems (Kumar et al., 2017).

In one of the recent study, Guduchi Ghan Vati (*Tinospora Cordifolia*) (*Ayurveda preparation*) was effective in clearing viral nasopharyngeal carriage of COVID-19 patients under medical observation within 5 days (Rastogi et al., 2020; Kumar et al., 2020). These results are of great importance since mean duration of viral shedding in patients suffering from COVID-19 in asymptomatic to mild symptoms is 14-21 days (even 37 days for the longest duration) (Kumar et al., 2020). Previous study also confirmed that asymptomatic patients have longer treatment cycle (16 days) compared to moderate Covid-19 case (13 days) (Kumar et al., 2020). Therefore, this study shortened the treatment period to 6 days in asymptomatic Covid-19 confirmed cases those who used *Ayurveda* intervention (Kumar et al., 2020). There is no previous clinical study available on efficacy of *Ayurveda* treatment for Covid-19 (Kumar et al., 2020). Further *Ayurveda* herb Guduchi or Giloy (*Tinospora cordifolia*) used in this experimental study is widely available worldwide with no side effects reported (Kumar et al., 2020).

Therefore, this study recommends that COVID-19 asymptomatic patients can be treated with Guduchi or Giloy (*Tinospora cordifolia*) to cure their viral infection and to limit the transmission of the coronavirus to other people in order to curb the spread of COVID-19 in the world (Kumar et al., 2020). In conclusion, first data on the efficacy and safety of Guduchi Ghant Vati (*Tinospora Cordifolia*) (*Ayurveda* Preparation) on asymptomatic Covid-19 patients has been conducted. Furthermore, the potential of Guduchi Ghan Vati (*Tinospora cordifolia*) treatment may also reduce the duration of viral shedding and prevent the disease from worsening symptoms or clinical condition (Kumar et al., 2020). This study could help in the management of the Covid-19 outbreak and further clinical trials should be conducted for the scientific validation (Kumar et al., 2020).

*7) Kutki* (*Picrorhiza kurroa*) Royle ex Benth, belongs to family *Scrophulariaceae* is found in the Himalayan regions of India, Bhutan, Nepal, China and Pakistan (Rathee et al., 2012; Kumar et al., 2010; Patial et al., 2012; Masood et al., 2015). It is considered as an important medicinal plant which is mostly used in the traditional medicinal system for asthama, jaundice, fever, malaria, snake bite and liver disorders (Rathee et al., 2012; Kumar et al., 2010; Patial et al., 2012; Masood et al., 2015). The oral cosumption of rhizome part of Kutki (*Picrorhiza kurroa*) during covid-19 outbreak has helped patients as a immunity booster preventing further infections of coronavirus. The results of clinical trials are yet to be conducted.

*8) Triphala* (Sanskrit; tri = three and phala = fruits) is a well recognized polyherbal medicine consisting of dried fruits of the three plant species *Emblica officinalis* (Family *Euphorbiaceae*), *Terminalia bellerica* (Family *Combretaceae*), and *Terminalia chebula* (Family *Combretaceae*) that are native to the Indian subcontinent (Peterson et al., 2017; Pulok et al., 2005; Shanbag, 2015; Belapurkar et al., 2014). *Triphala* (an ayurvedic herbal Rasayana) is a rich source of vitamin C and flavonoids (Peterson et al., 2017; Pulok et al., 2005; Shanbag, 2015; Belapurkar et al., 2014). *Triphala* (an ayurvedic herbal Rasayana) was also used as a immunity booster since *Triphala* is a rich source of vitamin C during covid-19 outbreak to prevent further coronavirus infections. *Triphala* is a powerful polyherbal formula which provides therapeutic value for multiple pathologies including stress reducing potential (Peterson et al., 2017; Pulok et al., 2005; Shanbag, 2015; Belapurkar et al., 2014). Both *Triphala* water decoctions (12%) and ethanol extracts (14%) have demonstrated antibacterial activity *in vitro* against bacterial isolates derived from patients infected with human immunodeficiency virus (Peterson et al., 2017; Pulok et al., 2005; Shanbag, 2015; Belapurkar et al., 2014).

*Triphala* is classified as a *tridoshic rasayana* in *Ayurvedic* medicine as it promotes longevity and rejuvenation in patients of all constitutions and ages (Peterson et al., 2017; Pulok et al., 2005; Shanbag, 2015; Belapurkar et al., 2014; Pradeep et al., 2016). Triphala has been used traditionally in *Ayurvedic* medicine as an antimicrobial agent (Peterson et al., 2017;

Pulok et al., 2005; Shanbag, 2015; Belapurkar et al., 2014). Numerous controlled clinical trials have shown that *Triphala* significantly reduces the abundance of oral bacteria, dental plaque, and gingivitis in human subjects in addition to antimicrobial effects against oral bacteria (Pradeep et al., 2016; Peterson et al., 2017; Pulok et al., 2005; Shanbag, 2015; Belapurkar et al., 2014). *Triphala* has also been demonstrated the potential to eradicate enteric pathogens *in vitro* (Peterson et al., 2017; Pulok et al., 2005; Shanbag, 2015; Belapurkar et al., 2014).

*9) Amla (Phyllanthus emblica) Indian gooseberry and Aloe vera (Aloe barbadensis) juice*

*Amla* (*Phyllanthus emblica*) or *Emblica officinalis* Gaertn belongs to family *Euphorbiaceae* is widely used in the Indian system of medicine and believed to increase defensive against viral, bacterial and fungal diseases (Kulkarni and Ghurghure, 2018; Khan, 2009; Srivasuki, 2012). Amla juice is used as a immunity booster. Amla is a very rich source of vitamin C (Kulkarni and Ghurghure, 2018; Khan, 2009; Srivasuki, 2012). In *Ayurveda*, amla is considered to be a potent rejuvenator and immunomodulator effective in stalling degenerative processes and senescence, and to promote longevity, enhance digestion, treat constipation, reduce fever and cough, alleviate asthma, strengthen the heart, benefit the eyes, stimulate hair growth, enliven the body, and enhance intellect (Kulkarni and Ghurghure, 2018; Khan, 2009; Srivasuki, 2012).

The botanical name of Aloe vera is *Aloe barbadensis* miller. It belongs to *Asphodelaceae* (*Liliaceae*) family, which is a shrubby or arborescent, perennial, xerophytic, succulent, pea-green color plant. During outbreak of covid-19, a juice mixture of Amla (*Phyllanthus emblica*) and Aloe vera (*Aloe barbadensis*) was also given to covid-19 patients as a immunity booster. This is a very common, less expensive approach to combat many diseases.

*10) Lavang (Syzygium aromaticum*)

Cloves (*Syzygium aromaticum*) are the aromatic flower buds of a tree in the family *Myrtaceae* (Milind and Deepa, 2011; Gopalakrishnan et al., 1988; Narayanan and Natu, 1974). Clove is known to possess antibacterial, antivial and antifungal properties and is used in various dental creams, tooth pastes, mouth washes, and throat sprays to cleanse bacteria (Milind and Deepa, 2011). It is also used to relive pain from sore gums and improves overall dental health. In dentistry, eugenol in combination with zinc oxide is used for temporary filling of cavities (Milind and Deepa, 2011; Gopalakrishnan et al., 1988; Narayanan and Natu, 1974).

During coronavirus outbreak, clove consumption was used as a immediate remedy for the throat infections and clove has relieved the pain. Dried cloves are the key ingredient in Indian masala tea. Therefore, consumption of clove is one of the powerful remedy for the throat infections. Clove and clove oil boost the immune system by purifying the blood and help to fight against various diseases (Singh et al., 2021; Milind and Deepa, 2011). The aromatic clove oil, when inhaled can help soothe certain respiratory conditions like cold, cough, asthma, bronchitis, and sinusitis. It also helps in clearing the nasal tract (Milind and Deepa, 2011; Singh et al., 2021).

*11) Dalchini* (*Cinnamomum verum*)

The "True Cinnamon" or Sri Lankan Cinnamon is the dried inner stem bark of *Cinnamomum verum* belongs to a family *Lauraceae* (Rao and Gan, 2014). Cinnamon being an antioxidant, anti-inflammatory, antidiabetic, antimicrobial, anticancer, lipid-lowering, and cardiovascular-disease-lowering compound. Cinnamon has also been reported to have activities against neurological disorders, such as Parkinson's and Alzheimer's diseases (Vangalapati et al., 2012; Sangal, 2011; Rao and Gan, 2014).

During covid-19 outbreak, the oral consumption of stem bark of *Cinnamomum verum* has helped to relive the pain of throat infections since bark has the antifungal, antiviral and antibacterial properties (Singh et al., 2021). Throat infection is one of the symptom of the covid-19 (Singh et al., 2021). Therefore, clinical trials of the herbal medicines are very much needed for further investigation. This may be a benchmark for the economical clinical trials of specific plant material to treat the viral diseases in the future (Singh et al., 2021).

*12) Ayurvedic* herbs including *Tinospora cordifolia*, G*lycyrrhiza glabra*, *Adhatoda vasica*, *Andrographis paniculata*, *Swertia chirata*, *Moringa oleifera*, and Trikatu. These herbs are proposed for the reason that these are known to be broad-spectrum antivirals and protease inhibitors (Rastogi et al., 2020; Singh et al., 2021).

*13) Flavones* such as amentoflavone, quercetin, luteolin and apigenin obtained from *Torreya nucifera* have also been proven to inhibit 3CLpro protease function and RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2 virus (Ryu et al., 2010; Prasad et al., 2020). The Indian system of holistic medicine known as "*Ayurveda*" uses mainly plant-based drugs or formulations to treat various ailments, including viral diseases (Prasad and Aggarwal, 2011; Ammon and Wahl, 1991; Apisariyakul et al., 1995; Araujo and Leon, 2001; Arora et al., 1971; Dixit et al., 1988).

*14)* A recent study by Shawky et al., (2020) demonstrated that the potential use of medicinal plants and more than 16, 500 of their constituents against SARS-CoV-2 (Shawky et al., 2020). This study investigated two therapeutic strategies in the fight against SARS-CoV-2 including prevention of SARS-CoV-2 RNA synthesis and replication, through targeting viral proteins and enzymes as well as modulation of the host's immunity through production of virulence factors (Shawky et al., 2020). Molecular docking studies on the viral enzymes 3Clpro, PLpro and RdRp suggested that rocymosin B, verbascoside, rutin, caftaric acid, luteolin 7-rutinoside, fenugreekine and cyanidin 3-(600-malonylglucoside) act as

promising molecules for further drug development (Shawky et al., 2020). Meanwhile, the medicinal plants *Glycyrrhiza glabra, Hibiscus sabdariffa, Cichorium intybus, Chrysanthemum coronarium, Nigella sativa, Anastatica hierochuntica, Euphorbia species, Psidium guajava* and *Epilobium hirsutum* were enriched in compounds with the multi-targets PTGS2, IL2, IL1b, VCAM1 and TNF such as quercetin, ursolic acid, kaempferol, isorhamnetin, luteolin, glycerrhizin and apigenin (Shawky et al., 2020). Enriched pathways of the molecular targets included cytokine–cytokine receptor interaction, TNF signaling pathway, NOD-like receptor signaling pathway, Toll-like receptor signaling pathway, NFkappa B signaling pathway and JAK-STAT3 signaling pathway which are all closely related to inflammatory, innate and adaptive immune responses (Shawky et al., 2020). Therefore this study identified natural compounds targeting SARS-CoV-2 for further *in vitro* and *in vivo* studies and emphasizes the potential role of medicinal plants in the mitigation of SARS-CoV-2 (Shawky et al., 2020). Several constituents identified may inhibit SARS-CoV-2 activity through the inhibition of virus replication (Shawky et al., 2020). These results demonstrated a potential role of medicinal plants in the management of the current SARS-CoV-2 infection (Shawky et al., 2020).

*15)* Yu et al., (2020) reported that water extract of *Houttuynia cordata* has an antiviral activity against SARS-CoV due to its inhibitory effect on 3C-like protease (3CLpro) and RNA-dependent RNA polymerase (RdRp) of the virus (Yu et al., 2020; Prasad et al., 2020). Myricetin, a flavonoid obtained from *Myrica rubra*, and Scutellarein, a flavone obtained from *Scutettaria baicalensis* and *Asplenium belangeri* are known to inhibit the ATPase activity of SARS-CoV helicase nsP13 (Yu et al., 2020; Prasad et al., 2020).

*16)* Many of the medicinal plants and their constituents have a potential for use in the mitigation of the new SARS-CoV-2 infection (Shawky et al., 2020). Additionally, in an investigation covering 23 Chinese provinces, it was reported that the most frequently prescribed Chinese herbs used in the prevention of COVID-19 were (in descending order): *Radix astragali*, *Glycyrrhizae* Radix Et Rhizome, Radix *Saposhnikoviae*, Rhizoma *Atractylodis macrocephalae*, *Lonicerae japonicae* Flos, *Fructus forsythia*, *Atractylodis* Rhizoma, Radix *Platycodonis*, *Pogostemonis* Herba, *Cyrtomium fortunei* J. Sm (Luo et al., 2020; Shawky et al., 2020).

*17)* The randomized controlled trials confirmed that the *Glycyrrhiza glabra* demonstrated a reduction of mortality and viral activity in SARS-CoV-2 related coronavirus (Wu et al., 2017; Shen et al., 2013; Xie et al., 2013; Luo et al., 2020; Shawky et al. 2020). Meanwhile, the plants *Hibiscus sabdariffa* and *Cichorium intybus* are rich sources of caffeic acid derivatives which have been widely investigated concerning their antiviral potential (Wu et al., 2017; Shen et al., 2013; Xie et al., 2013; Luo et al., 2020; Shawky et al., 2020). The performed network pharmacology analysis revealed the synergistic nature of the compounds within each medicinal plant. Combination of the most enriched plants in the created network i.e. *Glycyrrhiza glabra* (liquorice), *Hibiscus sabdariffa*, *Cichorium intybus*, could be chosen for the mitigation of SARS-CoV-2 (Wu et al., 2017; Shen et al., 2013; Xie et al., 2013; Luo et al., 2020; Shawky et al., 2020).

*18)* Recently, a natural stilbene derivative named resveratrol (trans-3, 5, 4′-trihydroxystilbene) present abundantly in *Vitis vinifera*, *Polygonum cuspidatum*, and *Vaccinium macrocarpon* showed inhibition of MERS-CoV infection (Lin et al., 2017; Prasad et al., 2020).

*19) Expression of SARS-coronavirus (CoV) spike protein (S protein) in tobacco plants***:** Recent studies indicated that SARS-coronavirus (CoV) spike protein (S protein) and its truncated fragments are considered as the best candidates for a generation of the recombinant vaccine (Pogrebnyak et al., 2005). Toward the development of a safe, effective, and inexpensive vaccine candidate, Pogrebnyak et al., (2005) expressed the N-terminal fragment of SARS-CoV S protein (S1) in tomato and low-nicotine tobacco plants (Pogrebnyak et al., 2005). Mice showed significantly increased levels of SARS-CoV-specific IgA after oral ingestion of tomato fruits expressing S1 protein (Pogrebnyak et al., 2005). Therefore, this study demonstrated that, the successful expression of SARS-CoV S protein in transgenic tobacco plants in amounts sufficient to induce antibody response after feeding mice with transgenic material (Pogrebnyak et al., 2005). The mice parenterally primed with plant-derived antigen developed an immune response after a booster immunization (Pogrebnyak et al., 2005).

*20)* Lectins of plants could be potential inhibitors of viruses. A study by Keyaerts et al., (2007) has screened 33 lectins isolated from different plant species for their activity against both SARS-CoV and Feline coronavirus (FCoV) (Keyaerts et al., 2007; Prasad et al., 2020). They identified mannose-binding lectin to possess a robust anti-coronaviral activity by targeting the entry as well as the release of the virus particles (Keyaerts et al., 2007: Prasad et al., 2020). Another lectin, agglutinin isolated from *Galanthus nivalis*, was able to effectively act against FCoV when administered in combination with nelfinavir, a synthetic drug (Hsieh et al., 2010; Prasad et al., 2020). This underlines the need for studying the combined effect of plant-based compounds and synthetic molecules to circumvent the viral load in the host system. However, minimal efforts were invested in this direction to study the synergistic antiviral effect of biomolecules and drugs (Prasad et al., 2020).

*21) Recombinant SARS-CoV-2 proteins M and N produced in tobacoo plants:* Demurtas et al., (2016) reported the characterization of the N and M proteins of SARS- CoV and provided a proof of principle for using plants as a robust, rapid and flexible production system for protein reagents suitable to face potential recurring SARS-CoV outbreaks (Demurtas et al., 2016). This study demonstrated the transient

expression in *Nicotiana benthamiana* of two important antigenic determinants of the SARS-CoV, the nucleocapsid protein (N) and the membrane protein (M) using a virus-derived vector or agro-infiltration (Demurtas et al., 2016). The availability of recombinant N and M proteins from plants opens the new way to furthere evaluation of their potentiality for the development of diagnostic and protection/therapy tools to be quickly manufactured, at a low cost and with minimal risk, to face a new highly infectious SARS-CoV-2 outbreaks (Demurtas et al., 2016).

*22)* Lycorine, an alkaloid extracted from *Lycoris radiata*, has an antiviral activity against Poliomyelitis virus and Herpes simplex virus, and is also effective against SARS-CoV (Li et al., 2005; Prasad et al., 2020). Emodin, sinigrin and hesperetin extracted from *Isatis indigotica* have also shown 3CLpro inhibition (Lin et al., 2005; Prasad et al., 2020).

*23) Recombinant SARS-CoV-2 proteins produced in tobacoo plants in South Africa*. Makatsa et al., (2020) established an indirect enzyme-linked immunosorbent assay (ELISA) using the S1 and receptor-binding domain (RBD) portions of the spike protein from SARS-CoV-2, expressed in *Nicotiana benthamiana* (Makatsa et al., 2020). This study measured antibody responses in sera from South African patients (n=77) who had tested positive by PCR for SARS-CoV-2 (Makatsa et al., 2020). Samples were taken a median of six weeks after the diagnosis, and the majority of participants had mild and moderate COVID-19 disease (Makatsa et al., 2020). This study also determined whether the assay could detect SARS-CoV-2-specific IgG and IgA in saliva (Makatsa et al., 2020).

Makatsa et al., (2020) demonstrated that recombinant SARS-CoV-2 proteins produced in plants enabled robust detection of SARS-CoV-2 humoral responses. This assay could be used for sero epidemiological studies and to measure the strength and durability of antibody responses to SARS-CoV-2 in an infected patients in our setting (Makatsa et al., 2020). This study demonstrated that recombinant SARS-CoV-2 proteins produced in plants enable the robust detection of SARS-CoV-2-specific antibodies and SARS-CoV-2 humoral immunity (Makatsa et al., 2020). This could be achieved by the use of plants for the production of viral antigens, which has the benefit of rapid scale-up, and sourcing reagents that were available locally and thus available at a lower cost (Makatsa et al., 2020). ELISA can be used to evaluate the SARS-CoV-2 sero prevalence and describe the kinetics of the humoral immune response in infected individuals (Makatsa et al., 2020).

*24) Quinine*, an alkaloid obtained from the bark of *Cinchona officinalis* has been used in the treatment of malaria since the 1960s (Prasad et al., 2020; Achan et al., 2011). Chloroquine (Cq) and hydroxychloroquine (Hcq) are structural analogs of quinine. In SARS-CoV-2, hydroxychloroquine in combination with azithromycin, is found to be more effective in reducing the viral load (Prasad et al., 2020; Gautreta et al., 2020).

*25) Glycyrrhizin*, a saponin isolated from *Glycyrrhiza glabra* roots, is reported to be effective against SARS-CoV by inhibiting the viral replication (Prasad et al., 2020; Cinatl et al., 2003). Considering the structural similarities and comparable modes of replication between SARS-CoV and SARS-CoV-2, glycyrrhizin might also be effective in treating the current covid-19 pandemic (Cinatl et al., 2003; Prasad et al., 2020).

*26) Quercetin derivatives extracted from Malus sp, Allium sp, Camellia sp*, etc demonstrated an antiviral activity aganst SARS-CoV (Park et al., 2012; Prasad et al., 2020). Tetra-O-galloyl-β-d-glucose and luteolin isolated from *Euphorbia jolkinin* and *Reseda luteola* inhibited the SARS-CoV (Yi et al., 2004; Prasad et al., 2020). Ethanolic extract of *Euphorbia neriifolia* showed antiviral activity against SARS-CoV (Chang et al., 2012; Prasad et al., 2020). Water extract of tender leaves of *Toona sinensis* demonstrated the inhibition of viral replication of SARS-CoV and HCoV 229E (Chen et al., 2008; Prasad et al., 2020). Emodin from *Rheum* sp and *Polygonum* sp blocked ACE-2 and S-glycoprotein interaction of SARS-CoV (Ho et al., 2007; Prasad et al., 2020). Aescin, reserpine isolated from *Aesculus hippocastanum* and *Rauvolfia serpentina* inhibited the viral replication of SARS-CoV (Wu et al., 2004; Prasad et al., 2020). Phenanthroindolizidines and Phenanthroquinolizidines isolated from *Asclepiadaceae* and *Moraceae* plant families inhibited the viral replication of SARS-CoV (Yang et al., 2010; Prasad et al., 2020).

*27)* In case of SARS-CoV-2, the Ministry of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy), Government of India, has recommended a formulation composed of 15 plants, namely, *Zingiber officinale*, *Piper longum*, *Syzygium aromaticum*, *Tragia involucrata*, *Anacyclus pyrethrum*, *Hygrophilla auriculata*, *Terminalia chebula*, *Adhatoda vasica*, *Plectranthus amboinicus*, *Saussurea costus*, *Tinospora cordifolia*, *Clerodendrum serratum*, *Andrographis paniculate*, *Sida acuta*, and *Cyperus rotundus*, *Artemisia annua* against SARS-CoV-2 (6.6% each; PIB 2020; Sivaraman and Pradeep, 2020; Vellingiri et al., 2020; MPIKG, 2020; Prasad et al., 2020).

*28) The S protein of the SARS-CoV was used for the expression in two plant species (tobacco and lettuce)* and produced a potential SARS-CoV recombinant antigen (Li et al., 2006). Lettuce is an easy-to-transform crop plant with abundant edible leaf tissue available for direct utilization and or downstream processing (Li et al., 2006). Tobacco is an extremely efficient plant transformation system and is frequently used in plant biotechnology as the system of choice (Li et al., 2006). This study provides a possibility of establishing a safe and inexpensive vaccination strategy against SARS since the plant chloroplast genome sequences are highly conserved (Li et al., 2006). The same construct used here in tobacco plastid-transformation could be applied to tomato, which would constitute an oral vaccine in its edible fruit (Li et al., 2006).

*29) Tobacco- plant-expressed recombinant SARS-CoV N protein*. Plants are now considered as promising bioreactors for pharmaceutical protein due to their safety, low cost, high output, simple storage requirement, and benefits of eukaryotic post-translational modifications (Zheng et al., 2009). Zheng et al., (2009) demonstrated that the post-transcriptional gene silencing suppressor p19 protein from tomato bushy stunt virus substantially enhanced the transient expression of recombinant SARS-CoV nucleocapsid (rN) protein in *Nicotiana benthamiana* (Zheng et al., 2009). The rN protein in the agrobacteria-infiltrated plant leaf accumulated up to a concentration of 79µg per g fresh leaf weight at 3 days post infiltration (Zheng et al., 2009). Antibodies of the subclasses IgG1 and IgG2a were abundantly present in the mouse sera (Zheng et al., 2009). During vaccination of rN protein, the expression of IFN-¥ and IL-10 was evidently up-regulated in splenocytes at different time points, while the expression of IL-2 and IL-4 was not (Zheng et al., 2009). This is the first study that plant-expressed recombinant SARS-CoV N protein can induce strong humoral and cellular responses in mice (Zheng et al., 2009).

*30) The Ministry of AYUSH, Government of India* has recommended '*Ayush Kwath'* to improve the immunity and combat the COVID-19 infection (Gautam et al., 2020). Herbs such as Tulsi, Marich, Sunthi, Dalchini are the most commonly used and easily available drugs in home (Gautam et al., 2020). Thus, *Ayush Kwath* due to its immune-modulatory, antiviral, anti-oxidant, anti-inflammatory, antiplatelet, anti-atherosclerotic, hepato-protective, reno-protective properties; seems to be effective in immuno-regulation for controlling viral infections like COVID-19 (Gautam et al., 2020). Further pre-clinical and clinical trials need to be done for the evaluation of safety and efficacy of this polyherbal formulation (Gautam et al., 2020; Li et al., 2020).

*31)* The different herbal products (extracts) and purified molecules may exert their anti-SARS-CoV-2 actions by direct inhibition of the virus replication or entry (Benarba and Pandiella, 2020; Li et al., 2020). Interestingly, some of the products may block the ACE-2 receptor or the serine protease TMPRRS2 required by SARS-CoV-2 to infect human cells (Benarba and Pandiella, 2020). In addition, natural products were shown to inhibit the SARS-CoV-2 life-cycle related proteins such as papain-like or chymotrypsin-like proteases (Benarba and Pandiella, 2020). Therefore, the natural products could be used alone or in combination as an alternative medicines to treat/ prevent COVID-19 infection (Benarba and Pandiella, 2020) Moreover, their structures may offer clues for the development of anti-SARS-CoV-2 drugs (Benarba and Pandiella, 2020).

*32)* Runfeng et al., (2020) studied the inhibitory effects and antiinflammatory potential of a Chinese herbal mixture called *Lianhuaqingwen* (a mixture of 11 medicinal species, a mineral medicine called gypsum and menthol) against SARS-CoV-2 (Runfeng et al., 2020; Benarba and Pandiella, 2020). The Chinese herbal mixture called Lianhuaqingwen inhibited SARS-CoV-2 replication in a dose-dependent manner with an IC50 of 411.2 µg/ml (Runfeng et al., 2020; Benarba and Pandiella, 2020). Plant metabolites can serve as potential anti-SARS-CoV-2 lead molecules for further optimization and drug development processes to combat COVID-19 and future pandemics caused by viruses (Bhuiyan et al., 2020). Therefore, further analysis by the scientific community will boost antiviral plant-based research followed by the novel drug designing (Bhuiyan et al., 2020).

*33) The* antiviral effects of *Soshihotang* (SSHT, Xiao Chai Hu Tang in Chinese, Shosaikoto in Japanese), which has been used in the past mainly for infectious diseases with chronic progression (Kwon et al. 2020). Kwon et al., (2020) demonstrated the possibility of utilizing Soshihotang (SSHT, Xiao Chai Hu Tang in Chinese, Shosaikoto in Japanese), as a new therapeutic option for COVID-19 (Kwon et al., 2020). In a number of recent clinical studies, treatment with Soshihotang (SSHT, Xiao Chai Hu Tang in Chinese, Shosaikoto in Japanese), improved the infection status of the respiratory and hepatobiliary systems (Kwon et al., 2020). Experimental studies demonstrated that the antiviral effect of Soshihotang (SSHT) and its components against SARS-CoV-2 (Kwon et al., 2020). Furthermore, Soshihotang (SSHT) are being used in China where COVID-19 outbreak first took place and offered a new option for the treatment of COVID-19 (Kwon et al., 2020). Therefore, it is believed that Soshihotang (SSHT) is likely to be a new therapeutic option for COVID-19 (Kwon et al., 2020). Conducting further studies might provide an improved understanding regarding the use of Soshihotang (SSHT) in treating COVID-19 (SARS-CoV-2) (Kwon et al., 2020). Therefore, Soshihotang (SSHT) could be prescribed for COVID-19 patients with persis-tent fever, respiratory symptoms such as cough or sputum, and liver injury caused by the conventional therapies (Kwon et al., 2020). Based on the evidence so far, it is believed that Soshihotang (SSHT) is likely to be a repurposing medication for COVID-19 (Kwon et al., 2020). Conducting further studies might provide an improved understanding regarding the use of Soshihotang (SSHT) in the treatment of COVID-19 (Kwon et al., 2020).

*34)* Wen et al., (2011) evaluated 200 Chinese herbal extracts for their anti-SARS-CoV effect using a cell-based assay (Wen et al., 2011; Benarba and Pandiella, 2020). Among them, six extracts [rhizomes of *Gentiana scabra* Bunge; tuber of *Dioscorea polystachya* Turcz.; seed of *Senna tora* (L.) Roxb.; stem and leaves of *Taxillus chinensis* (DC.) Danser; and two extracts of *Cibotium barometz* (L.) J.Sm. rhizome] were found to significantly inhibit SARS-CoV-2 growth and replication (Wen et al., 2011; Benarba and Pandiella, 2020). The impression of plant based medicine constitutes an applicable way for the expansion of vaccines with attractive features (Divya et al., 2020). Some studies demonstrated that traditional herbal extracts can interact with key viral proteins which are associated with virus virulence (Mirzaie et al.,

2020). The use of *Indian, Chinese, and Iranian* traditional herbal medicines, suggested that some of the herbs were used for the prevention, treatment and rehabilitation of the diseases including COVID-19 (Li et al., 2020; Mirzaie et al., 2020; Girija and Sivan, 2020). However, the beneficial effects of these traditional herbal medicines and their clinical trials remained to be known (Mirzaie et al., 2020).

*35)* Currently, there are limited number of allopathic medicines considered as effective against COVID-19 (Panyod et al., 2020; Girija and Sivan, 2020; Farooq and Ngaini, 2020). The design and development of drugs and vaccines require elucidation of the mechanism of SARS-CoV-2 (Panyod et al., 2020). Foods and herbs could be used as dietary or complementary therapy to prevent the coronavirus infection and strengthen immunity, as antiviral agents for masks, as disinfectants to curb aerosol transmission, or as sanitizing agents to disinfect surfaces (Panyod et al., 2020). Current literature provides an obvious evidence supporting dietary therapy and herbal medicine as a potential effective antivirals against SARS-CoV-2 and as preventive agents against COVID-19 (Panyod et al., 2020). Thus, dietary therapy and herbal medicine could be a complementary preventive therapy for COVID-19 (Panyod et al., 2020). Therefore, foods and herbs possess a potential antiviral ability against SARS-CoV-2 and can prevent COVID-19 (Panyod et al., 2020). However, these hypotheses require experimental validation in SARS-Cov-2 infection models with COVID-19 patients (Panyod et al., 2020).

*36) A plant expression system* can rapidly and effectively produce a functional ACE2-Fc fusion protein on a large scale **(Siriwattananon et al., 2021**). Moreover, the plant produced ACE2-Fc fusion protein exhibits anti-SARS-CoV-2 activity in a post-entry treatment under *in vitro* conditions suggesting that, it could be used as a post-exposure therapeutic to treat COVID-19 (Siriwattananon et al., 2021). A recent study of Siriwattananon et al., (2021) reported that, the transiently produced human ACE2 fused with the Fc region of human IgG1 in *Nicotiana benthamiana* and the *in vitro* neutralization efficacy of the plant-produced ACE2-Fc fusion protein was assessed (Siriwattananon et al., 2021). The recombinant ACE2-Fc fusion protein was expressed in *N. benthamiana* at 100 µg/g leaf fresh weight on day 6 post-infiltration (Siriwattananon et al., 2021). The recombinant fusion protein showed potent binding to the receptor binding domain (RBD) of SARS-CoV-2 (Siriwattananon et al., 2021). Importantly, the plant-produced fusion protein exhibited potent anti SARS-CoV-2 activity *in vitro* (Siriwattananon et al., 2021). Treatment with ACE2-Fc fusion protein after viral infection dramatically inhibited the SARS-CoV-2 infectivity in Vero cells with an IC50 value of 0.84 µg/ml. Moreover, treatment with ACE2-Fc fusion protein at the pre-entry stage suppressed the SARS-CoV-2 infection with an IC50 of 94.66 µg/ml (Siriwattananon et al., 2021). These findings put a spotlight on the plant-produced ACE2-Fc fusion protein acts as a potential therapeutic candidate against SARS-CoV-2 (Siriwattananon et al., 2021).

*37) Rattanapisit et al.,* (2020) explored the possibility of producing the receptor binding domain (RBD) of SARSCoV-2 and an anti-SARS-CoV monoclonal antibody (mAb) CR3022 in *Nicotiana benthamiana* (Rattanapisit et al., 2020). Both receptor binding domain (RBD) and mAb CR3022 were transiently produced with the highest expression level of 8 µg/g and 130 µg/g leaf fresh weight respectively at 3 days post-infltration (Rattanapisit et al., 2020). The plant-produced receptor binding domain (RBD) exhibited specifc binding to the SARS-CoV-2 receptor, angiotensin-converting enzyme 2 (ACE2) (Rattanapisit et al., 2020). Furthermore, the plant-produced mAb CR3022 binds to SARS-CoV-2, but failed to neutralize the virus *in vitro* (Rattanapisit et al., 2020). This is the frst report showing the production of anti-SARS-CoV-2 RBD and mAb CR3022 in plants (Rattanapisit et al., 2020). Overall these fndings provided a proof-of-concept for using plants as an expression system for the production of SARS-CoV-2 antigens and antibodies or similar other diagnostic reagents against SARS-CoV-2 rapidly, especially during epidemic or pandemic situation (Rattanapisit et al., 2020).

*38) In South Africa*, Margolin et al., (2020) investigated new approaches to support the production of a soluble and putatively trimeric SARS-CoV-2 spike protein in *Nicotiana benthamiana via* transient *Agrobacterium*-mediated expression (Margolin et al., 2020). The co-expression of human calreticulin dramatically improved the accumulation of the viral spike, which was barely detectable in the absence of the co-expressed accessory protein (Margolin et al., 2020). In contrast, the spike protein was not efficiently processed when expressed in mammalian cells as a control, although the co-expression of furin improved processing considerably (Margolin et al., 2020). This study supported plant-based production of SARS-CoV-2 spike-based vaccines and reagents for the serological assays (Margolin et al., 2020).

**39)** The host enzyme transmembrane protease serine 2 (TMPRSS2) facilitates viral particle entry into host cells (Huang et al., 2020; Kumar et al., 2020). Inhibiting of this enzyme (TMPRSS2) blocks virus fusion with ACE2, making it a potential target to inhibit virus entry (Huang et al., 2020; Kumar et al., 2020). By molecular docking and molecular dynamics simulations, Kumar et al., (2020) have shown that withanone derived from Ashwagandha leaves (*Withania somnifera* (L.) Dunal) could bind and stably interact at the catalytic site of TMPRSS2 (His296, Asp345 and Ser441) (Huang et al., 2020; Kumar et al., 2020). In addition, they have also been confirmed that withanone significantly downregulated TMPRSS2 in MCF-7 cells, suggesting its dual potential to ramp down TMPRSS2 function (Huang et al., 2020; Kumar et al., 2020).

*40)* In another major development, SARS-CoV-2 papain-like protease (PL pro) cleaves the viral polyproteins a/b which is essential for its survival and replication (Goswami et al.,

2020; Huang et al., 2020; Kumar et al., 2020). Thus, papain-like protease (PL pro) is one of the prospective drug targets of SARS-CoV-2 (Goswami et al., 2020; Huang et al., 2020; Kumar et al., 2020). Furthermore, Goswami et al., (2020) established a library of small molecules found in the rhizomes, *Alpinia officinarum* (*Alpinia officinarum* Hance), ginger (*Zingiber officinale* Roscoe), and curcuma (*Curcuma longa* L.) (Goswami et al., 2020; Huang et al., 2020; Kumar et al., 2020). The compounds were docked into the solvent accessible S3-S4 pocket of PLpro. In silico results showed that eight lead compounds from galangal (*Alpinia officinarum* Hance) and ginger (*Zingiber officinale* Roscoe) bound with high affinity to SARS-CoV-2 PLpro, suggesting their potential role as inhibitors against SARS-CoV-2 (Goswami et al., 2020; Huang et al., 2020; Kumar et al., 2020). However, subsequent *in vitro* and *in vivo* experiments are needed to elucidate their efficacy against SARS-CoV-2 (Goswami et al., 2020; Huang et al., 2020; Kumar et al., 2020; Farooq and Ngaini, 2020).

*41)* A herbal formulation recommended by National Health Commission of the P.R. China (NHC) was effective in attenuating acute respiratory distress syndrome in a mild COVID-19 patient (Huang et al., 2020; Xu and Zhang, 2020; Li et al., 2020). It was the first-of-its-kind to report the potential benefit of herbs in treating COVID-19 (Huang et al., 2020; Xu and Zhang, 2020; Li et al., 2020). More recently several reviews systemically summarized the herbal medicines frequently used in China during COVID-19 pandemic and performed meta analysis to illustrate its therapeutic outcome (Huang et al., 2020; Zhang et al., 2020; Li et al., 2020). Furthermore, widely distributed herbal medicines, Liquoric Root (*Glycyrrhiza glabra* L.), Baical Skullcap Root (*Scutellaria baicalensis* Georgi), Pinellia Rhizome [*Pinellia ternata* (Thunb.) Makino], Forsythia Fruit [*Forsythia suspensa* (Thunb.) Vahl], and Bitter Apricot Seed (*Prunus armeniaca* L.) are the most frequently prescribed herbs (Zhang et al., 2020; Huang et al., 2020; Xu and Zhang, 2020; Li et al., 2020). Their meta-analysis showed that herbal medicines are effective in halting the disease progression from mild to critical, decreasing hospitalization rate, shortening time of hospital stay, as well as alleviating COVID-19 associated symptoms like fever, cough, fatigue, and inflammation (Zhang et al., 2020; Huang et al., 2020; Xu and Zhang, 2020; Li et al., 2020).

*42)* Nugraha et al., (2020) reported that, some of the herbal agents extracted from various plants, including *Echinacea*, *Cinchona*, *Curcuma longa*, and *Curcuma xanthorrhiza*, which were considered for the treatment of COVID-19 (Nugraha et al., 2020). However, the results of these investigations showed that the drug candidates were not significantly effective against the disease (Nugraha et al., 2020). Meanwhile, people believe that consuming herbal immunomodulators can prevent or even cure COVID-19 (Nugraha et al., 2020). Unfortunately, specific preclinical and clinical trials to evaluate the effects of herbal immunoregulators have not been conducted (Nugraha et al., 2020). Certain natural compounds might be effective for the treatment of COVID-19 based on general concepts from previous experiments (Nugraha et al., 2020). Herbal medicines might have the capabilities to regulate the production and release of proinflammatory cytokines, interfere with the development of the virus in host cells, and modify certain molecular pathways. Herbal agents might be useful as treatments to fight COVID-19 (Nugraha et al., 2020).

*43)* Islam et al., (2020b) reported that *Nigella sativa* seed and oil can be considered as a first-aid kit as a preventive measure against COVID-19 (Islam et al., 2020b). The bioactive compounds of *Nigella sativa* such as thymoquinone, α-hederin, or nigellidine could be tested preclinically and clinically for drug development, efficacy, and potency under a specific pathophysiological condition in pursuit to control the deadliest covid-19 pandemic (Islam et al., 2020b).

*44)* A very recent study demonstrated that, some of the biologically active compounds present in the medicinal plants acts as potential COVID-19 inhibitors, using molecular docking methods (Alrasheid et al., 2021). The Docking study was performed by Molecular Operating Environment software (MOE) (Alrasheid et al., 2021). About 20 compounds were screened in this study; these compounds were selected based on the classifcation of their chemical origin and their antiviral activity from literature (Alrasheid et al., 2021). These compounds might be used to inhibit the COVID-19 infection (Alrasheid et al., 2021). The results demonstrated in this study are significant in controlling coronavirus outbreak (Alrasheid et al., 2021). Furthermore, the efectiveness of this screening strategy, which can lead to a rapid drug discovery in response to new infectious diseases (Alrasheid et al., 2021). Therefore experimental results confirmed that many compounds isolated from medicinal plants such as; Gallic acid (− 17.45), Quercetin (− 15.81), Naringin (− 14.50), Capsaicin (− 13.90), and Psychotrine (− 13.5) are important sources for novel antiviral drugs targeting COVID-19 (Alrasheid et al., 2021). These molecules could be utilized for further innovation and development of antiviral compounds against coronavirus. However, further researches warranted to investigate the potential uses of the medicinal plants containing these compounds (Alrasheid et al., 2021).

*45)* Kanjanasirirat et al., (2020) reported the screening for the antiviral candidates using fuorescence-based SARS-CoV-2 nucleoprotein detection in Vero E6 cells coupled with plaque reduction assay for 122 Thai natural herbal products (Kanjanasirirat et al., 2020). This study demonstrated that *Boesenbergia rotunda* extract and its phytochemical compound, panduratin A, exhibited the potent anti-SARS-CoV-2 activity (Kanjanasirirat et al., 2020). Treatment with *Boesenbergia rotunda* extract and panduratin A after viral infection drastically suppressed SARS-CoV-2 infectivity in Vero E6 cells (Kanjanasirirat et al., 2020). Also, the treatment of panduratin A at the pre-entry phase inhibited SARS-CoV-2 infection (Kanjanasirirat et al., 2020).

Therefore, this study demonstrated, for the frst time, that panduratin A exerts the inhibitory efect against SARSCoV-2 infection at both pre-entry and post-infection phases in the major target cells in human (Kanjanasirirat et al., 2020). Hence panduratin A may serve as the promising candidates for therapeutic purposes with economic advantage during COVID-19 situation (Kanjanasirirat et al., 2020).

*46)* Upadhyay et al., (2020) reported the screening of 51 medicinal plants and found that Tea (*Camellia sinensis*) and Haritaki (*Terminalia chebula*) has potential role against SARS-COV-2 3CLpro, with an IC50 for Green Tea as 8.9 ± 0.5 µg/ml and Haritaki 8.8 ± 0.5 µg/ml (Upadhyay et al., 2020). The in-silico studies suggested that tea component thearubigins binds to the cysteine 145 of protease active site and could be a pharmacoactive molecule (Upadhyay et al., 2020). Hence, the inhibition in protease activity may be able to halt the SARS-CoV-2 replication cycle. Therefore, Green Tea, Black Tea, and Haritaki (*Terminalia chebula*) plant extracts could be the potential therapeutic candidates for SARS-CoV-2 infection (Upadhyay et al., 2020). Further investigation on role of bioactive constituents of extracts is needed to establish the molecular basis of inhibition and towards expedited drug discovery (Upadhyay et al., 2020).

*47)* Natural compounds need to be evaluated as treatment and preventive agents in coronavirus infection (Dave et al., 2020). A total of 30 compounds of *Solanum tuberosum* and *Brassica juncea* residue *smoke water* were selected for the virtual screening against SARS-CoV-1, SARSCoV- 2 and cellular proteins involved in the mechanism of infection (Dave et al., 2020). Docking analysis identified lead molecules with favorable binding energy, number of poses and hydrogen bond interactions, which indicates the effective modulation of ACE2 and TMPRSS2 receptors (Dave et al., 2020). These Results indicated (a) curcumenol, (b) N-desmethylselegiline, (c) phentermine and (d) sphingolipid derivatives as a selective and potent candidates in comparison to hydroxychloroquine for COVID-19 treatment (Dave et al., 2020).

*48)* Islam et al., (2020a) reported that some of the natural plant products have antiviral activity in the nanomolar concentration (e.g., lycorine, homoharringtonine, silvestrol, ouabain, tylophorine, and 7-methoxycryptopleurine), and could be leads for the further drug development on their own or as a template for drug design (Islam et al., 2020). In addition, a good number of natural products with anti-corona virus activity are the major constituents of some common dietary supplements, which can be exploited to improve the immunity of the general population in certain epidemics (Islam et al., 2020).

*49)* Natural plant products have been in constant use since ancient times and are proven by time to be effective (Adhikari et al., 2020). Crude extract or pure compounds isolated from medicinal plants and/or herbs such as *Artemisia annua, Agastache rugosa, Astragalus membranaceus, Cassia alata, Ecklonia cava, Gymnema sylvestre, Glycyrrhizae uralensis, Houttuynia cordata, Lindera aggregata, Lycoris radiata, Mollugo cerviana, Polygonum multiflorum, Pyrrosia lingua, Saposhnikoviae divaricate, Tinospora cordifolia* etc. have shown promising inhibitory effect against coronavirus (Adhikari et al., 2020). Adhikari et al., (2020) reported 93 antiviral drug candidates which could be a potential area of research in drug discovery and warrant further investigation (Adhikari et al., 2020).

*50) Thapsia garganica* belongs to the family *Apiaceae* commonly known as the deadly carrots, is a poisonous traditional medicinal plant (Al-Beltagi et al., 2021; Rasmussen et al., 1981; Smitt et al., 1995; Makunga et al., 2003). The center of diversity is around the western Mediterranean, extending into the Atlantic coasts of Portugal and Morocco (Al-Beltagi et al., 2021; Rasmussen et al., 1981; Smitt et al., 1995). *Thapsigargin* is obtained from the intact fruits and roots of *Thapsia garganica* that are collected from the wild (Makunga et al., 2003; Rasmussen et al., 1981; Smitt et al., 1995; Al- eltagi et al., 2021). The resin of *Thapsia garganica* causes a contact dermatitis and is extensively used by the Northern African Arabs for medicinal purposes (Rasmussen et al., 1981; Smitt et al., 1995; Makunga et al., 2003). The major bioactive compounds synthesised by *Thapsia garganica* are thapsigargin, thapsigargicin, notrilobolid and thapsivillosin (Rasmussen et al., 1981; Smitt et al., 1995; Makunga et al., 2003). The chemical compound thapsigargin has been isolated from *Thapsia garganica* (Rasmussen et al., 1981; Smitt et al., 1995; Makunga et al., 2003). A synthetic prodrug of *thapsigargin* called "G-202" is in preliminary clinical trials for prostrate cancer treatment (Al-Beltagi et al., 2021; Rasmussen et al., 1981; Smitt et al., 1995; Makunga et al., 2003). The active constituent kills tumor cells by destroying their calcium balance. Researchers from Britains, Nottingham University belived that an experimental cancer drug isolated from poisonous plant ***Thapsia garganica* could halt covid-19**. Thapsigargin inhibits SARS-CoV-2 activity using a range of cellular responses rather than targeting the virus directly (Al-eltagi et al., 2021). The antiviral duration of at least 48 h post-Thapsigargin exposure experiments, proposed that Thapsigargin (or its derivatives) is a promising broad-spectrum inhibitor against SARS-CoV-2, OC43, RSV and influenza virus (Al- eltagi et al., 2021). However, further analysis and clinical trials shoud be conducted in order to confirm the antiviral activity of the plant *Thapsia garganica* against SARS-CoV-2.

*51) Moringa oleifera (Drumstick; Nuggekai* in Kannada) belongs to the family *Moringaceae* is a powerful medicinal plant used to combat many human diseases. Aerial parts of ***Moringa oleifera*** particularly fruits and leaf extracts along with turmeric (*Curcuma longa* L.) were used as immunity booster during covid-19 outbreak. The combination of *Moringa oleifera* leaf extract with turmeric (*Curcuma longa* L.) has played an important role in boosting immunity during SARS-CoV-2 outbreak. The plant has an effective

antimicrobial and antiviral activity and clinical studies should be conducted for the scientific validation as inhibior against SARS-CoV-2. *Moringa oleifera* has shown an antidengue activity and recommened for controlling dengue virus infections (Malabadi et al., 2018). In another study reported by Arifan et al., (2021), *Moringa oleifera* leaves were used to make hand saintizers to prevent the spread of the covid-19 virus (Arifan et al., 2021).

The researchers used computer modelling for the identification of the phytochemicals from *Moringa oleifera* (drumstick) plant which inhibit the SARS-CoV-2 virus (Shaji, 2020; Nair and James, 2021). They found that several of the phytochemicals showed a high binding affinity with the coronavirus and could act as virus inhibitors (Shaji, 2020; Nair and James, 2021). The compound with the highest activity was apigenin-7-O-rutinoside and also found that several of the phytochemicals had antioxidant properties which would ameliorate the post-COVID secondary infection (Shaji, 2020; Nair and James, 2021) (Can Moringa Leaf Curtail SARS-CoV-2 Growth? - Chromatography Explores Chromatography Today) (Shaji, 2020; Nair and James, 2021). Using molecular docking, an attempt was made to find out whether the compounds from *Moringa Oleifera* inhibit the COVID-19 drug targets Mpro and RdRp (Shaji, 2020). The results of this study suggested that, the compounds kaempferol, pterygospermin, morphine and quercetin exhibited best binding energy against Mpro and RdRp (Shaji, 2020). Therefore, these natural compounds could be promising candidates for further evaluation of COVID-19 prevention (Shaji, 2020). Moreover, the Mpro residues Leu141, Gly143, Ser144 and Cys145 play an important role in hydrogen bonding and hydrophobic interactions (Shaji, 2020). In another study, an in silico-based approach which revealed that the possibility of identication of potent SARS-CoV-2 Mpro inhibitors from *Moringa Oleifera* (Nair and James, 2021). Therefore, this study gives an idea of the action of phytoconstituents from *Moringa Oleifera* leaf against the main protease of coronavirus (Nair and James, 2021). Among the 19 compounds screened, apigenin-7-O-rutinoside showed the highest activity against SARS CoV-2 Mpro (Nair and James, 2021). Moreover, these compounds are also found to have antioxidant property which would ameliorate the post-COVID secondary infection (Nair and James, 2021).

Top of Form Bottom of Form

*52) Cissampelos pariera Linn (Kannada name-Padavali)*

*Cissampelos pariera Linn* is a sub erect dioecious flowering herb belongs to family *Menispermaceae* is one of the important Indian traditional herbal medicine (Malabadi et al., 2018). The plant has antidengue activity and inhibited the dengue virus during outbreak (Malabadi et al., 2018). During recent SARS-CoV-2 outbreak, the cosumption of fruits, and leaf extract with hot water has shown inhibitory activity against SARS-CoV-2. *Cissampelos pariera* was used as an immunity booster during recent SARS-CoV-2 outbreak and prevented further virus infections. Therefore, clinical experiments of *Cissampelos pariera* should be conducted in order to have a scientific validation for the further development of antiviral drug therapy against SARS-CoV-2.

A team of scientists from India has recently investigated the antiviral potency of a traditional medicinal plant *Cissampelos pareira L.* in preventing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (Haider et al., 2021). These findings reveal that both whole-plant extracts and bioactive compounds can inhibit SARS-CoV-2 replication by modulating estrogen receptor 1 (ESR1) activity. The study is currently available on the *bioRxiv** preprint server (*Cissampelos pareira* L. extracts demonstrate anti-SARS-CoV-2 activity in vitro (news-medical.net) (Haider et al., 2021).

*53) Momordica charantia (Kannada- Hagalkai): Bitter melon*

*Momordica charantia* (Hagalakai) commonly known as bitter melon in India belongs to family ***Cucurbitaceae.*** *Momordica charantia* fruit has distinguishing bitter taste, which is more pronounced as it ripens, hence the name bitter melon or bitter gourd or balsam pear. *Momordica charantia* is widly grown in India and consumed as a vegetable. The cosumption of fruits has a strong antidengue activity (Malabadi et al., 2018). The plant has antimicrobial and antiviral activity (Malabadi et al., 2018; Pongthanapisith et al., 2013). Among the medicinal plants investigated, *Momordica charantia* L. has been reported to contain many potent antiviral activities that might be a good candidate against SARS-CoV-2. The proteins from this plant strongly inhibit several viruses including hepatitis B virus, dengue virus, herpes simplex virus, and Human immunodeficiency virus (Pongthanapisith et al., 2013). Therefore, during recent outbreak of SARS-CoV-2, oral cosumption of fruit juice of *Momordica charantia* with turmeric (*Curcuma longa* L.) in hot water was given to patients as a immunity booster in order to develop the immunity against SARS-CoV-2 virus in rural parts of Karnataka, India. Clinical study is yet to be conducted for the scientific validiation.

Furthermore, the protein purified from *Momordica charantia* possessed effective antiviral activity to a broad range of influenza A subtypes including H1N1, H3N2, and H5N1. Thus, this plant protein holds a great promise to be developed as an effective therapeutic agent against various and even new emerging subtypes of influenza A such as H7N9 (Pongthanapisith et al., 2013).

## II. CONCLUSION

Severe acute respiratory syndrome (SARS), an emerging respiratory infectious diseases present a major threat to public health. Epidemiological investigations have suggested that the outbreak was associated with a seafood market in Wuhan. Furthermore the sequence analysis confirmed that SARS-CoV-2 has been originated from bats. In this review paper, the use of medicinal plants combating SARS-CoV-2 has been

highligthed and listed. Among the listed medicinal plants, some of the medicinal plants showed antibacterial activity, others under *in vitro* conditions, and animal studies demonstrated the blockage or inhibited the SARS-CoV-2 activity. The use of herbal formulations inhibited the host enzyme transmembrane protease serine 2 (TMPRSS2) facilitates viral particle entry into host cells blocks virus fusion with ACE2, making it a potential target to inhibit virus entry. Furthermore, foods and herbs possess a potential antiviral ability against SARS-CoV-2 and can prevent COVID-19. This has opened a new ray of hope for developing traditional herbal medicine remedies for SARS-CoV-2 infection. This will help in prevention and treatment of diseases covid-19.

However, these hypotheses require experimental validation in SARS-Cov-2 infection models and COVID-19 patients. In addition, subsequent *in vitro* and *in vivo* experiments are needed to elucidate their efficacy against SARS-CoV-2. However, much of the evidence comes from animal and *in vitro* studies and overall clinical Evidence-Based Complementary and Alternative Medicine evidence to support these herbal interventions remains weak and lacking. Furthermore, there are many experimental issues and data presented is not enough for the scientific validation. The treatment durations in the existing trials are also of concern. This uncertainty is mainly caused by methodological limitations such as poor study design, relatively small sample sizes, inappropriate outcome measures and primary and secondary end-point selection, and invalid statistical analysis. Future epidemiological and clinical studies are required to further assess the benefits of herbal medicines for the prevention of SARS-CoV-2.

Herbal remedies consist of portions of plants or unpurified plant extracts containing several constituents which are often generally believed to work together synergistically. Herbal-derived remedies need a powerful and deep assessment of their pharmacological qualities and safety issues. The other problems of herbal-based treatments is the lack of definite and complete information about the composition of extracts. Although some herbal medicines have promising potential and are widely used, many of them remain untested and their use also not monitored. This makes knowledge of their potential adverse effects very limited and identification of the safest and most effective therapies as well as the promotion of their rational use more difficult. Herbs are natural products and their chemical composition varies depending on several factors, such as botanical species, used chemotypes, the anatomical part. Herbal medicine has become a popular form of healthcare; even though several differences exist between herbal and conventional pharmacological treatments. An herbal medicine needs to be tested for efficacy using conventional trial methodology and several specific herbal extracts have been demonstrated to be efficacious for specific conditions. Drug regulatory framework should also be applied immidiately to ensure that they conform to required standards of safety, quality, and efficacy.

Finally, there is a possibility that these treatments might be associated with the induction of harmful effects. In addition, preclinical and clinical trial evaluations of these herbal agents for COVID-19 have not specifically been conducted, so further investigations related to this are warranted.

## CONFLICT OF INTEREST STATEMENT

Authors declare that they have no conflict of interest.

## REFERENCES


[1] Achan J, Talisuna AO, Erhart A et al., (2011) Quinine, an old antimalarial drug in a modern world: Role in the treatment of malaria. Malaria Journal. 10:144. (https ://doi.org/10.1186/1475-2875-10-144).

[2] Adhikari B, Marasini BP, Rayamajhee B, Bhattarai BR, Lamichhane G, Khadayat K, Adhikari A, Khanal S, Parajuli N (2020) Potential roles of medicinal plants for the treatment of viral diseases focusing on COVID-19: A review. Phytotherapy Research. 1–15. (https://doi.org/10.1002/ ptr.6893).

[3] Ahmad A, Rehman MU, Ahmad P, Alkharfy KM (2020) Covid-19 and thymoquinone: Connecting the dots. Phytotherapy Research. 34:2786–2789.

[4] Akindele AJ et al., (2020) COVID-19 Pandemic: A case for phytomedicines. Natural Product Communications. 15(8): 1–9. (DOI: 10.1177/1934578X20945086).

[5] Alrasheid AA, Babiker MY, Awad TA (2021) Evaluation of certain medicinal plants compounds as new potential inhibitors of novel coronavirus (COVID-19) using molecular docking analysis. In Silico Pharmacology. 9:10. (https://doi.org/10.1007/s40203-020-00073-8).

[6] Al-Beltagi S, Preda CA, Goulding LV, James J, Pu J et al., (2021) Thapsigargin is a broad-spectrum inhibitor of major human respiratory viruses: Coronavirus, Respiratory Syncytial virus and Influenza A virus. Viruses. 13: 234. (https://doi.org/10.3390/v13020234).

[7] Ammon HP, Wahl MA (1991) Pharmacology of *Curcuma longa*. Planta Med. 57:1–7.

[8] Anderson RM, Vegvari C, Truscott J, Colly BS (2020) Challenges in creating herd immunity to SARS-CoV-2 infection by mass vaccination. The Lancet. (DOI: https://doi.org/10.1016/S0140-6736(20)32318-7).

[9] Ang L, Song E, Lee HW, Lee MS (2020) Herbal medicine for the treatment of coronavirus disease 2019 (COVID-19): A Systematic review and meta-analysis of randomized controlled trials. Journal of Clinical Medicine. 9: 1583. (doi:10.3390/jcm9051583).

[10] Antonelli M, Donelli D, Maggini V, Firenzuoli F (2020) Phytotherapic compounds against coronaviruses: Possible streams for future research. Phytotherapy Research. 34:1469–1470.

[11] Apisariyakul A, Vanittanakom N, Buddhasukh D (1995) Antifungal activity of turmeric oil extracted from *Curcuma longa* (*Zingiberaceae*). J. Ethnopharmacol. 49:163–9.

[12] Araujo CC, Leon LL (2001) Biological activities of *Curcuma longa* L. Mem Inst Oswaldo Cruz. 96:723–8.

[13] Arifan F, Broto RW, Sapatra EF, Pujiastuti A (2021) Utilization of *Moringa oleifera* leaves for making hand sanitizers to prevent the spread of COVID-19 virus. IOP Conf. Series: Earth and Environmental Science 623 (2021) 012015. (doi:10.1088/1755-1315/623/1/012015).

[14] Arora RB, Kapoor V, Basu N, Jain AP (1971) Anti-inflammatory studies on *Curcuma longa* (turmeric). Indian J. Med Res. 59:1289–95.

[15] Baden LR et al., (2020) Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. The New England Journal of Medicine. 1-14. (DOI: 10.1056/NEJMoa2035389).

[16] Bahrami M, Kamalinejad M, Latif SA, Seif F, Dadmehr M (2020) Cytokine storm in COVID-19 and parthenolide: Preclinical evidence. Phytotherapy Research. 34:2429–2430.

[17] Baliga MS et al., (2012) Scientific validation of the ethnomedicinal properties of the ayurvedic drug Triphala: A review. Chin J Integr Med. 18:946–954.

[18] Bar-On YM, Flamholz A, Phillips R, Milo R (2020) Science forum of SARS-CoV-2 (COVID-19) by the numbers. eLife future article. :e57309. (OI: https://doi.org/10.7554/eLife.57309).

[19] Bartlam M, XuY, Rao Z (2007) Structural proteomics of the SARS coronavirus:A model response to emerging infectious diseases. J. Struct. Funct. Genomics. 8: 85–97. (doi:10.1007/s10969-007-9024-5).

[20] Barrett JR, Belij-Rammerstorfer S, Dold C, Ewer KJ, Folegatti PM, Gilbride C, et al., (2020) Phase 1/2 trial of SARS-CoV-2 vaccine ChAdOx1 nCoV-19 with a booster dose induces multifunctional antibody responses. Nature Medicine. (https://doi.org/10.1038/ s41591-020-01179-4.).

[21] Bast F, Rani P, Meena D (2014) Chloroplast DNA phylogeography of holy basil (*Ocimum tenuiflorum*) in Indian subcontinent. Scientific World Journal. 6 :847–482.

[22] Belapurkar P, Goyal P, Tiwari-Barua P (2014) Immunomodulatory effects of Triphala and its individual constituents: A review. Indian J Pharm Sci 76:467–475.

[23] Benarba B, Pandiella A (2020) Medicinal plants as a sources of active molecules against COVID-19. Frontiers in Pharmacology. 11(1189): 1-16

[24] Bhat J, Damle A, Vaishnav PP, Albers R, Joshi M, Banerjee G (2010) *In vivo* enhancement of natural killer cell activity through **Tea** fortified with *Ayurvedic* herbs. Phytother Research 24: 129-35. (https://doi.org/10.1002/ptr.2889).

[25] Bhuiyan FR, Howlader S, Raihan T, Hasan M (2020) Plant metabolites: Possibility of natural therapeutics against the COVID-19 pandemic. Frontiers in Medicine. 7 (444): 1-26. (doi: 10.3389/fmed.2020.00444).

[26] Blanco-Melo D, Benjamin E, Nilsson-Payant J, Wen-Chun L, Møller R, Panis M, Sachs D, Albrecht RA, Ten Oever RB (2020) SARS-CoV-2 launches a unique transcriptional signature from *in vitro*, *ex vivo*, and *in vivo* systems. bioRxiv preprint. (doi: https://doi.org/10.1101/2020.03.24.004655).

[27] Bouchentouf S, Missoum N (2020) Identification of compounds from *Nigella sativa* as new potential inhibitors of 2019 novel coronavirus (Covid-19): Molecular docking study. ChemRxiv Preprint. Retrieved from (https://doi.org/10.26434/chemrxiv.12055716.v1).

[28] Brendler T, Al-Harrasi A, Bauer R, Gafner S, Hardy ML, Heinrich M, Hosseinzadeh H, Izzo AA, Michaelis M, Nassiri-Asl M, Panossian A, Wasser SP, Williamson EM (2020) Botanical drugs and supplements affecting the immune response in the time of COVID-19: Implications for research and clinical practice. Phytotherapy Research. 1–19. (https://doi.org/10.1002/ptr.7008).

[29] Britton T, Ball F, Trapman P (2020) A mathematical model reveals the influence of population heterogeneity on herd immunity to SARS-CoV-2. Science. 369: 846-849.

[30] Burgers W et al., (2020) SARS-CoV-2 antigens expressed in plants detect antibody responses in COVID-19 patients. *medRxiv* (doi: https://doi.org/10.1101/2020.08.04.20167940).

[31] Caccuri F, Zani A, Messali S, Giovanetti M, Bugatti A, Campisi G, Filippini F, Scaltriti E, Ciccozzi M, Fiorentini S, Aruso A (2020) A persistently replicating SARS-CoV-2 variant derived from an asymptomatic individual. Journal of Translational Medicine. 18:362. ( https://doi.org/10.1186/s12967-020-02535-).

[32] Capell T, Twyman RM, Armario-Najera V, Ma JKC, Schillberg S, Christou P (2020) Potential applications of plant biotechnology against SARS-CoV-2. Trends in Plant Science. 25 (7): 635-643. (https://doi.org/10.1016/j.tplants.2020.04.009).

[33] Chang FR, Yen CT, Ei-Shazly M et al., (2012) Anti-human coronavirus (anti-HCoV) triterpenoids from the leaves of *Euphorbia neriifolia*. Nat Prod Commun. 7:1415–1417. (https ://doi. org/10.1177/19345 78x12 00701 103).

[34] Chan JF, Lau SK, TO KK, Cheng VC, Woo PC, Yuen KY (2015) Middle East respiratory syndrome coronavirus: Another zoonotic betacoronavirus causing SARS-like disease. Clin Microbiol Rev. 28: 465–522. (doi: 10.1128/CMR.00102-14 PMID: 25810418).

[35] Chen CJ, Michaelis M, Hsu HK et al., (2008) *Toona sinensis* Roem tender leaf extract inhibits SARS coronavirus replication. J. Ethnopharmacol. 120:108–111. (https ://doi.org/10.1016/j. jep.2008.07.048).

[36] Cheng VCC, Lau SKP, Woo PCY, Yuen KY (2007) Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. Clinical Microbiology Reviews. 20 (4) 660–694 (doi:10.1128/CMR.00023-07).

[37] Chin AWH, Chu JTS, Perera MRA et al., (2020) Stability of SARS-CoV-2 in different environmental conditions. Lancet Microbe. 1: e10.

[38] Chrzanowski J, Chrzanowska A, Grabo W (2020) Glycyrrhizin: An old weapon against a novel coronavirus. Phytotherapy Research. 1–8. (https://doi. org/10.1002/ptr.6852).

[39] Ciavarella C, Motta I, Valente S et al., (2020) Pharmacological (or synthetic) and nutritional agonists of PPAR-γ as candidates for cytokine storm modulation in COVID-19 disease. Molecules. 25*:* 2076.

[40] Cinat J, Morgenstern B, Bauer G et al., (2003) Glycyrrhizin, an active component of liquorice roots, and replication of SARS associated coronavirus. Lancet. 361:2045–2046. (https ://doi.org/10.1016/S0140 -6736(03)13615 -X).

[41] Coronavirus (2020a) domestic abuse calls up 25% since lockdown, charity says, BBC News [Internet]. [cited 2020 Apr 7]. Available from: https://www.bbc.co.uk/news/uk- 52157620.

[42] Coronavirus (2020b) 25% increase in calls to national domestic abuse helpline since lockdown measures began - refuge charity - domestic violence help, [Internet]. [cited 2020 Apr 7]. Available from: https://www.refuge.org.uk/25-increase-in-calls-to-nationaldomestic- abuse-helpline-since-lockdown-measures-began/.

[43] Coronaviridae Study Group of the International Committee on Taxonomy of Viruses (2020) The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 5:536-44.

[44] Corman VM, Baldwin HJ, Tateno FA, Zerbinati MR, Annan A, Owusu M, Nkrumah EE, Maganga GD, Oppong S, Adu-Sarkodie Y, Vallo P, da Silva Filho LV, Leroy EM, Thiel V, van der Hoek L, Poon LL, Tschapka M, Drosten C, Drexler JF (2015) Evidence for an ancestral association of human coronavirus 229E with bats. Journal of Virology. 89: 11858–11870. (doi: 10.1128/JVI.01755-15 PMID: 26378164).

[45] Crance JM, Scaramozzino N, Jouan A, Garin D (2003) Interferon, ribavirin, 6-azauridine and glycyrrhizin: Antiviral compounds active against pathogenic flaviviruses. Antivir. Res. 58: 73–79.

[46] Cui J, Li F, Shi ZL (2019) Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 17(3):181–92.

[47] Damle M (2014) *Glycyrrhiza glabra* (Liquorice) - A potent medicinal herb. International Journal of Herbal Medicine. 2(2): 132-136.

[48] Das S, Sarmah S, Lyndem S, Roy AS (2020) An investigation into the identification of potential inhibitors of SARS-CoV-2 main protease using molecular docking study. J Biomol Struct Dyn. 13:1–11.

[49] Dave GS, Rakholiya KD, Kaneria MJ, Galvadiya BP, Vyas SR, Kanbi VH, Patel MP (2020) High affinity interaction of *Solanum tuberosum* and *Brassica juncea* residue smoke water compounds with proteins involved in coronavirus infection. Phytotherapy Research. 34:3400–3410. (https://doi.org/10.1002/ptr.6796).

[50] Davies NG, Barnard RC, Jarvis CI et al., (2020) Estimated transmissibility and severity of novel SARS-CoV-2 variant of concern 202012/01 in England. CMMID. Preprint published online December 23, 2020. Updated December 31, 2020. (doi:10.1101/2020.12.24.20248822).

[51] Demurtas OC, Massa S, Illiano E, Martinis DD, Chan PKS, Bonito PD, Franconi R (2016) Antigen production in plant to tackle infectious diseases flare up:The case of SARS. Frontiers in Plant Science. 7(54):1-12. (doi: 10.3389/fpls.2016.00054).

[52] Derosa G, Maffioli P, D'Angelo A, Di Pierro F (2020) A role for quercetin in coronavirus disease 2019 (COVID-19). Phytotherapy Research. 1–7. (https://doi. org/10.1002/ptr.6887).

[53] Dhama K, Sachan S, Khandia R, et al., (2017) Medicinal and beneficial health applications of *Tinospora cordifolia* (Guduchi): A miraculous herb countering various diseases/disorders and its immunomodulatory effects. Recent Pat Endocr Metab Immune Drug Discov. 10(2): 96-111. (doi:10.2174/1872214811666170301105101).

[54] Dinka H, Milkesa A (2020) Unfolding SARS-CoV-2 viral genome to understand its gene expression regulation. Infection, Genetics and Evolution. 84: 104386.

[55] Dixit VP, Jain P, Joshi SC (1988) Hypolipidaemic effects of *Curcuma longa* L. and *Nardostachys jatamansi*, DC in triton-induced hyperlipidaemic rats. Indian J Physiol Pharmacol. 32:299–304.

[56] Divya M, Vijayakumar S, Chen J, Vaseeharan B, Duran-Lara EF (2020) South Indian medicinal plants can combat deadly viruses along with COVID-19? - A review. Microbial Pathogenesis. 147. (https://doi.org/10.1016/j.micpath.2020.104277).

[57] Dong L, Hu S, Gao J (2020) Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther. 14:58–60.

[58] Duffy S (2018) Why are RNA virus mutation rates so damn high? PLoS Biol. 16(8):e3000003. (https:// doi.org/10.1371/journal.pbio.3000003).

[59] Ewer KJ et al., (2020) T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial. Nature Medicine. (https://doi.org/10.1038/ s41591-020-01194-5).

[60] Fakhri S, Nouri Z, Moradi SZ, Farzaei MH (2020) Astaxanthin, COVID-19 and immune response: Focus on oxidative stress, apoptosis and autophagy. Phytotherapy Research. 34:2790–2792.

[61] Farooq S, Ngaini Z (2020) Natural and synthetic drugs as potential treatment for coronavirus disease 2019 (COVID-2019). Chemistry Africa. (https://doi.org/10.1007/s42250-020-00203-x).

[62] Firenzuoli F, Gori L (2007) Herbal medicine today: Clinical and Research Issues. eCAM. 4(S1):37–40 (doi:10.1093/ecam/nem09).

[63] Fisher D, Heymann QA (2020) The novel coronavirus outbreak causing COVID-19. BMC Med. 18 (1):1–3.

[64] Folegatti PM, Ewer KJ, Aley PK, et al., (2020) Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: A preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 396: 467–78.

[65] Ganguly S, Bakhshi S (2020) Traditional and complementary medicine during COVID-19 pandemic. Phytotherapy Research. 34:3083–3084.

[66] Gautreta P, Lagiera JC, Parola P et al., (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. J Anti microb Agents. (https ://doi.org/10.1016/j.ijant imica g.2020.105949).

[67] Gautam S, Gautam A, Chhetri S, Bhattarai U (2020) Immunity against COVID-19: Potential role of *Ayush Kwath*. J. Ayurveda Integr Med. (https://doi.org/ 10.1016/j.jaim.2020.08.003).

[68] Girija PLT, Sivan N (2020) Ayurvedic treatment of COVID-19/SARS-CoV-2: A case report. Journal of Ayurveda and Integrative Medicine. (https://doi.org/10.1016/j.jaim.2020.06.001).

[69] Gopalakrishnan N, Narayanan CS, Mathew AG (1988) Chemical composition of Indian clove bud, stem and leaf oils. Indian Perfumers. 32: 229–235.

[70] Goswami D, Kumar M, Ghosh SK, and Das A (2020) Natural product compounds in *Alpinia officinarum* and *Ginger* are potent SARS-CoV-2 papain like protease Inhibitors. chemRxiv. (doi: 10.26434/chemrxiv.12071997.v1).

[71] Gralinski LE, Menachery VD (2020) Return of the coronavirus: 2019-nCoV. Viruses. 12(2):135.

[72] Grubaugh ND, Petrone ME, Holmes EC (2020) We shouldn't worry when a virus mutates during disease outbreaks. Nat Microbiol. 5(4):529-530. (doi:10.1038/s41564-020-0690-4).

[73] Grzanna R, Lindmark L, Frondoza CG (2005) Ginger: An herbal medicinal product with broad anti-inflammatory actions. J Med Food. 8:125–32.

[74] Guan Y, Zheng BJ, He YQ, Liu XL, Zhuang ZX, Cheung CL, Luo SW, Li PH, Zhang LJ, Guan YJ et al., (2003) Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. Science. 302: 276–278.

[75] Guo G, Ye L, Pan K, Chen Y, Xing D, Yan K, et al., (2020) New insights of emerging SARS-CoV-2: Epidemiology, etiology, clinical features, clinical treatment, and prevention. Front Cell Dev Biol. 8:410. (https ://doi.org/10.3389/ fcell .2020.00410).

[76] Gupta H, Gupta M, Bhargava S (2020) Potential use of turmeric in COVID-19. Clinical and Experimental Dermatology. 45(7): 891-921 (doi: 10.1111/ced.14357).

[77] Habtemariam S, Nabavi SF, Berindan-Neagoe I, Cismaru CA, Izadi M, Sureda A, Nabavi SM (2020) Should we try the anti-inflammatory natural product, celastrol, for COVID-19?. Phytotherapy Research. 34:1189–1190.

[78] Haider M et al., (2021) Traditional use of *Cissampelos pareira* L. for hormone disorder and fever provides molecular links of ESR1 modulation to viral inhibition. *bioRxiv*. https://www.biorxiv.org/content/10.1101/2021. 02.17.431579v1.

[79] Haq FU, Roman M, Ahmad K, Ur Rahman S, Ali Shah SM, Suleman N, Ullah S, Ahmad I, Ullah W (2020) *Artemisia annua*: Trials are needed for COVID-19. Phytotherapy Research. 34:2423–2424. (https://orcid.org/0000-0002-9391-0032).

[80] Hirose R, Ikegaya H, Naito Y, Watanabe N, Yoshida T, Bandou R, Daidoji T, Itoh Y, Nakaya T (2020) Survival of SARS-CoV-2 and influenza virus on the human skin: Importance of hand hygiene in COVID-19. Clinical Infectious Diseases. Published by Oxford University Press for the Infectious Diseases Society of America.

[81] Hamre D, Procknow JJ (1966) A new virus isolated from the human respiratory tract. Proc. Soc. Exp. Biol. Med. 121: 190–193.

[82] Han HJ, Wen HL, Zhou CM, Chen FF, Luo LM, Liu JW, Yu XJ (2015) Bats as reservoirs of severe emerging infectious diseases. Virus Res. 205: 1–6. (doi: 10.1016/j.virusres.2015.05.006 PMID: 25997928).

[83] Ho TY, Wu SL, Chen JC et al., (2007) Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. Antivir Res. 74:92–101. (https ://doi.org/10.1016/j.antiv iral.2006.04.014).

[84] Hoek LVD, Pyrc K, Jebbink MF, Vermeulen-Oost W, Berkhout RJM, Wolthers KC, Dillen PMEWV, Kaandorp J, Spaargaren J, Berkhout B (2004) Identification of a new human coronavirus. Nature Medicine. 10(4) 368-373. (Doi:10.1038.nm1024).

[85] Hoffmann M, Schroeder S, Kleine-Weber H, Müller MA, Drosten C, Pöhlmann S (2020) Nafamostat mesylate blocks activation of SARS-CoV-2: New treatment option for COVID- 19. Antimicrob Agents Chemother. 64:e00754- 20. (https://doi.org/10.1128/AAC.00754-20).

[86] Hoffmann M. et al., (2020) SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 181: 271–280.

[87] Hossain G, Paul D, Ali A, Huda N, Alam S, Mahmood S, Hamooh BT (2020) The perspectives of medicinal plants for COVID-19 treatment: A Review. Journal of Agricultural Science & Engineering Innovation. 1(2): 1-10. (DOI: http://doi.org/10.5281/zenodo.4250485).

[88] Hsieh LE, Lin CN, Su BL et al., (2010) Synergistic antiviral effect of *Galanthus nivalis* agglutinin and nelfinavir against feline coronavirus. Antivir Res. 88:25–30. (https ://doi.org/10.1016/j.antiv iral.2010.06.01).

[89] Huang J, Tao G, Liu J, Cai J, Huang Z, Chen JX (2020) Current prevention of COVID-19: Natural Products and Herbal Medicine. Front. Pharmacol. 11:588508. (doi: 10.3389/fphar.2020.588508).

[90] Irigoyen N, Firth AE, Jones JD, Chung BYW, Siddell SG, Brierley I (2016) High-resolution analysis of coronavirus gene expression by RNA sequencing and ribosome profiling. PLOS Pathogens. 5 (2) | (DOI:10.1371/journal.ppat.1005473).

[91] Islam MT, Sarkar C, El-Kersh DM, Jamaddar S, Uddin SJ, Shilpi JA, Mubarak MS (2020a) Natural products and their derivatives against coronavirus: A review of the non-clinical and pre-clinical data. Phytotherapy Research. 34:2471–2492. (https://doi.org/ 10.1002/ptr.6700).

[92] Islam MN, Hossain KS, Sarker PP, Ferdous J, Hannan A, Rahman M, Chu DT, Uddin J (2020b) Revisiting pharmacological potentials of *Nigella sativa* seed: A promising option for COVID-19 prevention and cure. Phytotherapy Research. 2020;1–16. (https://doi.org/10.1002/ ptr.6895).

[93] Jia HP, Look DC, Shi L, Hickey M, Pewe L, Netland J et al., (2005) ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. J Virol. 79 (23):14614–21.

[94] Kanjanasirirat P et al., (2020) High-content screening of Thai medicinal plants reveals *Boesenbergia rotunda* extract and its component Panduratin A as anti-SARS-CoV-2 agents. Scientifc Reports. 10:19963 (https://doi.org/10.1038/s41598-020-77003-3).

[95] Kampf G, Todt D, Pfaender S, Steinmann E (2020) Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. J Hosp Infect. 104: 246–51.

[96] Kampf G (2020) Potential role of inanimate surfaces for the spread of coronaviruses and their inactivation with disinfectant agents. Infect Prev Pract. 2: 100044.

[97] Kapepula PM, Kabengele JK, Kingombe M, Bambeke FV et al., (2020) Artemisia Spp. derivatives for COVID-19 treatment: Anecdotal use, political hype, treatment potential, challenges, and road map to randomized clinical trials. Am. J. Trop. Med. Hyg., 103(3): 960–964. (doi:10.4269/ajtmh.20-0820).

[98] Kataria R, Hemraj, Singh G, Gupta A, Jalhan S, Jindal A et al., (2013) Pharmacological activities on *Glycyrrhiza glabra*–a review. Asian J Pharm Clin Res. 6(1):5-7.

[99] Keyaerts E, Vijgen L, Pannecouque C et al., (2007) Plant lectins are potent inhibitors of coronaviruses by interfering with two targets in the viral replication cycle. Antivir Res. 75:179–187. (https ://doi. org/10.1016/j.antiv iral.2007.03.003).

[100] Khan SA, Al-Balushi K (2020) Combating COVID-19: The role of drug repurposing and medicinal plants. Journal of Infection and Public Health. (doi:https://doi.org/10.1016/j.jiph.2020.10).

[101] Khan RI, Abbas M, Goraya K, Zafar-ul-Hye M, Danis S (2020) Plant derived antiviral products for potential treatment of COVID-19: A Review. Phyton-International Journal of Experimental Botany. 89(3):437-452. (DOI:10.32604/phyton.2020.010972).

[102] Khan MI, Khan ZA, Baig MH, Ahmad I, Farouk A-EAziem, Song YG, et al., (2020) Comparative genome analysis of novel coronavirus (SARS-CoV-2) from different geographical locations and the effect of mutations on major target proteins: An *in silico* insight. PLoS ONE. 15(9): e0238344. (https://doi.org/10.1371/journal pone.0238344).

[103] Khan H (2009) Role of *Emblica officinalis* in medicine. Bot Res. Int. 2(4):218-228.

[104] Kirkcaldy RD, King BA, Brooks JT (2020) COVID-19 and post infection immunity limited evidence, many remaining questions. JAMA. 323 (22) :2245-2246. (doi:10.1001/jama.2020.7869).

[105] Korber, B. et al.,(2020) Tracking changes in SARS-CoV-2 Spike: Evidence that D614Gincreases infectivity of the COVID-19 virus. Cell. 182: 812–827.

[106] Ksiazek TG, Erdman D, Goldsmith CS et al., (2003) A novel coronavirus associated with severe acute respiratory syndrome. N. Engl. J. Med. 348: 1953–1966.

[107] Kuiken T, Fouchier RAM, Schutten M et al., (2003) Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet. 362: 263–270.

[108] Kulkarni KV, Ghurghure SM (2018) Indian gooseberry (*Emblica officinalis*): Complete pharmacognosy review. International Journal of Chemistry Studies. 2 (2) 05-11.

[109] Kumar PV, Sivaraj A, Madhumitha G, Saral AM, Kumar BS (2010) *In vitro* antibacterial activities of *Picrorhiza kurroa* rhizome extract using agar well diffusion method. Int J Curr Pharm Res. 2(1): 30-33.

[110] Kumar A, Prasad G, Srivastav S, Gautam VK, Sharma N (2020) A Retrospective study on efficacy and safety of **Guduchi** ghan vati for Covid-19 asymptomatic Patients. medRxiv preprint. (doi: https://doi.org/10.1101/2020.07.23.20160424).this version posted July 29, 2020.

[111] Kumar DV, Geethanjali B, Avinash KO, Kumar JR, Chandrashekrappa GK, Basalingappa K M (2017) *Tinospora cordifolia*: the antimicrobial property of the leaves of *Amruthaballi*. Journal of Bacteriology & Mycology. (5):363–371.

[112] Kumar V, Dhanjal JK, Bhargava P, Kaul A, Wang J, Zhang H et al.,(2020). Withanone and Withaferin-A are predicted to interact with transmembrane protease serine 2 (TMPRSS2) and block entry of SARS-CoV-2 into cells. J. Biomol. Struct. Dyn. 1–13. doi: 10.1080/07391102.2020.1775704.

[113] Kwon S, Lee W, Jin C, Jang I, Jung WS, Moon SK, Cho KH (2020) Could herbal medicine (Soshihotang) be a new treatment option for COVID-19?: A narrative review. Integrative Medicine Research. 9: 100480.

[114] Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR (2020) Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID- 19): the epidemic and the challenges. Int J Antimicrob Agents. 105924.

[115] Lai Y, Yan Y, Liao S et al., (2020) 3D-quantitative structure–activity relationship and antiviral effects of curcumin derivatives as potent inhibitors of influenza H1N1 neuraminidase. Arch Pharm Res. 43*:* 489–502.

[116] Lau SKP, Woo PCY, Yip CCY, Tse H, Tsoi HW, Cheng VCC, Lee P, Tang BSF, Cheung CHY, Lee RA, So LY, Lau YL, Chan KH, Yuen KY (2006) Coronavirus HKU1 and other coronavirus infections in Hong Kong. Journal of Clinical Microbiology. 44 (6) :2063–2071.

[117] Lauring AS, Hodcroft EB (2021) Genetic variants of SARS-CoV-2—What do they mean. JAMA. **(**https://jamanetwork.com/ on 01/15/2021).

[118] Lima WG, Brito JCM, da Cruz Nizer WS (2020) Bee products as a source of promising therapeutic and chemoprophylaxis strategies against COVID-19 (SARS-CoV-2). Phytotherapy Research. 1–8.(https://doi. org/10.1002/ptr.6872)

[119] Lin SC, Ho CT, Chuo WH et al., (2017) Effective inhibition of MERS-CoV infection by resveratrol. BMC Infect Dis. 17:144. (https ://doi. org/10.1186/s1287 9-017-2253-8).

[120] Li HY, Ramalingam S, Chye ML (2006) Accumulation of recombinant SARS-CoV spike protein in plant cytosol and chloroplasts indicate potential for development of plant-derived oral vaccines. (1535-3702/06/2318-1346$15.00) Copyright © 2006 by the Society for Experimental Biology and Medicine. 1346-1351.

[121] Li HY, Yang M, Li Z, Meng Z (2017) Curcumin inhibits angiotensin-II induced inflammation and proliferation of rat vascular smooth muscle cells by elevating PPAR-c activity and reducing oxidative stress. Int J Mol Med. 39(5):1307–16.

[122] Li Y, Liu X, Guo L, Li J, Zhong D, Zhang Y, Clarke M, Jin R (2020) Traditional Chinese herbal medicine for treating novel coronavirus (COVID-19) pneumonia: Protocol for a systematic review and meta-analysis. Systematic Reviews. 9:75. (https://doi.org/10.1186/s13643-020-01343-4).

[123] Li W et al., (2003) Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 426: 450–454.

[124] Li SY, Chen C, Zhang HQ et al., (2005) Identification of natural compounds with antiviral activities against SARS-associated coronavirus. Antivir Res. 67:18–23. (https ://doi.org/10.1016/j.antiv iral.2005.02.007).

[125] Lin CW, Tsai FJ, Tsai CH et al., (2005) Anti-SARS coronavirus 3C-like protease effects of *Isatis indigotica* root and plant-derived

phenolic compounds. Antivir Res. 68:36–42. (https ://doi.org/10.1016/j. antiv iral.2005.07.002).

[126] Machado-de-Abreu DJ, Araújo de Barros HE, Natarelli CVL (2020) Therapeutic approach for COVID- 19: The power of herbal medicine. Research, Society and Development. v. 9, n. 10, e6789108907, 2020 (CC BY 4.0) | ISSN 2525 - 3409 | DOI: (http://dx.doi.org/10.33448/rsd v9i 10 . 8907).

[127] Lu R, Zhao X, Li J et al., (2020) Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. Lancet. 395:565-74.

[128] Luo H, Tang QL, Shang YX, Liang SB, Yang M, Robinson N, Liu JP (2020) Can Chinese medicine be used for prevention of coronavirus disease 2019 (COVID-19)? A Review of historical classics, research evidence and current prevention programs. Chin. J. Integr. Med. 26: 243–250.

[129] Mahmood N, Nasir SB, Hefferon K (2021) Plant-based drugs and vaccines for COVID-19. Vaccine. 9: 15. (https://doi.org/10.3390/ vaccines9010015).

[130] Makatsa MS, Tincho MB, Wendoh JM, Ismail SD, Nesamari R, Pera F, Beer SD, David A, Jugwanth S, Gededzha MP, Mampeule N, Sanne I, Stevens W, Scott L, Blackburn J, Mayne ES, Keeton RS, Burgers WA (2020) SARS-CoV-2 antigens expressed in plants detect antibody responses in COVID-19 patients. 1-26. (doi: medRxiv preprint (doi: https://doi.org/10.1101/2020.08.04.20167940).

[131] Makunga NP, Jager AK, van Staden J (2003) Micropropagation of *Thapsia garganica*—a medicinal plant. Plant Cell Reports. 21:967–973. (DOI 10.1007/s00299-003-0623-8).

[132] **Malabadi RB**, Meti NT, Chalannavar RK (2021) Recent updates on role of herbal medicine for **Alzheimer's disease** (Dementia). International Journal of Current Research in Biosciences and Plant Biology. **8(1)**, xxx-xxx. (**doi:** https://doi.org/10.20546/ijcrbp.2020.801.xxx).

[133] **Malabadi RB, Chalannavar RK** (2020) Safed musli (*Chlorophytum borivilianum*): Ethnobotany, phytochemistry and pharmacological updates. Int. J. Curr. Res. Biosci. Plant Biol. 7(11): 25-31.

[134] **Malabadi RB** (2008) Production of edible vaccines for oral immunization in transgenic plants, current and future prospective. Journal of Phytological Research. 21(1): 1-10.

[135] Malabadi RB, Vijaykumar S (2008) Evaluation of antifungal property of medicinal plants. Journal of Phytological Research. 21(1):139-142.

[136] Malabadi RB, Mulgund GS, Nataraja K (2009) Triacontanol induced somatic embryogenesis and plantlet regeneration in *Catharanthus roseus*. Journal of Medicinal and Aromatic Plant Sciences. 31: 147-151.

[137] Malabadi RB, Mulgund GS, Nataraja K (2010a) Evaluation of antifungal activity of selected medicinal plants. Journal of Medicinal and Aromatic Plant Sciences. 32(1):42-45.

[138] Malabadi RB, Parashar A, Ganguly A, Suresh MR (2010b) Expression of dengue virus envelope protein in a different plant system. Faculty Research and Development day, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Canada, 19th November 2010. Abstract No-69, page.

[139] **Malabadi RB**, Ganguly A, Teixeira da Silva JA, Parashar A, Suresh MR, Sunwoo HH (2011a) Overview of plant-derived vaccine antigens: dengue virus. J. Pharm. Pharm. Sci. 14: 400–413.

[140] Malabadi RB, Vijayakumar S, Mulgund GS, Nataraja K (2011b) Induction of somatic embryogenesis in papaya (*Carica papaya*). Research in Biotechnology. 2(5):40-55.

[141] Malabadi RB, Chalannavar RK, Meti NT, Mulgund GS, Nataraja K, Vijayakumar S (2012a) Synthesis of antimicrobial silver nanoparticles by callus cultures and *in vitro* derived plants of *Catharanthus roseus*. Research in Pharmacy. 2(6);18-31.

[142] Malabadi RB, Meti NT, Mulgund GS, Nataraja K, Vijayakumar S (2012b) Synthesis of silver nanoparticles from *in vitro* derived plants and callus cultures of *Costus speciosus* (Koen.); Assessment of antibacterial activity. Research in Plant Biology. 2(4):32-42.

[143] Malabadi RB, Mulgund GS, Meti NT, Nataraja K, Vijayakumar S (2012c) Antibacterial activity of silver nanoparticles synthesized by using whole plant extracts of *Clitoria ternatea*. Research in Pharmacy. 2(4):10-21.

[144] Malabadi RB, Lokare-Naik S, Meti NT, Mulgund GS, Nataraja K, Vijayakumar S (2012d) Synthesis of silver nanoparticles from *in vitro* derived plants and callus cultures of *Clitoria ternatea*; Evaluation of antimicrobial activity. Research in Biotechnology. 3(5): 26- 38.

[145] **Malabadi RB,** Chalannavar RK, Sowmyashree K, Supriya S, Nityasree BR, Gleiser RM, Meti NT, Vijayakumar S, Mulgund GS, Gani RS, Nasalapure A, Chougale R, Masti S, Chougale A, Divakar MS, Kasai D, Odhav B, Baijnath H (2016a) Ebola virus: Updates on plant made vaccine development. International Journal of Research and Scientific Innovations. 3(6):4-12.

[146] Malabadi RB, Chalannavar RK, Meti NT, Gani RS, Vijayakumar S, Mulgund GS, Masti S, Chougale R, Odhav B, Sowmyashree K, Supriya S, Nityasree BR, Divakar MS (2016c) Insulin plant, *Costus speciosus*: Ethnobotany and pharmacological updates. Int.J. Curr. Res. Biosci. Plant Biol. 3(7): 151-161.

[147] Malabadi RB, Chalannavar RK, Meti NT, Vijayakumar S, Mulgund GS, Gani RS, Supriya S, Sowmyashree K, Nityasree BR, Chougale A, Divakar MS (2016d) Antidiabetic Plant, *Gymnema sylvestre* R. Br., (Madhunashini): Ethnobotany, phytochemistry and pharmacological updates. International Journal of Current Trends in Pharmacobiology and Medical Sciences. **1**(4): 1-17.

[148] **Malabadi RB**, Chalannavar RK, Supriya S, Nityasree BR, Sowmyashree K, Mulgund GS, Meti NT (2017a) **Dengue** virus disease: Recent updates on vaccine development. International Journal of Research and Scientific Innovations. 4(7):08-29.

[149] **Malabadi RB**, Chalannavar RK, Supriya S, Nityasree BR, Sowmyashree K, Mulgund GS, Meti NT (2017b) Dengue virus disease: Current updates on the use of *Carica papaya* leaf extract as a potential herbal medicine. International Journal of Research and Scientific Innovations. 4(8):36-50.

[150] **Malabadi RB,** Chalannavar RK, Supriya S, Nityasree BR, Sowmyashree K, Meti NT (2018) Role of botanical drugs in controlling dengue virus disease. International Journal of Research and Scientific Innovations. 5(7): 134-159.

[151] Manoharan Y, Haridas V, Vasanthakumar KC, Muthu S, Thavoorullah FF, Shetty P (2020) Curcumin: A wonder drug as a preventive measure for COVID19 management. Indian Journal of Clin Biochem. 35(3):373–375 (https://doi.org/10.1007/s12291-020-00902-9).

[152] Margolin E, Verbeek M, Meyers A, Chapman R, Williamson AL, Rybicki EP (2020) Calreticulin co-expression supports high level production of a recombinant SARS-CoV2 spike mimetic in *Nicotiana benthamiana*. bioRxiv preprint (doi: https://doi.org/10.1101/2020.06.14.150458; this version posted June 14, 2020).

[153] Masiello P, Novelli M, Beffy P, Menegazzi M (2020) Can *Hypericum perforatum* (SJW) prevent cytokine storm in COVID-19 patients?. Phytotherapy Research. 34:1471–1473. ( https://orcid.org/0000-0003-1310-9227).

[154] Masood M, Arshad M, Qureshi R, Sabir S, Amjad MS, Qureshi H, Tahir Z (2015) *Picrorhiza kurroa*: An ethnopharmacologically important plant species of Himalayan region. Pure Appl. Biol. 4(3): 407-417.

[155] Masters PS (2006) The molecular biology of coronaviruses. Adv. Virus Res. 65: 193–292.

[156] MPIKG (2020) Max Planck Institute for colloids and interfaces press release. https ://www.mpikg .mpg.de/62880 44/news_publi catio n_14663 263_trans ferre d?c=13230 5. Accessed 10 May 2020.

[157] Ministry of AYUSH, Government of India, (2020) Ayurveda's immunity boosting measures for self-care during COVID 19 Crisis (2020).

[158] Milind P, Deepa K (2011) CLOVE: A champion spice. International Journal of Research in Ayurveda & Pharmacy. 2(1): 47-54.

[159] Mirzaie A, Halaji M, Dehkordi FS, Ranjbar R, Noorbazargan H (2020) A narrative literature review on traditional medicine options for the treatment of corona virus disease 2019 (COVID-19). Complementary Therapies in Clinical Practice. 40 : 101214.

[160] Moderna (2020) Moderna's COVID-19 vaccine candidate meets its primary efficacy endpoint in the first interim analysis of the phase 3 COVE study. Nov 16, 2020.https://investors.modernatx.com/newsreleases/news-release-details/modernas-covid-19-vaccine-candidatemeets-its-primary-efficacy (accessed Nov 17, 2020).

[161] Mondal S, Mirdha BR, Mahapatra SC (2009) The science behind sacredness of Tulsi (*Ocimum sanctum* Linn.). Indian J Physiol Pharmacol. **53**:291–306.

[162] Mondal S, Varma S, Bamola VD, Naik SN, Mirdha BR, Padhi MM, et al., (2011) Double-blinded randomized controlled trial for immunomodulatory effects of Tulsi (*Ocimum sanctum* Linn.) leaf extract on healthy volunteers. J. Ethnopharmacol. 136:452–6.

[163] Narayanan CR, Natu AA (1974) Triterpene acids of Indian clove buds. Phytochemistry. 13(9):1999–2000.

[164] Nair AD, James TJ (2021) Computational screening of phytocompounds from *Moringa oleifera* leaf as potential inhibitors of SARS-CoV-2 Mpro. Research Square. 1-14. (DOI: https://doi.org/10.21203/rs.3.rs-71018/v1).

[165] Nicolaa M, Alsafib Z, Sohrabic C, Kerwand A, Al-Jabird A, Iosifidisc C, Aghae M, Aghaf R (2020) The socio-economic implications of the coronavirus pandemic (COVID-19): A review. International Journal of Surgery. 78: 185–193 (https://doi.org/10.1016/j.ijsu.2020.04.018).

[166] Nishiura H, Jung SM, Linton NM, Kinoshita R, Yang, Y, Hayashi K, Kobayashi T,Yuan B, Akhmetzhanov AR (2020) The extent of transmission of novel coronavirus in Wuhan, China. J. Clin. Med. 9: 330.

[167] Nugraha RV, Ridwansyah H, Ghozali M, Khairani AF, Atik N (2020) Traditional herbal medicine candidates as complementary treatments for COVID-19: A review of their mechanisms, pros and cons. Evidence-Based Complementary and Alternative Medicine. 1-12. 2560645, (https://doi.org/10.1155/2020/2560645).

[168] Oladele JO, Ajayi EI, Oyeleke OM, Oladele OT, Olowookere BO, Adeniyi BM, Oyewole OI, Oladiji AT (2020) A systematic review on COVID-19 pandemic with special emphasis on curative potentials of Nigeria based medicinal plants. Heliyon. 6(9): e04897. (https://doi.org/10.1016/j.heliyon.2020.e04897).

[169] Omer SB, Yildirim I, Forman HP (2020) Herd immunity and implications for SARS-CoV-2 control. JAMA. 324 (20): 2095.

[170] Oude-Munnink BB, Sikkema RS, Nieuwenhuijse DF et al., (2020) Transmission of SARS-CoV-2 on mink farms between humans and mink and back to humans. Science. eabe5901. (doi:10.1126/ science.abe5901).

[171] Pachetti M, Marini B, Benedetti F, Giudici F Mauro E, Storici P Masciovecchio C, Angeletti S, Ciccozzi M, Gallo RC, Zella D, Ippodrino R (2020) Emerging SARS-CoV-2 mutation hot spots include a novel RNA-dependent-RNA polymerase variant. Journal of Translational Medicine. 18: 179. (https://doi.org/10.1186/s12967-020-02344-6).

[172] Pandeya SC, Pandea V, Satia D, Upretia S, Samanta M (2020) Vaccination strategies to combat novel corona virus SARS-CoV-2. Life Sciences. 256: 117956. (https://doi.org/10.1016/j.lfs.2020.117956).

[173] Pang XF, Zhang LH, Bai F, Wang NP, Garner RE, McKallip RJ et al., (2015) Attenuation of myocardial fibrosis with curcumin is mediated by modulating expression of angiotensin II AT1/AT2 receptors and ACE2 in rats. Drug Des Devel Ther. 9:6043–54.

[174] Panyod S, Ho CT, Sheen LY (2020) Dietary therapy and herbal medicine for COVID-19 prevention: A review and perspective. Journal of Traditional and Complementary Medicine. 10: 420-427.

[175] Pardi N, Hogan MJ, Porter FW, Weissman D (2018) mRNA vaccines — A new era in vaccinology. Nature Reviews. Drug Discovery. 17(4):261-279.

[176] Pardi N, Tuyishime S, Muramatsu H, Kariko K, Mui BL, Tam YK, Madden TD, Hope MJ, Weissman D (2015) Expression kinetics of mucleoside-modified mRNA delivered in lipid nanoparticles to mice by various routes. J. Controlled Release. 217: 345−351.

[177] Park HR, Yoon H, Kim MK et al., (2012) Synthesis and antiviral evaluation of 7-O-arylmethylquercetin derivatives against SARS-associated coronavirus (SCV) and hepatitis C virus (HCV). Arch Pharm Res. 35:77–85. (https ://doi.org/10.1007/s1227 2-012-0108-9).

[178] Parida MM, Upadhyay C, Pandya G, Jana AM (2002) Inhibitory potential of neem (*Azadirachta indica* Juss) leaves on dengue virus type-2 replication. Journal of Ethnopharmacology. 79(2): 273-278.

[179] Parida PK, Paul D, Chakravorty D (2020) The natural way forward: Molecular dynamics simulation analysis of phytochemicals from Indian medicinal plants as potential inhibitors of SARS-CoV-2 targets. Phytotherapy Research. 34:3420–3433.**(**https://doi.org/10.1002/ptr.6868).

[180] Parthipan M, Aravindhan V, Rajendran A (2011) Medico-botanical study of Yercaud hills in the eastern Ghats of Tamil Nadu, India. Anc Sci Life. 30:104–9.

[181] Patial V, Devi K, Sharma M, Bhattacharya A, Ahuja PS (2012). Propagation of *Picrorhiza kurroa* Royle ex Benth: An important medicinal plant of Western Himalaya. J Med Plants Res. 6(34): 4848-4860.

[182] Patwardhan B, Chavan-Gautam P, Gautam M, Tillu G, Chopra A, Gairola S (2020) Ayurveda rasayana in prophylaxis of covid-19. Curr Sci.118:1158–1160.

[183] Paules CI, Marston HD, Fauci AS (2020) Coronavirus infections-more than just the common cold. JAMA. 323: 707.

[184] Paz S, Mauer C, Ritchie A, Robishaw JD, Caputi M (2020) A simplified SARS-CoV-2 detection protocol for research laboratories. PLoS ONE. 15(12): e0244271. (https://doi.org/10.1371/ journal.pone.024427).

[185] Perlman S, Netland J (2009) Coronaviruses post-SARS: Update on replication and pathogenesis. Nat. Rev. Microbiol. 7: 439–450.

[186] Peterson CT, Denniston K, Chopra D (2017) Therapeutic uses of Triphala in ayurvedic medicine. The Journal of Alternative and Complementary Medicine. 23(8):607-614.

[187] Pfizer. Pfizer and BioNTech (2020) announce vaccine candidate against COVID-19 achieved success in first interim analysis from phase 3 study. Nov 9, 2020. https://www.pfizer.com/news/press-release/ press-release-detail/pfizer-and-biontech-announce-vaccinecandidate-against accessed Nov 15, 2020). COVID-19 achieved success in first interim analysis from phase 3 study. Nov 9, 2020. https://www.pfizer.com/news/press-release/ press-release-detail/pfizer-and-biontech-announce-vaccinecandidate-against (accessed Nov 15, 2020).

[188] PIB (2020) Press Information Bureau, India. https ://pib.gov.in/newsi te/ Print Relea se.aspx?relid =20000 5. Accessed 10 May 2020.

[189] Pogrebnyak N, Golovkin M, Andrianov V, Spitsin S, Smirnov Y, Egolf R, Koprowski (H) (2005) Severe acute respiratory syndrome (SARS) S protein production in plants: Development of recombinant vaccine. PNAS. 102 (25): 9062–9067.

[190] Pongthanapisith V, Ikuta K, Puthavathana P, Leelaman W (2013) Antiviral protein of *Momordica charantia* L. inhibits different subtypes of Influenza A.Hindawi Publishing Corporation Evidence-Based Complementary and Alternative Medicine. ID 729081, 6 (http://dx.doi.org/10.1155/2013/729081).

[191] Pradeep AR et al., (2016) Triphala, a new herbal mouthwash for the treatment of gingivitis: A randomized controlled clinical trial. J. Periodontol. 87:1352–1359.

[192] Praditya D, Kirchhoff L, Bruning J, Rachmawati H, Steinmann J, Steinmann E (2019) Anti-infective properties of the golden spice curcumin. Front Microbiol. 10:912.

[193] Prasad S, Aggarwal BB (2011) Turmeric, the golden spice: From traditional medicine to modern medicine. In: Benzie IFF, Wachtel-Galor S, editors. Herbal Medicine: Biomolecular and Clinical Aspects. 2nd edition. Boca Raton (FL): CRC Press/Taylor & Francis; 2011. Chapter 13. (https://www.ncbi.nlm.nih.gov/books/NBK92752).

[194] Prasad A, Muthamilarasan M, Prasad M (2020) Synergistic antiviral effects against SARS-CoV-2 by plant-based molecules. Plant Cell Reports. (https://doi.org/10.1007/s00299-020-02560-w).

[195] Prasad S, Tyagi AK (2015) Curcumin and its analogues: A potential natural compound against HIV infection and AIDS. Food Funct. 6: 3412–19.

[196] Pulok K, Mukherjee SR, Bhattacharyya S et al., (2005) Clinical study of 'Triphala'—A well known phytomedicine from India. Iran J Pharmacol Ther. 5:51–54.

[197] Pyrc K, Berkhout B, Hoek LVD (2007) The Novel Human Coronaviruses NL63 and HKU1. Journal of Virology. 81 (7): 3051–3057.

[198] Ramasamy M, Minassian AM (2020) Safety and immunogenicity of ChAdOx1 nCoV-19 (AZD1222) vaccine administered in a primeboost regimen in older adults (COV002): a phase 2/3 single blind, randomised controlled trial. Lancet 2020; published online Nov 18. https://doi.org/10·1016/S0140–6736(20)32466–1.

[199] Rasmussen U, Christensen SB, Sandberg F (1981) Phytochemistry of the genus *Thapsia*. Plant Med. 43:336–341.

[200] Rana V, Thakur K, Sood R, Sharma V, Sharma TR (2012) Genetic diversity analysis of *Tinospora cordifolia* germplasm collected from northwestern Himalayan region of India. J Genet. 91:99–103.

[201] Rao VP, Gan SH (2014) Cinnamon: A multifaceted medicinal plant. Hindawi Publishing Corporation. Evidence-Based Complementary and Alternative Medicine Article ID 642942. 1-12 (http://dx.doi.org/10.1155/2014/642942).

[202] Rastogi S, Pandey DN, Singh RH (2020) COVID-19 pandemic: A pragmatic plan for *ayurveda* intervention. Journal of *Ayurveda* and Integrative Medicine. (https://doi.org/10.1016/j.jaim.2020.04.002).

[203] Rathee D, Rathee P, Rathee S, Rathee D (2012) Phytochemical screening and antimicrobial activity of *Picrorrhiza kurroa*, an Indian traditional plant used to treat chronic diarrhoea. Arab J Chem. (http://dx.doi.org/10.1016/j.arabjc.2012.02.009).

[204] Rattanapisit K, Shanmugaraj B, Manopwisedjaroen S, Purwono PD, Siriwattananon K, Khorattanakulchai N, Hanittinan O, Boonyayothin W, Thitithanyanont A, Smith DR, Phoolcharoen W (2020) Rapid production of SARS-CoV-2 receptor binding domain (RBD) and spike specifc monoclonal antibody CR3022 in *Nicotiana benthamiana*. Scientifc Reports (Nature Research). 10:17698. ( https://doi.org/10.1038/s41598-020-74904-1).

[205] Richart SM, Li YL, Mizushina Y et al., (2018) Synergic effect of curcumin and its structural analogue (Monoacetylcurcumin) on anti-influenza virus infection. J Food Drug Anal. 26: 1015–23.

[206] Riddell S, Goldie S, Hill A, Eagles D, Drew TW (2020) The effect of temperature on persistence of SARS-CoV-2 on common surfaces. Virology Journal. 17: 145. (https://doi.org/10.1186/s12985-020-01418-7).

[207] Rocha FAC, Assis MRd (2020) Curcumin as a potential treatment for COVID-19. Phytotherapy Research. 34:2085–2087. (https://orcid.org/0000-0002-6567-4570).

[208] Roy A, Sarkar B, Celik C, Ghosh A, Basu U, Jana M, Jana A, Gencay A, Sezgin GC, Ildiz N, Dam P, Mandal AK, Ocsoy I (2020) Can concomitant use of zinc and curcumin with other immunity-boosting nutraceuticals be the arsenal against COVID-19?. Phytotherapy Research. 34:2425–2428. (https://orcid.org/0000-0001-9249-5052).

[209] Runfeng L, Yunlong H, Jicheng H, Weiqi P, Qinhai M, Yongxia S. et al., (2020) Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2). Pharmacol. Res. 156: 104761. (doi: 10.1016/j.phrs.2020.104761).

[210] Ryu YB, Jeong HJ, Kim JH et al., (2010) Biflavonoids from *Torreya nucifera* displaying SARS-CoV 3CLpro inhibition. Bioorganic Med Chem. 18:7940–7947. (https ://doi.org/10.1016/j. bmc.2010.09.035).

[211] Saha S, Ghosh S (2012) *Tinospora cordifolia*: One plant, many roles. Anc Sci Life. 31(4): 151–159. (doi: 10.4103/0257-7941.107344).

[212] Saif LJ (2004) Animal coronaviruses: what can they teach us about the severe acute respiratory syndrome? Rev. Sci. Tech. 23: 643–660.

[213] Salemi M, Fitch WM, Ciccozzi M, Ruiz-Alvarez MJ, Rezza G, Lewis MJ (2004) Severe acute respiratory syndrome coronavirus sequence characteristics and evolutionary rate estimate from maximum likelihood analysis. J Virol. 2004; 78(3):1602–3. (https://doi.org/10.1128/jvi.78.3.1602-1603.2004) .

[214] Sangal A (2011)"Role of cinnamon as a beneficial antidiabetic food adjunct: A review." Advances in Applied Science Research. 2 (4): 440–450.

[215] Saxena S (2005) *Glycyrrhiza glabra*: Medicine over the millennium. Natural Product Radiance. 4(5):358-367.

[216] Shaji D (2020) Computational identification of drug lead compounds for COVID-19 from *Moringa Oleifera*. ChemRixv. (Computational Identification of Drug Lead Compounds for COVID-19 from *Moringa Oleifera* (chemrxiv.org). 1-9.

[217] Shanbhag VK (2015) Triphala in prevention of dental caries and as an antimicrobial in oral cavity—A review. Infect Disord Drug Targets. 15:89–97.

[218] Shang J et al., (2020) Cell entry mechanisms of SARS-CoV-2. Proc. Natl Acad. Sci. USA. 117: 11727–11734.

[219] Shanmugaraj B, Malla A, Phoolcharoen W (2020) Emergence of novel coronavirus 2019-nCoV: Need for rapid vaccine and biologics development. Pathogens. 9:148. (doi:10.3390/pathogens 9020148). (www.mdpi.com/journal/pathogens).

[220] Sharma U, Bala M, Kumar N, Singh B, Munshi RK, Bhalerao S (2012) Immunomodulatory active compounds from *Tinospora cordifolia*. J. Ethnopharmacol. 141:918–26.

[221] Shawky E, Ahmed A, Nada AA, Ibrahim RS (2020) Potential role of medicinal plants and their constituents in the mitigation of SARS-CoV-2: Identifying related therapeutic targets using network pharmacology and molecular docking analyses. The Royal Society of Chemistry. 0: 27961–27983 | 27961. (DOI: 10.1039/d0ra05126h).

[222] Shen H, Yamashita A, Nakakoshi M, Yokoe H, Sudo M, Kasai H, Tanaka T, Fujimoto Y, Ikeda M, Kato N, Sakamoto N, Shindo H, Maekawa S, Enomoto N, Tsubuki M, Moriishi K (2013) Inhibitory effects of caffeic acid phenethyl ester derivatives on replication of hepatitis C virus. PLoS One. 8: e82299.

[223] Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R (2020) COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. Journal of Advanced Research. 24 : 91–98.

[224] Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, Bucci E, Piacentini M, Ippolito G, Melino G (2020) COVID- 19 infection: The perspectives on immune responses. Cell Death Differ. 27: 1451–1454.

[225] Shin MD, Shukla S, Chung YH, Beiss V, Chan SK, Ortega-Rivera OA, Wirth DM, Chen A, Sack M, Pokorski JK, Steinmetz NF (2020) COVID-19 vaccine development and a potential nanomaterial path forward. Nature Nanotechnology. 15:646-655.

[226] Singh NA, Kumar P, Jyoti S, Kumar N (2021) Spices and herbs: Potential antiviral preventives and immunity boosters during COVID-19. Phytotherapy Research. 1–13. (https://doi.org/10.1002/ptr.7019).

[227] Singhal T et al., (2020) A Review of coronavirus disease-2019 (COVID-19). The Indian Journal of Pediatrics. 87(4):281–286. (https://doi.org/10.1007/s12098-020-03263-6).

[228] Siriwattananon K, Manopwisedjaroen S, Kanjanasirirat P, Budi-Purwono P, Rattanapisit K, Shanmugaraj B, Smith DR, Borwornpinyo S, Thitithanyanont A, Phoolcharoen W (2021) Development of plant-produced recombinant ACE2-Fc fusion protein as a potential therapeutic agent against SARS-CoV-2. Front. Plant Sci. 11:604663. (doi: 10.3389/fpls.2020.604663).

[229] Smitt UW, Jager AK, Adsersen A, Gudiksen L (1995) Comparative studies in phytochemistry and fruit anatomy of *Thapsia garganica* and *T. transtagana*, Apiaceae (Umbelliferae). Bot J Linn Soc. 117:281–292.

[230] Sivaraman D, Pradeep PS (2020) Revealing anti-viral potential of bioactive therapeutics targeting SARS-CoV2-polymerase (RdRp) in combating COVID-19: molecular investigation on Indian traditional medicines. Preprints. (https ://doi.org/10.20944 /prepr ints2 02003 .0450.v1).

[231] Srivasuki KP (2012) Nutritional and health care benefits of Amla. Journal of Pharmacognosy. 3(2):141-51.
[232] Sunwoo HH, Palaniyappan, A, Ganguly A, Bhatnagar PK, Das P, EI-Kadi AOS, Suresh MR (2013) Quantitative and sensitive detection of the SARS-CoV spike protein using bispecific monoclonal antibody-based enzyme-linked immunoassay. Journal of Virological Methods. 187(1): 72-78.
[233] Suresh MR, Bhatnagar PK, Das D (2008) Molecular targets for diagnostic sand therapeutics of severe acute respiratory syndrome (SARS-CoV). J. Pharm Pharm. Sci. 11: 1–13.
[234] Tang LIC, Ling APK, Koh RY, Chye SM, Voon KGL (2012) Screening of anti-dengue activity in methanolic extracts of medicinal plants. BMC Complement Altern Med. 12:3.
[235] Tang X, Wu C, Li X, Song Y, Yao X, Wu X et al., (2020) On the origin and continuing evolution of SARS-CoV-2. Natl Sci Rev. (https ://doi.org/10.1093/nsr/ nwaa0 36).
[236] Tegally H et al., (2020) Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. medRxiv. (doi: https://doi.org/10.1101/2020.12.21.20248640).
[237] Teixeira RR, Pereira WL, Oliveira AFCDS, da Silva AM, de Oliveira AS, da Silva ML, da Silva CC, de Paula SO (2014) Natural products as source of potential dengue antivirals. Molecules. 19: 8151-8176. (doi:10.3390/molecules19068151).
[238] Tian JH, Patel N, Haupt R, Zhou H, Weston S, Hammond H et al., (2021) SARS-CoV-2 spike glycoprotein vaccine candidate NVX-CoV2373 immunogenicity in baboons and protection in mice. Nature Communications. 12(372):1-14. (https://doi.org/10.1038/s41467-020-20653-8).
[239] The Gamaleya National Centre (2020) The first interim data analysis of the Sputnik V vaccine against COVID-19 phase III clinical trials in the Russian Federation demonstrated 92% efficacy. Nov 11, 2020. https://sputnikvaccine.com/newsroom/pressreleases/the-firstinterim-data- analysis-of-the-sputnik-v-vaccine-against-covid-19- phase-iii-clinical-trials-/ (accessed Nov 15, 2020).
[240] Thota SM, Balan V, Sivaramakrishnan V (2020) Natural products as home-based prophylactic and symptom management agents in the setting of COVID-19. Phytotherapy Research. 34:3148–3167. (https://doi.org/10.1002/ptr.6794).
[241] Tian JH, Patel N, Haupt R, Zhou H, Westo S et al., (2021) SARS-CoV-2 spike glycoprotein vaccine candidate NVX-CoV2373 immunogenicity in baboons and protection in mice. Nature Communications. 12(372):1-14 |(https://doi.org/10.1038/s41467-020-20653-8).
[242] Tutunchi H, Naeini F, Ostadrahimi A, Hosseinzadeh-Attar MJ (2020) Naringenin, a flavanone with antiviral and anti-inflammatory effects: A promising treatment strategy against COVID-19. Phytotherapy Research. 34: 3137–3147. (https://doi.org/10.1002/ptr.6781).
[243] Tyrrell, DAJ, Bynoe ML (1965) Cultivation of novel type of common-cold virus in organ cultures. Br. Med. J. 1: 1467–1470.
[244] Udugama B, Kadhiresan P, Kozlowski HN, Malekjahani A, Osborne M, Li VYC, Chen H, Mubareka S, Gubbay JB, Chan WCW (2020) Diagnosing COVID-19: The disease and tools for detection. ACS Nano. 14(4) 3822-3835.
[245] Uno Y (2020) Camostat mesilate therapy for COVID-19. Internal and Emergency Medicine. (https://doi.org/10.1007/s11739-020-02345-9).
[246] Upadhyay S, Tripathi PK, Singh M, Raghavendhar S, Bhardwaj M, Patel AK (2020) Evaluation of medicinal herbs as a potential therapeutic option against SARS-CoV-2 targeting its main protease. Phytotherapy Research. 34:3411–3419.
[247] Vangalapati M, Satya SN, Surya-Prakash D, Avanigadda S (2012) "A review on pharmacological activities and clinical effects of cinnamon species," Research Journal of Pharmaceutical, Biological and Chemical Sciences. 3 (1): 653–663.
[248] Vellingiri B, Jayaramayya K, Iyer M et al., (2020) COVID-19: A promising cure for the global panic. Sci Total Environ. 725:138277. (https://doi.org/10.1016/j.scito tenv.2020.13827 7).
[249] Voysey M et al., (2021) Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: An interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. The Lancet. 397: 99-111.
[250] V'kovski P, Kratzel A, Steiner S, Stalder H, Thie V (2020) Coronavirus biology and replication: Implications for SARS-CoV-2. Nature Reviews Microbiology. 1-16. ( https://doi.org/10.1038/s41579-020-00468-6).
[251] Weng JK (2020) Plant solutions for the COVID-19 pandemic and beyond: Historical reflections and future perspectives. Molecular Plant. 13: 803–807.
[252] Wang C, Horby PW, Hayden FG, Gao GFA (2020) Novel coronavirus outbreak of global health concern. Lancet. 395: 470–473.
[253] Wen CC, Shyur LF, Jan JT, Liang PH, Kuo CJ, Arulselvan P. et al., (2011) Traditional Chinese medicine herbal extracts of *Cibotium barometz*, *Gentiana scabra*, *Dioscorea batatas*, *Cassia tora*, and *Taxillus chinensis* inhibit SARS-CoV replication. J. Trad. Compl. Med. 1 (1): 41–50. (doi: 10.1016/S2225-4110(16)30055-4).
[254] Wise J et al., (2020) Covid-19: New coronavirus variant is identified in UK. BMJ. 16:371: m4857. (doi: 10.1136/bmj.m4857).
[255] Woo PC, Lau SK, Chu CM, Chan KH, Tsoi HW, Huang Y, Wong BH, Poon RW, Cai JJ, Luk WK, Poon LL, Wong SS, Guan Y, Peiris JS, Yuen KY (2005) Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. Journal of Virology. 79:884–895.
[256] Woo PC, Lau SK, Wong BH, Tsoi HW, Fung AM, Chan KH, Tam VK, Peiris JS, Yuen KY (2004) Detection of specific antibodies to severe acute respiratory syndrome (SARS) coronavirus nucleocapsid protein for serodiagnosis of SARS coronavirus pneumonia. J. Clin Microbiol. 42:2306–2309.
[257] Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, Hu Y, Tao ZW, Tian JH, Pei YY, Yuan ML, Zhang YL, Dai FH, Liu Y, Wang QM, Zheng JJ, Xu L, Holmes EC, Zhang YZ (2020a) A new coronavirus associated with human respiratory disease in China. Nature. 579 (7798) 265-269.
[258] Wu YQ, Zou L, Yu X, Sun D, Li SB, Tang L, Yang JR, Chen XY, Wu YG, Fang H (2020b) Clinical effects of integrated traditional Chinese and western medicine on COVID-19: A systematic review. Shanghai J. Tradit. Chin. Med. 1–8.
[259] Wu CY, Jan JT, Ma SH et al., (2004) Small molecules targeting severe acute respiratory syndrome human coronavirus. Proc Natl Acad Sci USA. 101:10012–10017. (https ://doi.org/10.1073/pnas.04035 96101).
[260] Wu YH, Zhang BY, Qiu LP, Guan RF, Ye ZH, Yu XP (2017) Structure properties and mechanisms of action of naturally originated phenolic acids and their derivatives against human viral infections. Curr. Med. Chem. 24: 3995–4008.
[261] Wyllie AL, Fournier J, Casanovas-Massana A, Campbell M, Tokuyama M, Vijayakumar P et al., (2020a) Saliva or nasopharyngeal swab specimens for detection of SARS-CoV-2. N Engl J Med. 383 (13):1283–6. (https://doi.org/10.1056/NEJMc2016359).
[262] Wyllie AL, Fournier J, Casanovas-Massana A, Campbell M, Tokuyama M, Vijayakumar P et al., (2020b) Saliva is more sensitive for SARS-CoV-2 detection in COVID-19 patients than nasopharyngeal swabs. medRxiv. 04.16.20067835. (https://doi.org/10.1101/2020.04.16.20067835).
[263] Xie Y, Huang B, Yu K, Xu W (2013) Further discovery of caffeic acid derivatives as novel influenza neuraminidase inhibitors. Bioorg. Med. Chem. 21: 7715–7723.
[264] Xu X, Chen P, Wang J, Feng J, Zhou H, Li X et al., (2020) Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci. 1–4.
[265] Xu J, Zhang Y (2020) Traditional Chinese medicine treatment of COVID19. Complement. Ther. Clin. Pract. 39:101165. (doi: 10.1016/j.ctcp.2020.101165).

[266] Xu R, Cui B, Duan X, Zhang P, Zhou X, Yuan Q (2020) Saliva: Potential diagnostic value and transmission of 2019-nCoV. Int J Oral Sci. 12(1):11. (https://doi.org/10.1038/s41368-020-0080-z).

[267] Yang CW, Lee YZ, Kang IJ et al., (2010) Identification of phenanthroindolizines and phenanthroquinolizidines as a novel potent anti-coronaviral agents for porcine enteropathogenic coronavirus transmissible gastroenteritis virus and human severe acute respiratory syndrome coronavirus. Antivir Res. 88:160–168. (https ://doi. org/10.1016/j.antiv iral.2010.08.009).

[268] Yang (2021) Application of nanotechnology in the COVID-19 pandemic. International Journal of Nanomedicine. 6 :623–649.

[269] Yao H, Lu X, Chen Q, Xu K, Chen Y, Cheng L, et al., (2020) Patient-derived mutations impact pathogenicity of SARS-CoV-2. MedRxiv preprint. (https ://doi. org/10.1101/2020.04.14.20060 160).

[270] Yamauchi Y, Helenius A (2013) Virus entry at a glance. J. Cell Sci. 126 ( 6): 1289-1295.

[271] Yi L, Li Z, Yuan K et al., (2004) Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. J. Virol. 78:11334–11339. (https ://doi.org/10.1128/jvi.78.20.11334 -11339 .2004).

[272] Yonesi M, Rezazadeh A (2020) Plants as a prospective source of natural anti-viral compounds and oral vaccines against COVID-19 coronavirus. Preprints 2020040321. (doi: 10.20944/preprints202004.0321.v1).

[273] Yu M, Lee J, Moo J et al., (2020) Identification of myricetin and scutellarein as novel chemical inhibitors of the SARS coronavirus helicase, nsP13. Bioorganic Med Chem Lett. 22:4049–4054.

[274] Yuen KS, Ye ZW, Fung SY, Chan CP, Jin DY(2020) SARS-CoV-2 and COVID-19: The most important research questions. Cell Bioscience. 10:40.2.

[275] Zahedipour F, Hosseini SA, Sathyapalan T, Majeed M, Jamialahmadi T, Al-Rasadi K, Banach M, Sahebkar A (2020) Potential effects of **curcumin** in the treatment of COVID-19 infection. Phytotherapy Research. 4:2911–2920. (https://doi.org/10.1002/ptr.6738).

[276] Zaman W, Saqib S, Ullah F, Ayaz A, Ye J (2020) COVID-19: Phylogenetic approaches may help in finding resources for natural cure. Phytotherapy Research.. 34:2783–2785.

[277] Zhang E, Du RH, Li B, Zheng XS, Yang XL, Hu B, Wang YY, Xiao GF, Yan B, Shi ZL, Zhou P (2020b) Molecular and serological investigation of 2019-nCoV infected patients: Implication of multiple shedding routes. Emerging Microbes and Infections. 9: 386-89.

[278] Zhang D, Zhang B, Lv JT, Sa RN, Zhang XM, Lin ZJ (2020a) The clinical benefits of Chinese patent medicines against COVID-19 based on current evidence. Pharmacol. Res. 157:104882. (doi: 10.1016/j.phrs.2020.104882).

[279] Zhang R, Lib Y, Zhangc AL, Wangd Y, Molinae MJ (2020c) Identifying airborne transmission as the dominant route for the spread of COVID-19. Proc. Natl. Acad. Sci. USA. 117(26): 14857–14863.

[280] Zheng N, Xiaa R, Yang C, Yin B, Li Y, Duan C, Liang L, Guo H, Xie Q (2009) Boosted expression of the SARS-CoV nucleocapsid protein in tobacco and its immunogenicity in mice. Vaccine. 27: 5001–5007.

[281] Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W et al., (2020a) Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. Nature. 579: 270–273. (doi: 10.1038/s41586-020-2012-7).

[282] Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W et al., (2020b) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 579: 270–273.

[283] Zhu N, Zhang D, Wang W et al., (2020) China novel coronavirus investigation research team. A novel coronavirus from patients with pneumonia in China 2019. N Engl J Med. 382:727-33.