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MECHANISTIC INSIGHTS INTO CORONA VIRUSES AND COVID-19: UNRAVELLING THE POSSIBLE TREATMENT STRATEGIES WITH EMPHASIS ON PLANT-DERIVED BIOACTIVE COMPOUNDS

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Abstract

Pandemic coronaviruses being zoonotic have been the potential cause of worldwide social, economic, and mortality stress causing certain illnesses like severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) in 2002, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2013, and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in 2019. Because of severity of illness, various types of organs are damaged or even destroyed by these coronaviruses that in turn cause neurological, hepatic, and respiratory issues. Several vaccines are now either licensed or through phase III studies. Majority of vaccines use a recombinant spike glycoprotein, either based on mRNA (the Moderna and Pfizer-BioNTech vaccines), via adenovirus vector (the Oxford-AstraZeneca and Johnson & Johnson vaccines), via whole inactivated SARS-CoV-2 virus (Sinovac Biotech vaccines), or by injection of the protein itself (the Novavax vaccine). Moreover, nano vaccines and nano antiviral drugs could be prepared for targeted and sustained delivery. In the current scenario, there is a need to analyze the bestowing role of non-pharmacological mediators like nutraceuticals along with dietary supplements besides nano-biotechnological approaches to minimize the risk of SAR-CoV-2 infection by moderating the signs and symptoms related with COVID -19. A good dietary pattern is essential for individuals in preventing them from getting immunocompromised due to weakened immune system resulting from poor nutritional status. Phytochemicals biosynthesized by plants have potent antiviral activities to fight against SAR-CoV-2 by disrupting virus life cycle. Evidently, this development driven a concentration on phytochemicals from therapeutic plants to search new lead molecules, with an emphasis specifically on antiviral drugs. Such natural products inspire community efforts to raise funds that help researchers to investigate more phytochemicals for COVID-19 antiviral drug development. Most importantly, inclusion of plant-derived bioactive compounds along with the contemporary allopathic regimens have been anticipated to improve the evolvement of therapeutics against COVID 19.

Key words: Natural compounds, SARS-CoV-2, Dietary supplements, Phytoconstituents, Nutraceuticals, Nanobiotechnology.

Introduction

In China, Wuhan hospitals began reporting cases of unknown cause of pneumonia in December 2019. Many patients initially identified were connected to a local wholesale wet seafood market (Columbus *et al*., 2020) and virus spread very quickly across 200 countries worldwide. By using the next-generation sequencing approach, a novel coronavirus was recognized within respiratory tract which was different from more strains of coronaviruses known to affect humans, severe acute respiratory syndrome coronavirus 2 is a highly contagious virus that can be passed from one person to another (SARS-CoV-2). The World Health Organization (WHO) designated the condition as coronavirus disease-2019 in February 2020, COVID-19 caused by SARS-CoV 2 infectious virus (Velavan & Meyer, 2020). According to a report published by the WHO on 21st April 2021, the outcome was 143,587,922 confirmed cases and 3,058,567 deaths globally. At the beginning of this pandemic, a prospective learning was performed that recorded an incubation time for COVID-19 of almost 5-14 days; furthermore, latest report suggests that the time of incubation may be as long as 24 days (Lauer *et al*., 2020).

These drugs being tested as investigational satisfying agents for the cure of COVID-19 are repurposed treatments, normally given to affected persons with other viral diseases, such as anti-HIV medications for the influenza treatment. Lung damage and acute respiratory distress syndrome (ARDS) brought on by an immune-mediated cytokine storm are the most harmful outcomes seen within COVID-19 patients (Xu *et al*., 2020). Laboratory testing demonstrated a hyperactive condition of systemic CD4 and CD8 cells, and histopathological findings of lung biopsy tissue from a deceased COVID-19 patient revealed bilateral widespread alveolar destruction and fibroblastic proliferation in lung airspaces (Tian *et al*., 2020). Multiple drugs, including Remdesivir, Tocilizumab (interleukin [IL]-6 receptor inhibitor), Interferon, Ribavirin, Lopinavir/Ritonavir, Favipirvir, the antimalarial drug hydroxychloroquine (or chloroquine), and the Arbidol, have been suggested as potential treatments for COVID-19 due to the hyperactive immune system present in some patients with extreme COVID-19.

In China, through the spread period of SARS-CoV-2, allopathic treatment was applied for the Corona management in Jinyintan Hospital of Wuhan (centered on almost 99 patients), involving intravenous immunoglobulin

cure (27%), oxygen therapy (75%), treatment using antibiotics (71%), and antiviral action (76%) (Chen *et al*., 2020). Whereas a lot of clinical trials are ongoing to discover possible plant-derived drugs used in COVID-19 treatment. Natural herbal medicines comprise a well-recognized antiviral strength to be complementary in the preventive cure of SARS-CoV-2. In 2003, after the outbreak of SARS-CoV-1, scientists were dynamically attempting to explore plant-based antiviral drugs and herbs. Comprehensive antiviral properties of medicinal plants based on their native region have been investigated. In this era, African, Indian, and Chinese traditional medicine systems have been used to combat COVID-19. It has been reported that in Asian and African countries, against SARS-CoV-2, a cocktail of extracts and distilled herbals enriched in natural products have been in use. There are many potential antiviral drug lead compounds that can be derived from traditional medicines and are used for treating influenza, SAR-CoV-1, and SAR-CoV-2 for symptoms common to these diseases. Therefore, secondary metabolites or phytochemicals from medicinal plants are providing optimism to include phytocompounds that can either kill the SARS-CoV-2 or interfere with its multiplication and/or strengthen the human body's immunity to combat it. For example, one recently discovered natural substance with antiviral properties against SARSCoV-2 is hypericin (Matveeva *et al*., 2020).

This led to the screening of almost 200 medicinal plants including aromatic herbs exhibiting antiviral properties against SARS-CoV-1. A variety of medicinal plants such as *Lycoris radiata* (red spider lily), *Lindera aggregate*, *Pyrrosia lingua,* and *Artemisia annua* have been found to show moderate inhibitory effect against the mechanism of SARS-CoV (Boukhatem & Setzer, 2020). Flavonoids, alkaloids, phenolics, fatty acids, steroids, and terpenoids are some of the chemical components that are biosynthesized by plants. The present review aims to appraise the structural insights of coronaviruses as well as their pathogenesis and treatment strategies by the involvement of natural products. This study not only highlights the importance of ethnomedicinally significant plants and effectiveness of herbal remedies but also identifies promising phytochemicals for drug development against viruses.

Genomic organization and receptor binding domain (RBD) of coronaviridae family: The single-stranded (ss) RNA virus known as SARS-CoV-2, with a genomic size of about 30 kb, is a member of genus Coronavirus and family Coronaviridae (Ye *et al*., 2020). The zoonotic origin of SARS-CoV-2 has been revealed by genome research (Ye *et al*., 2020). SARS-CoV-2 shares similar ten open reading frames (ORFs) and 9680 amino acid polyproteins in its genome as other coronavirus strains. About two-thirds of the viral RNA is encoded by the first ORFs (ORF1a/b), which are translated into two big polyproteins, pp1a and pp1ab, are then processed into non-structural proteins (nsp1-nsp16), with remaining ORFs encoding a few accessory and structural proteins (Phan, 2020). The SARS-CoV-2 virion size ranges from 70 to 90 nm, and it can be identified by multiple 20 nm spike-like extensions that are present on its surface (Kim *et al*., 2020). Four structural proteins S (spike), E (envelope), N (nucleocapsid), and M (membrane) are encoded in the genome of SARS-CoV-2 that are required to assemble entire virus particles. There are crucial questions about origin and evolution of coronaviruses raised by the presence of accessory proteins on genome of SARS-CoV-2 (Spaan *et al*., 1988). The SARS-CoV-2 structure is shown in (Fig. 1).

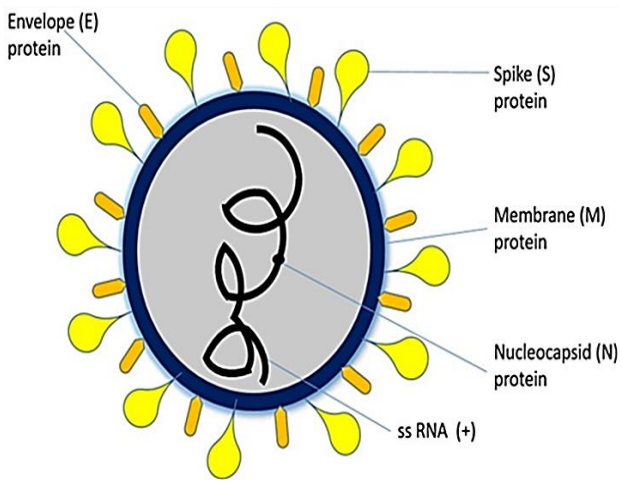

Fig. 1. Structure of SARS-CoV-2.

Spike protein has a receptor-binding domain (RBD), composed of S1 and S2 subunits. S1 subunit functions in cellular attachment and communicates with host cell surface receptors accelerating endocytosis, while S2 subunit is involved in membrane fusion. Further, S1 subunit comprises of 2 more domains, C-terminal domain (S1-CTD) and N-terminal domain (S1-NTD). These two main domains accelerate communication of viruses with host cell receptors (Li *et al*., 2005). Human coronavirus-229E binds with Aminopeptidase N (APN) receptor of the host cell (Bonavia *et al*., 2003); HCoV-OC43 binds to sugar receptor; HcoV-HKU1 binds to the Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) receptor (Hulswit *et al*., 2019); MERS-CoV binds with Dipeptidyl peptidase 4 (DPP4) receptor (Wang *et al*., 2013); HcoV-NL63, SARS-CoV-1, and SARS-CoV2 binds to ACE2 (Angiotensin-converting enzyme-2) receptor (Tai *et al*., 2020).

Human coronaviruses: (HCoV-22HCoV-OC43 and HCoV-HKU1) Acute respiratory syndrome CoV-2 belongs to family Coronaviridae, sub-family Orthocoronavirinae, and order Nidovirales. Human corona virus consists of four different sub-types, i.e., αlpha, βeta, gamma, and delta-coronavirus. α- and β-type coronaviruses are the basic reasons to infect the mammals, whereas gamma and delta strains infect animals and birds (Ge *et al*., 2017). Being a zoonotic virus, that could be transferred from animals to human beings and once acquired among humans through airborne droplets and aerosols. Among the animals, the bat is one of the most active carriers for causing human infections while animal repositories extend to camels, pigs, cats, goats, rats, mink, and ferrets (Anthony *et al*., 2017).

Table 1. Comparison of different human coronavirus strains.

Corona virus strains	Timeline	Genera	Receptor	Incubation period	Case fatality	Epidemiology	Transmission	Detection method	References
HCoV-229E	1966	Alpha	APN	2-5 days	N/A	Globally peak in winter	Respiratory droplets Fomites	RT-PCR	(Vabret *et al.*, 2001, Vallet *et al.*, 2004, Dominguez *et al.*, 2009, Vassilara *et al.*, 2018)
HCoV-OC43	1967	Beta	Sugar	2-5 days	N/A	Globally peak in winter	Respiratory droplets Fomites	RT-PCR	(Vabret *et al.*, 2001, Lau *et al.*, 2005, Patrick *et al.*, 2006, Dominguez *et al.*, 2009)
SARS-CoV-1	2002	Beta	ACE-2	2-11 days	9.6%	2002-2003 in China and then spread to a global level	Respiratory droplets Fomites; Fecal oral	ELISA qRT-PCR	(Seto *et al.*, 2003, Vallet *et al.*, 2004)
HCoV-NL63	2004	Alpha	ACE-2	2-4 days	N/A	Globally peak in winter	Respiratory droplets Fomites	RT-LAMP RT-PCR	(Dominguez *et al.*, 2009, Abdul-Rasool and Fielding, 2010, Geng *et al.*, 2016).
HCoV-HKU1	2004	Beta	CEACA-M1	2-4 days	N/A	Globally peak in winter	Respiratory droplets Fomites	RT-PCR	(Vabret *et al.*, 2006, Dominguez *et al.*, 2009, Tang *et al.*, 2014, Zhang *et al.*, 2016)
MERS-CoV	2012	Beta	DPP4	2-13 days	34.4%	2012 in the Middle East; 2015 in South Korea; Mostly spread to the Middle East	Respiratory droplets Fomites	rRT-PCR ELISA RT-LAMP-VF	(Huang *et al.*, 2018)
SARS-CoV-2	2019	Beta	ACE-2	3-7 days	4.25% up to 19th July	2019-2020 in China; then spread to global level	Respiratory droplets. Fomites. Fecal-oral. Aerosol transmission.	Whole-genome sequencing. Real-time qRT-PCR. Nano pore target sequencing.	(Li *et al.*, 2020, Zu *et al.*, 2020)

The very first coronavirus infections were identified as a root of the common cold in 1960. Since 2002, four coronavirus subtypes have been identified to infect people; they include 229E and NL63 coronaviruses, as well as the OC43 and HKU1 coronaviruses, which are frequently involved in non-infectious diseases of the respiratory system. (Geller *et al*., 2012). However, the revelation of a coronavirus that promotes severe acute respiratory syndrome in 2002 marked a defining moment to perceive coronavirus disease. Comparable to SARS-CoV-2, SARS CoV-1 was first diagnosed in Guangdong province in China, transmitted from one person to other individuals, infecting at least 8,096 people in 29 different nations, and killing 774 sufferers. (Wang *et al*., 2006). MERS CoV, a different novel beta coronavirus, triggered Middle Eastern Respiratory Disorder and was initially diagnosed in humans in Saudi Arabia, had infected approximately 2,494 persons in over 27 countries and even been attributed to the mortality of 858 people as of November 2019. Camels were the predominant animal hosts for such a coronavirus. (Badawi & Ryoo, 2016). On December 8, 2019, a new coronavirus with pneumonia-like symptoms was detected in Wuhan, China. After that, a novel coronavirus subtype member was isolated and designated SAS CoV 2. The virus rapidly spread through human contact at first called 2019 nCoV and renamed "SAS CoV 2. (Chin *et al*., 2020). Comparative analysis between different human coronavirus strains is given in (Table 1).

Zoonotic spillover: Zoonotic diseases have influenced the life of human beings for centuries. The processes and changes constantly evolve difference in the incidence, emergence, and re-emergence of these conditions. Zoonotic spillover is the pathogenic transmission from an animal to a human and globally represents a significant public health threat (Plowright *et al*., 2017). Zoonotic spillover relies on a combination of many factors to initiate, such as environmental, behavioral, and epidemiological elements for pathogen vulnerability. (Rodriguez-Morales *et al*., 2020). Coronaviruses have been earlier on the mainstream of this discussion (Wilder-Smith, 2006), as viruses can damage respiratory, hepatic, gastrointestinal, CNS, and cardiac activity of humans, birds, cattles, rodents, bats, and numerous wild animals. In nature, coronaviruses, including influenza virus, occur in various animal species (Zhou *et al*., 2020). Gamma and delta groups of corona viruses tend to infect birds, though alpha- and beta coronaviruses can infect mammals and some animal species while many of them can sometimes be transmitted to mammals (Chen *et al*., 2020). These animals serve as the evolutionary host of human coronaviruses if they contain a closely related lineage that shares high structural similarity at the nucleotide sequence level (Cui *et al*., 2019). Before the epidemic of SARS-CoV-1, such zoonotic viruses were not known to be particularly hazardous to human health. Following the emergence of severe acute coronavirus respiratory syndrome, MERS-CoV, another highly virulent coronavirus, was reported in Middle Eastern regions.

Each of these instances involve wild animals, such as bats, that have been reported to act as the host organism of these viruses that have also spread out to humans utilizing camels and civets as significant intermediate hosts (Chan *et al*., 2020). The above-mentioned intermediate hosts may act as a zoonotic cause of human infectious disease and functions as an exacerbating host by permitting the virus to replicate temporarily and then transmit it to humans to intensify the human infection level as shown in Fig. 2. Unless it can maintain its transmission inside the intermediate host (Wang & Anderson, 2019), human coronaviruses can experience a dead-end infection. Current evidence indicates that bats are the original cause of the latest outbreak of COVID-19.

Intermediate hosts are now under investigation and deserve more comprehensive studies measuring infection and a person's immunity against this COVID-19. Another critical objective in zoonotic spillover analysis is to understand the functional and statistical links between spillover determinants, that are numerous, diverse, and not necessarily present in a consistent way in the necessary spatiotemporal overlap between them and human exposure in susceptible hosts so that such events are possible (Rodriguez-Morales *et al*., 2020).

Life Cycle of Severe acute respiratory syndrome-CoV-2: When SARS-CoV-2 attaches to the cell surface receptor, infects the host cell, and host cell proteases enable spike proteins to activate. Related to SARS-CoV-1, SARS-CoV-2 also adheres to host cell surfaces either through the ACE2 receptor or by priming of spike proteins using serine protease TMPRSS2. (Yan *et al*., 2020). Studies have revealed that the affinities of SARS-CoV-2 spike proteins are 10–20 times higher than those of SARS-CoV-1 spike proteins (Wrapp *et al*., 2020). Due to this binding, conformational changes are found in spike proteins that allow the endosomal pathway to be used for virus envelope proteins to merge with host cell membrane (Matsuyama & Taguchi, 2009). After binding, viral RNA is released into host cytoplasm, that is then translated and generates two large viral replicase proteins pp1-a and pp1-b, that further divide up into smaller proteins via virus-encoded proteinases.

This event is accompanied by de novo synthesis of structural and non-structural proteins (nsp1-nsp16). Different non-structural proteins have different roles; Nsp3 that is papain-like proteinase 2 and nsp5 that is 3C lie proteinase, they are necessary for viral replication and transcription. Nsp8 exhibits RNA dependent RNA polymerase activity. Nsp14 is involved in exoribonuclease activity that is checking ability during the viral transcription and replication. The non-structural proteins have an advantage of formation of Double Membrane Vesicles (DMVs) and replicase transcriptase complex in which virus replication and transcription takes place. After viral RNA replication and transcription, it is accompanied by the assembly stage where emergent structural proteins; Envelopes, Spikes, and Membrane proteins are integrated into the Endoplasmic Reticulum Golgi Intermediate Complex (ERGIC). Then RNA genome with nucleocapsid proteins is inserted into ERGIC through budding. After all these events, there is the formation of mature virions, these virions then migrate to cell surface within the vesicles and thus leave cells by exocytosis (Hoffmann *et al*., 2020). (Fig. 3) shows the action mechanism of SARS-CoV-2.

Research has been done to consider the dynamics of the enzyme Furin that is abundant in host cells and is required for the invasion of SARS-CoV-2. Since SARS-CoV-1 doesn't have Furin, this enzyme might function as a discriminating element in determining the extent of SARS-CoV-2. SARS-CoV-1 and MERS do not detect this active site on entry into the host cell, whereas this enzyme promotes entry of SARS-CoV-2. (Walls *et al*., 2020). Because Furin enzyme is found in many human organs, including the heart, small intestine, lungs, and liver, infection caused is incredibly dangerous and can be predicted to infect multiple human organs, leading to multiple organ damage. This placement may influence the virus's propagation and survival. (Kumar *et al*., 2020).

Pathogenesis of SARS-CoV-2: Pathological studies of SARS-CoV-2 patients seem to be very synonymous to MERS-CoV and SARS-CoV-1 patients. (Chen *et al*., 2010). Flow cytometric analysis of blood samples revealed substantial decrease in CD4 and CD8 T cell count and the observed status was found to be hyperactivated as the larger percentage of dual-positive (CD38 and HLA-DR) was detected (Xu *et al*., 2020). Chest X-ray scans indicated the rapid development of pneumonia, including several deviations within both lungs. Histopathological tests of liver, lungs, and cardiac tissue have been carried out and cellular fibro myxoid exudate with bilateral diffuse alveolar injury is revealed by a lung biopsy. The right lung exhibited substantial pneumocyte deposition and hyaline membrane formation, suggesting acute respiratory distress, whereas the left lung showed edema with hyaline membrane formation. Besides that, both lungs were found to have intercellular mononuclear patchy inflammatory cells dominated by immune cells (Tian *et al*., 2020). Multinucleated syncytial cells with unusually enlarged pneumocytes with a viral-induced cytopathic effect represented intra-alveolar spaces. Liver biopsy from SARS-CoV-2 patients showed considerable micro vesicular steatosis, along with lobular and mild portal activity, revealing that the virus or drug-induction might have caused an injury (Yan *et al*., 2020). In the cardiac tissue, some mononuclear inflammatory infiltrates have been observed. All these pathological findings may provide insights on SARS-CoV-2 pneumonia pathogenesis, enabling clinicians to efficaciously treat COVID-19 patients (Totura *et al*., 2015).

Treatment strategies of SARS-CoV-2: Clinical trials are being conducted to investigate potential antiviral therapy targets, for instance, inhibiting the viral enzymes responsible for replication of genome or inhibiting virus entry to human cells (Liu *et al.*, 2020). Some of the possible pharmacological approaches to combat COVID-19 are small-fragment synthetic drugs, vaccines, peptides, interferon treatments, monoclonal antibodies, and oligonucleotides (Dömling & Gao, 2020). Some of the currently used treatment strategies are:

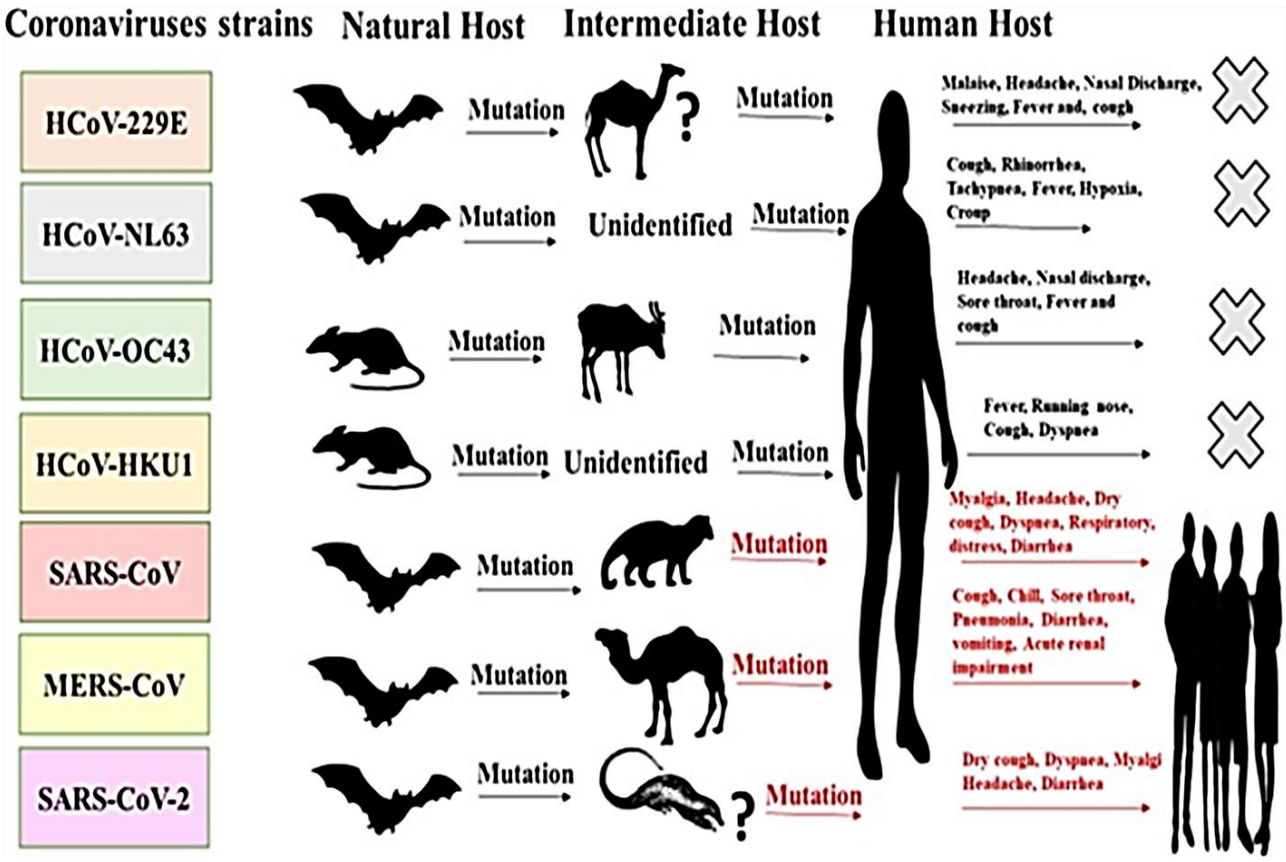

Fig. 2. Zoonotic spillover of human coronaviruses. Cross sign indicates that there is no spread from individual to individual. The red arrow states that human transmission of SARS-CoV-1, MERS-CoV, and SARS-CoV-2 is probable.

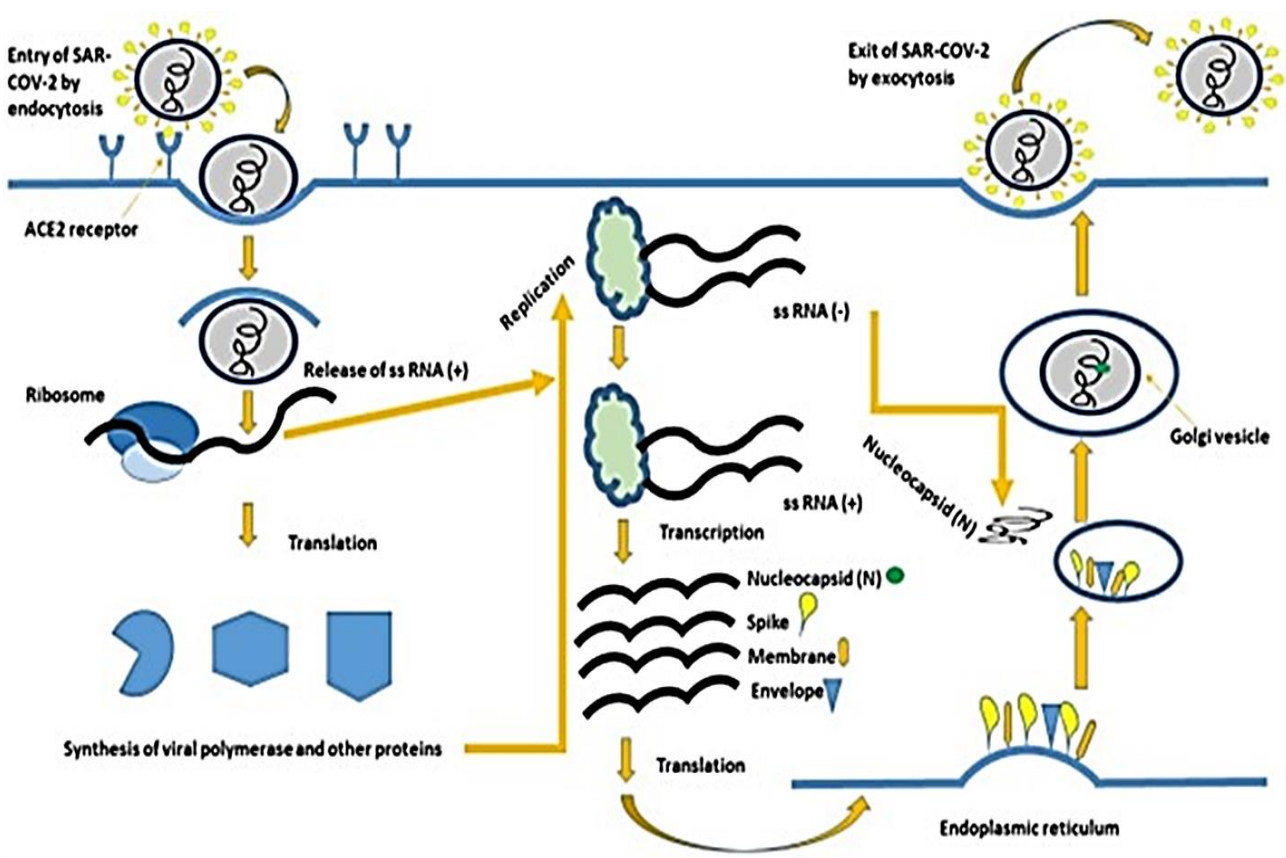

Fig. 3. Mechanism of replication cycle of COVID 19.

Chloroquine/Hydroxychloroquine: These drugs are known to be effective against malaria and have multidimensional action mode. *In vitro* studies suggest that these have anti-inflammatory, anti-parasitic, and anti-viral properties and are effective in suppressing SARS-CoV-2. These are known to block the virus entry by binding to ACE2 receptor on spike proteins (Balayla, 2020) and also prevent the virus entrance by pH-dependent endocytosis. They have an optimal level of safety and if taken at minimum micromolar concentration, they show effective results. However, there is no sufficient data available on their efficacy, so as a necessary consequence, FDA strongly recommends implementing clinical trials on COVID-19 patients. Besides the clinical trials, FDA has approved emergency use of hydroxychloroquine and chloroquine on an individual basis. Several studies show that these drugs are related to the fast improvement time, decreased virus shedding at the nasopharynx region, significantly improved findings for radiological CT images, and lower likelihood for the severe disease progression. However, these are also associated with side-effects. Therefore, it is necessary for every patient affected with severe acute respiratory syndrome-CoV-2 to use these drugs upon medical guidance (Shah *et al*., 2020).

Tocilizumab: Tocilizumab is an approved drug to be used in cytokine and chemokine to release distress. Recent research shows that patients with severe disease conditions are associated with a high level of cytokine release storm which can further lead to inflammatory storm and capillary leakage phenomena that results in acute respiratory distress syndrome (ARDS) and multiple organ damage (Zhang *et al*., 2020). IL-6 plays a major role in cytokine release storm (In Ah *et al*., 2018), produced by CD14 and CD16 inflammatory monocytes. These cytokines have been found to be more prevalent in COVID-19 patients. As for the mechanism, it binds with the receptor of IL-6 (including both soluble and membrane forms). Thus, by blocking the signaling cascade for the JAK-signal transducer and transcription activator, the production of inflammatory storm is limited. There are several ongoing studies which test the Tocilizumab's efficacy in COVID-19 patients. Studies conducted on animals have demonstrated that IL-6 is required for virus discharge and pulmonary inflammation regulation; suggesting a way that it may also interfere with the blocking of IL-6 receptors in humans (Tanaka *et al*., 2016).

Other synthetic drugs: *In vitro* studies found that Remdesivir has very potent activity against the SARS-CoV-2. It blocks the RNA dependent RNA polymerase (RdRp) enzyme, thus inhibiting virus genome replication and transcription. In addition to its *In vitro* studies, six ongoing clinical trials are supposed to provide further insight into the effective therapeutic dose, therapy period, and side effects in future. New preliminary research on this drug indicated that 68% (more than two-thirds) of the patients who received Remdesivir recovered out of 53 severe cases (Grein *et al*., 2020). Lopinavir and Ritonavir are used to treat Human Immunodeficiency Virus (HIV). Both agents are used in combination therapy to treat adults and children affected by HIV. *In vitro* studies showed inhibitory effect of this drug on SARS-Corona virus-2 (Stockman *et al*., 2006). Ribavirin is also considered to be an effective antimalarial drug such as Lopinavir. It is used in combination with Ritonavir/ Lopinavir and has been shown to decrease a patient's risk of developing ARDS. It also minimizes death risk in patients diagnosed with SARS-CoV-2 (Stockman *et al*., 2006). In some clinical trials, Favipirvir is proven to be helpful against the SARS-CoV-2. It inhibits the RNA polymerase enzyme. This drug also could block replication of some other RNA viruses such as alpha-, arena-, falvi-, filo- etc., and recently, this drug received approval to treat the Influenza virus. Arbidol is effective against the Influenza virus and if is given at 10-30 micromolar concentration, it also showed effective result against SARS-CoV-2. Similarly, IFN-α is a wide spectrum antiviral medicine applied for hepatitis treatment. *In vitro* studies show that it is a potent antiviral drug against SARS-CoV-2.

Convalescent plasma therapy: It is a passive antibody treatment and has recently been reported for its potential use in the treatment of patients infected with SARS-CoV-2 human coronavirus. In this therapy, plasma of the recovered patients is used that contain high neutralizing antibody titers. In the previous SARS pandemic, this treatment was considered useful too. In China, convalescent plasma therapy was used on five mechanically ventilated patients, and within a few days, they showed positive results. The analysis found a significant decrease in SARS-CoV-2 virus load at the nasopharynx region, and at end of 12 days of convalescent plasma therapy, there is an improved oxygenation and reduction in disease severity (Shen *et al*., 2020).

High-dose intravenous immunoglobulin (IVIg): IVIg is another blood material that consists of monoclonal and polyclonal immunoglobulins derived from healthy patients. It has a well-documented role in many viral, neuromuscular, autoimmune, and idiopathic diseases. Previous experimental findings have shown that it has a tune down and immunomodulatory effect via its interaction with cytokine releasing cells and antigen-presenting cells (APCs). Successful clinical trials have been reported for SARS-CoV-1 and MERS coronaviruses. Currently, this therapy has been used for treating SARS-CoV-2 coronavirus. Cao *et al*. reported that this therapy is linked with improved radiological findings, and all those patients which received this therapy were safely discharged (Ferrara *et al*., 2012).

Herbal Remedies: To alleviate numerous illnesses, herbal remedies have been extensively used in the form of traditional or alternative medicines because at minimum dose, they do not damage host cell and prevent viruses from multiplication process by curing contaminated host cells (Zhu *et al*., 2009). Certain scientific studies have been initiated to assess effectiveness of aromatic herbs and volatile oils against bacteria and fungi but currently, insufficient data is available to assess safe and effective resources for use against antiviral treatments (McCutcheon *et al*., 1995). The pandemic situation of COVID-19 has affected 177 countries, with almost 154,000 mortality rates. According to the guidelines of American Food and Drug Administration (FDA), up till

now although no drug has been fully proven effective against COVID-19, a variety of pharmacological managements were tested, however no therapeutic effectiveness has been declared in this regard.

Various studies exhibit clinical indications of herbal drugs in the cure of coronavirus SARS-CoV-1 and have shown significant outcomes. Aqueous extract of natural plant, *Houttuynia ordata* has shown to intervene antiviral mechanisms of SARS-CoV-1 by constraining activity of viral RNA polymerase, destruction of virus 3CL protease, hence preventing the entry of virus cell and inhibiting the process of replication. All of these combined features can lead to a possible target in the process of targeted drug therapy against COVID-19 (Sanders *et al*., 2020). According to various currently conducted clinical trials against COVID-19, plant-based anti-malarial drug, hydroxychloroquine is considered to diminish the viral load in patients of COVID-19, particularly when given in combination with antibiotic, Azithromycin. ForCOVID-19 cure, Remdesivir has proven its usefulness (Huang *et al*., 2020). Natural herbal medicines have a well-recognized antiviral action for cure and prevention of SARS-CoV-2. Some medicinal plants with their isolated constituents having promised antiviral activity against coronaviruses are discussed below in (Table 2).

Different plant-derived bioactive components have well-described anti-inflammatory, anti-oxidative, and immunomodulatory activities, thus may be employed as COVID-19 alternative treatments (Trivedi *et al.*, 2022) applied 3D human intestinal tissue and airway models to investigate the impact of 23 cannabis extracts on ACE2 activation. They revealed that 13 high CBD extracts suppressed the levels of TMPRSS2 and ACE2, proteins were essential for SARS-CoV-2 viral penetration into host cells. Endocannabinoids (eCBs) from *Cannabis sativa* had been implicated in immune system regulation and exhibited antiviral effects against viral hepatitis, influenza, and HIV, considering cannabinoids as a treatment therapy in COVID-19 patients (Wang *et al*., 2020). Phenols, terpenoids, flavonoids along with other classes of phytochemicals have been proven to have ability to inhibit the SARS-CoV-2 Mpro. Alkaloids, being an important group of natural phytoconstituents, have broad spectrum antiviral activities. In silico research has discovered capsaicin, a plant-derived alkaloid from the fruit of the genus Capsicum, to be a potential inhibitor of SARS-CoV-2 Mpro (Trivedi *et al*., 2022). Flavonoids are made up of numerous structurally different phytochemicals that frequently have synergistic effects, including antiviral characteristics, as in tea, vegetables, garlic, and fruits, etc. Certain plants derived dietary supplements including cocoa, wine, vinegar, and green tea contain catechins, a different subclass of polyphenolics. Epigallocatechin-3-O-gallate (EGCG), a prominent catechin abundant in green tea, was determined to have antiviral properties particularly against SARS-CoV-2 (Fraga *et al*., 2019). We draw the conclusion that bioactive components of diverse plants possess antiviral and anti-inflammatory activities, assist in minimizing organ damage due to reduced cytokine release, and enhance the healing process after COVID-19 infection. Vaccines for SARS-CoV-2 have been developed, however, if the virus mutates and transforms its immunogenicity, the vaccines may no longer be efficacious. Plant-derived bioactive substances like cannabinoids, prebiotic polysaccharides, polyphenols, plant lipids, and alkaloids all are being explored for *In vivo* and *In vitro* clinical trials. Furthermore, clinical research indicating the relationship between dietary components of plant-derived compounds and mitigating COVID-19 infection complications is ongoing. This will be helpful in proposing bioactive compounds as dietary supplements and their use as nutraceuticals to fight SARS-CoV-2 infection.

Natural composites accustomed to control SARS-CoV-2: Together with the development in the field of vaccines and drug trials, it has become an essential approach to explore a possible integrated alternative medicinal system that involves the use of natural products for the cure of SARS-CoV-2. Natural entities having immuno-modulatory action are effective against virus infections (Salehi *et al*., 2019). All these agents boost up immunity, strengthen the body, and defend it from the attack of viruses. Traditional and Complementary Medicines (TCM) along with a wide range of herbal measures and synthetic drugs are applied for treatment of SARS-CoV-1 (Zhang *et al*., 2004). These could prevent the replication of viruses and other types of infections. TCM and herbal remedies can undermine noxious responses and eradicate pathological disease conditions by improving the function of lungs through the involvement of blood flow within the body (Gitea *et al*., 2018). Snow Lotus (*Saussurea involucrate* Matsum) may heighten immune response and is proven to be advantageous for the handling of infection due to coronaviruses (Ma *et al*., 2020). The potential efficacy of herbal medicines has been reported against SARS-CoV-2 (Lin *et al*., 2005). For instance, glycyrrhizin derived from *Glycyrrhiza glabra* along with its derivatives obtained from roots of Licorice were established to have antiviral action against SARS-CoV-2 (Cinatl *et al*., 2003). In the cure of SARS-CoV-2, a non-steroidal anti-inflammatory drug, Indomethacin when administered in combination with herbal drugs, revealed strong antiviral action (Amici *et al*., 2006). The mechanism behind this might be discontinuation in the SARS-CoV-2 replication by inhibiting viral proteins like SARS-CoV-23CL protease, that is a significant factor to regulate proteolytic production of replicase polypeptides in the formation of functional proteins (Chen *et al*., 2002). Hence, SARS-CoV-23CL protease is an appropriate target designed for drug molecules against SARS-CoV. Plant extracts, different plant parts, the dried rhizome (*Gentiana scabra* Bunge and *Cibotium barometz*), dried seed *(Senna tora* (L.) Roxb), dried leaves (Torequl Islam *et al.*, 2020) and tuber (*Dioscorea polystachya* Turcz) are found to have a strong inhibitory effect against SARS-CoV-2 (Wen *et al*., 2011). The extracts of these herbs inhibit the process of replication and protease action of SARS-CoV-1, which suggests that herbal extracts may be employed as a drug against SARS-CoV-1 (Kakuda *et al*., 2004). Some other triterpenoids have also been reported to hinder the replication process of SARS-CoV-2, especially Secoiridoid (Kim *et al*., 2009).

Table 2. Medicinal plants having anti-corona virus activity along with their IC_{50} value.

No.	Medicinal plants	Local name	Mechanism against virus	Acting virus	IC_{50} value	References
1.	*Rosa nutkana*	Wild Rose or Nootka Rose	Reserve the action of unidentified enteric coronavirus-mechanisms	Bovine coronavirus	9.02 µM	(McCutcheon *et al*., 1995)
2.	*Astragalus membranaceus*	Chinese astragalus or Mongolian milkvetch	Immuno-enhancing effects through an increase in the lymphocytes count and fraction of CD4+ lymphocytes	MERS-CoV	9.02 µM	(Yuan *et al*., 2006)
3.	*Rheum officinale*	Chinese rhubarb	Inhibit the interface among SARS-CoV-1	SARS-CoV-1	1 to 10 µg/mL	(Ho *et al*., 2007)
4.	*Houttuynia cordata*	Fish mint or Chameleon-plant	Increase in the percentage of CD4+ and T cells required to fight against virus infection	MERS-CoV	1 to 10 µg/mL	(Lau *et al*., 2008)
5.	*Sambucus formosana*	Blue elder	By interfering with the involvement of the virus envelopes, impacts of chicken coronavirus NL63 and coronavirus strain is restricted, and are interpreted as non-infectious	HCoV-OC43	0.15-0.30 µM	(Weng *et al*., 2019)
6.	*Verbascum thapsus* (Verbascoside)	Great Mullein or Common mullein, Geedar Tambakoo	Active components inhibit inflammation response during infection of respiratory system	SARS-COV-1	8.3 µM	(Speranza *et al*., 2010)
7.	*Glycyrrhiza glabra, Licorice root*	Mulhati, Black sugar	Up regulates nitrous oxide synthase and nitrous oxide production	SARS-COV-1	39 µg/mL	(Cinatl *et al*., 2003)
8.	*Panax ginseng*	Ashwagandha	Stops glycoprotein activity	SARS-COV-1	ND	(Wu *et al*., 2004)
9.	*Aesculus hippocastanum*	Horse chestnut	Inhibits the effect of glycoprotein	SARS-COV-1	± 2.6 µg/mL	(Wu *et al*., 2004)
10.	*Boenninghausenia sessilicarpa*	Pissoo mar Buti	Inhibits glycoprotein action	SARS-COV-1	46.9mM	(Yang *et al*., 2007)
11.	*Lycoris radiata*	Red spider lily	Prevents viral replication	SARS COV-1	ND	(Li *et al*., 2005)
12.	*Triterygium regelii*	Thunder god vine	Inhibits level of SARS-CoV-1 3CLpro	SARS COV-1	9.9 ± 0.1 µM	(Park *et al*., 2016)
13.	*Black tea*	Tea	Inhibits RdRp action	SARS-CoV-2	9.5 µM	(Li *et al*., 2020)
14.	*Scutellaria baicalensis*	Chinese skull cap	Inhibits the activity of ATPase	SARS COV-1	16.50 µg/mL	(Yu *et al*., 2012)
15.	*Angelica keiskei*	Angelica, Leaves of Tomorrow	Competitively obstructs SARS-CoV-13CLpro concentration	SARS COV-1	ND	(Park *et al*., 2016)
16.	*Stephania tetrandra*	Hang Fang Ji	Inhibits the pathway p38 MAPK	HCoV-OC43	38.4 ± 2.4 µM	(Kim *et al*., 2019)

Two other specific polysaccharides obtained from *D. polystachya* tuber extracts showed a remarkable escalation in GM-CSF promoter activity and thus gave the expressions in COX-2 (Su *et al*., 2008). Inflammatory activity influencing COX-2 pathway also correlates with anti-SARS-CoV-2 activity and some other anti-virus activities. Trihydroxyanthraquinone, an emodin from Rhubarb and Japanese Knotweed, by inhibiting the entry of the virus into host has revealed antiviral properties against SARS-CoV-1. It exerts its action by interfering with the SARS-CoV-23CL protease (Ho *et al*., 2007) and a similar mechanism is shown by Luteolin and Quercetin (Yi *et al*., 2004). Natural molecules are considered as an outstanding prospect for advances in optimization and future clinical use for treatment of SARS-CoV-2, specifically by targeting the 3CL protease (Kumar *et al*., 2020). Some highlighted medicinal plants and herbal constituents that have demonstrated possible anti-SARS-CoVs activity are discussed in Table 2. All these mediators are not only involved as significant measures to fight against SARS-CoVs but play a chief character in the prevention of virus outbreaks (Denaro *et al*., 2020) (Fig. 4).

Ethnobotanically important plants exhibiting a potent antiviral activity: Ethnobotany is basically the science of human interactions with plants and their ecosystem. To discover the secret uses of plants, ethnobotany, has become an important part of our world. The herbal medicines occupy distinct position right from the primitive period to present day (Hazrat *et al.*, 2011). In developing and developed countries practice including China, Pakistan, India, Africa, and Thailand, the traditional use of plants as medicines is a mutual practice (Zed, 2020). According to Natural Health Product Canada Regulations, 2004, the trend of using the plants has become more prominent within developing countries. Traditional medicines have antiviral potential and, are considered as a good source of bioactive compounds/ phytochemicals that can be utilized not only to strengthen immune system but also kill these pathogens (Shinwari *et al.*, 2020). Nordihydroguaiaretic acid (NDGA) isolated from *Larrea divaricate* leaves was found to be efficient against HIV and HSV type- I, and II. Some other innovative antiviral composites like peptides, terpenoids, lignans, coumarins, sulfides, proteins, furyl compounds, saponins, and proteins have been previously identified from natural plants (Ho *et al*., 2009). Plants as source of tannins, pro-anthocyanidins, alkaloids, polyphenols, flavonoids, etc., are effectively verified against viruses, e.g., HBV, HIV, NDV, HSV, AIV H9N2 and might be valuable for the cure of COVID-19 (Table 3) (Mukhtar *et al*., 2008).

Dietary supplements and nutraceuticals' role in curing SARS-CoV-2 infection: Table 4 illustrates the effects of different dietary supplements against COVID-19 caused by SARS-CoV-2.

Dietary supplements

Vitamin C: Water soluble vitamins like vitamin C, act as an antioxidant and cofactor for the regulation of enzymes by facilitating cortisol production and catecholamines. Vitamin C is essential for body development and strengthens the immune system. Ascorbic acid acts as an endothelial barrier and sustains vasodilation by the reduction in pro-inflammatory modulators (May & Harrison, 2013). The crucial role of vitamin C includes phagocytosis improvement, ROS production, chemotaxis, and involvement in decline of tissue damage. In the second half of the century, the modulating role of vitamin C in immune system has received a lot of attention. In 1978, J.G. Atherton *et al*. presented improvement in the impaired respiratory epithelium of chicken by contamination of a coronavirus after being exposed to ascorbic acid (Atherton *et al*., 1978).

Dynamic collaboration between oxidative stress and genes (ICAM-1, IL-1, TNFα) essential for the initiation of inflammation must be shown, facilitated by the activation of NF-Kb. A considerable increase in level of glutathione, SOD and catalase have been exhibited due to the direct scavenging of oxidants by vitamin C. Pre-clinical data have shown beneficial effect of vitamin C in upregulating the defensive protein and antiviral potential against RNA and DNA viruses, nevertheless, no direct role of vitamin C against *In vivo* viral replication has been established (Jungeblut, 1937). The hypothesis based on ACE2 identification, as receptor, for entrance of SARS-CoV-2, acknowledged that an elevated risk of severe COVID-19 is important to be considered as a function of ACE2 upregulation. Although, many potential targets exist for virus replication.

Spike glycoprotein of SARS-CoV-2 bind with ACE2, and vitamin C significantly eliminated ACE2 upregulation stimulated by IL-7 production. Potential objectives exist for vitamin C in virus replication and pathology in COVID-19; several viral non-structural proteins are activated by the virus's key protease, Mpro has been suggested as a main target. During modelling study, using the crystalline structure of Mpro, it was found that, active site of this enzyme has maximum ability of binding with magnesium ascorbate, that is regarded as having the strongest binding out of 106 nutraceuticals (Ma *et al*., 2020). So, it is suggested that ascorbic acid might be considered as a potent inhibitor of enzyme, Mpro. A study demonstrated that pro-oxidant imbalance was exhibited within patients of COVID-19 and remarkably elevated levels of NO_3-lactate dehydrogenase, NO_2 and C-reactive protein have been recorded in comparison to healthy individuals. Intravenous administration of vitamin C for 3 days at dose of 1 g for every 8 h, to COVID-19 patients, decreased inflammation markers (D-dimer and ferritin), suggesting that vitamin C can rise the rate of survival in COVID-19 patients, by reducing extreme initiation of immune responses (Hiedra *et al*., 2020).

Vitamin C may inhibit hyper activation of immune cells by the prevention of GAPDH (glyceraldehyde 3-phosphate dehydrogenase), which regulates the rate of glycolysis in activated myeloid. Vitamin C oxidizes into its inactive form (dehydro ascorbate) that in turn is reduced to ascorbate while reduced glutathione (GSH) is oxidized. Due to antioxidant profile of Vitamin C, a high dose of ascorbate demonstrates pro-oxidant activity by decreasing GSH and NADPH (Holford *et al.*, 2020). As a result, vitamin C that suppresses GAPDH at a high dose may reduce the activation of immune cells by inhibiting the production of ATP in cells.

Table 3. Ethno-botanical plants of developing and developed countries evaluating potent activity against viruses.

No.	Botanical name	Common name	Geographical distribution	Reported activity	Mechanism	References
1.	*Allium porrum*	Leek	Asia and China	Inhibition of Human ACE2 enzymes and SARS-CoV-2 to cells	Using plant lectins for inhibition of the virus attachment	(Keyaerts *et al.*, 2007)
2.	*Senna alata*	Candle bush	Brazil, India, and Pakistan	Anti-influenza activity	Inhibit replication of viral RNA	(Violi *et al.*, 2009)
3.	*Utrica dioica*	Stinging nettle	Asia and Pakistan	Inhibit proliferation trend of the SARS-CoV	Plant lectins used for inhibition of the virus attachment	(Kumaki *et al.*, 2011)
4.	*Allium fistulosum*	Bunching onion, Spring onion	China, South Asia, and Europe	Anti-influenza virus properties	Allicin and other thiosulfinates act as immune modulators	(Lee *et al.*, 2012)
5.	*Sambucus nigra*	Elderberry Black elder	Pakistan (Punjab)	Anti-influenza virus properties	To reduce hemagglutination and inhibit the multiplication of influenza virus.	(Ajaib *et al.*, 2014)
6.	*Solanum surattense*	Kantakari	Pakistan (Cholistan)	Anti-avian influenza virus	Inhibit replication of AIV H9N2	(Shahzad *et al.*, 2019).
7.	*Azadirachta indica*	Neem	Pakistan	Anti-MERS-CoV	Contain a diterpenoid compounds, sugiol and mechanism of replication, involves 3CLpro	(Zain-ul-Abidin *et al.*, 2018)
8.	*Juniperus communis*	Juniper/ Gojar/Petthri/Bantha	North America and Asia	Anti-MERS CoV	Replication, 3CLpro	(Kim *et al.*, 2013)
9.	*Rauwolfia serpentina*	Indian snake root or chota chand	Pakistan (Himalayas)	Anti-MERS CoV	Des-methoxy reserpine Replication, 34CLpro and entry	(Kesel, 2005)
10.	*Artemesia annua*	Dona	Europe, Pakistan and India	Immuno-modulatory effect	Entry spike and CLpro	(Kim *et al.*, 2013)
11.	*Glycyrriza glabra*	Liquorice, Malathi	Pakistan, Afghanistan	Used as an Immuno-modulatory agent	Inhibits replication of SARS associated virus	(Cinatl *et al.*, 2003)
12.	*Camellia sinensis*	Tea	Lower montane forest on Asia	Anti-MERS CoV	Kaempferol PLpro, 3CLpro	(Wei *et al.*, 2011)
13.	*Lycium barbarum*	Wolf berry/ goji	China and range across Asia	Anti-MERS CoV	Replication-3CLpro	(Cui *et al.*, 2020)

Table 4. Awarding role of supplements in challenging the Covid-19 pathway.

No.	Main supplements	Pathway hypothesized against COVID-19	References
1.	Grouping of vitamin C, glycyrrhizic acid, and curcumin	Production of Interferons which have an effect on inflammatory response.	(Chen *et al.*, 2020)
2.	Vitamin C/Ascorbic acid	1. Vital for structural organization of epithelial, endothelial and barriers. 2. Essential for chemotaxis; protection from injury of ROS. 3. Administration via intravenous route proved to be effective for inflammation treatment and vascular injury during sepsis and ARDS; sensitivity consequence in infection of lower respiratory tract.	(Lau *et al.*, 2008)
3.	Vitamin-D	1. NF-kB regulation, heights IL-6, and TNF-α, invention of GM-CSF, VCAM-1, IL-5, ICAM-1, and E-selectin. 2. A protective role in treating acute respiratory tract infections was revealed by the weekly dose.	(Kim *et al.*, 2018)

Pre-clinical studies revealed that vitamin C suppresses extreme release of cytokine, causing cellular immunosuppression and sepsis-induced organ dysfunction. While high dose intravenous administration of vitamin C reserved negative immune regulatory effect of T regulatory cells, that in turn increased T cell-mediated cellular immune response, and as a result, an improvement occurs in the case of sepsis-induced multi-organ dysfunction syndrome. Consequently, vitamin C has a supportive role in treatment of septic shock that is very common complications accompanying COVID-19 (Gao *et al*., 2017).

Intravenous administration of vitamin C minimizes risk of inflammation by reducing vascular injury linked with ARDS (Fisher *et al*., 2012). Randomized studies in case of lung injury due to sepsis exhibited that vitamin C diminishes the pro-coagulant changes that are the prime reason for lung damage (Gombart *et al*., 2020). A recent clinical trial investing vitamin C's infusion effects for the management of serious attack of COVID-19 pneumonia has been ongoing (Carr, 2020). Furthermore, vitamin C is involved in conferring the resistance effect against the coronavirus and on the vulnerability to infections of inferior respiratory tract (Tripathi *et al*., 2013).

Vitamin D: The encouraging role of vitamin D in the process of bone mineralization and as therapeutic metabolite against several pathologies like cancer, depression, and many types of infectious diseases is well acknowledged. Mechanistic perspective hypothesized solid reason that vitamin D favorably influences the host responses to SARS-CoV-2 effectively, both in early and late hyper-inflammatory stages of COVID-19. Laboratory studies correlate with effects of vitamin D to SARS-CoV-2 on host responses are intermittent, but one study investigating four chemical libraries evaluated antiviral activity revealing that the active form of vitamin D metabolite had an inhibitory effect. As it binds with the nuclear receptor, the active metabolite (calcitriol) evolves the process of gene transcription by employing numerous effects on inflammatory and immune system responses (Grant *et al*., 2020).

Earlier studies suggested that vitamin D was considered as complementary therapy for managing COVID-19 and deficiency of this vitamin is linked with enhanced mortality ratio in patients of COVID-19. Vitamin D improves the physical barrier of body, reduces the chances of viral infections, and improves the body's physical barrier through regulation of protein production for gap junction and tight junctions that are disturbed due to the viral infection. Besides this, epithelial cells of lungs also express 1-α-hydroxylase that transforms 25-hydroxyvitamin D3 to 1,25-dihydroxyvitamin D3 (an active form of vitamin D) which enhances the expression of co-receptor CD14 and vitamin D-regulated genes, cathelicidin within human's tracheobronchial epithelial cells (Hansdottir *et al*., 2008).

Mostly viruses produce double-stranded RNA that proliferate the 1-α-hydroxylase's expression and leads to rise in production of active vitamin D. Consequently, adequate amount of vitamin D may diminish the invasion of coronaviruses by enhancing production of antimicrobial peptides within lungs and physical barriers. Vitamin D modifies the response of helper T cell responses and induces Th2 responses (Boonstra *et al*., 2001). Th1 cells are the main reason for the pro-inflammatory cytokines production, such as TNF-β and IFN-γ, whereas Th2 cells produce IL-13, IL-4 and IL-10. Vitamin D increases a shift from Th1 to Th2 phenotype, by decreasing Th1 cytokines but increases Th2 cytokines level in body.

Cytokine storms in patients of COVID-19 may be prevented by vitamin D. COVID-19 can give rise to immunogenic damage to alveolar and endothelium membrane (Liu *et al*., 2020), that can contribute to serious mortality in COVID-19 (Tang *et al*., 2020). Patients with severe illness may have a high level of inflammatory cytokines to promote the inflammation process, and increased level of IL-6 is correlated with the SARS-CoV-2 detection. Vitamin D can decrease the production of pro-inflammatory cytokines, such as IL-6, TNF-α, IFN-γ and IL-1β. Vitamin D receptor interrelates with κB kinase inhibitors to inhibit activation of NF-κB and this communication is heightened by vitamin D (Chen *et al*., 2013).

Clinical effects of vitamin D were studied which demonstrated that the deficiency of this vitamin had an interesting role in COVID-19 settings. It was found that supplementation with vitamin D not only reduced the risk of COVID-19 but also decreased the mortality rate in large, randomized trials (Ali N, 2020). Recent study suggested that using vitamin D at a loading dose of 200,000-300,000 IU strengthened immune system and decreased COVID-19 severity (Wimalawansa & Journal, 2020). A study in Italy anticipated nutritional procedure for COVID-19 patients that included 25-hydroxyvitamin D supplementation along with others (Caccialanza *et al*., 2020).

Nutraceuticals: Due to the risk of oxygen deprivation and systematic inflammation, there is a development of chronic respiratory failure and endothelial dysfunction comprising platelet aggregation and blood coagulation. In the pathophysiology of respiratory disorders, all these changes may lead to an irreversible damage of endothelial response (Loffredo *et al*., 2014). Consequently, compromised endothelial function is the sign of early-stage vascular modification that could progress to pulmonary, renal, and cardiovascular problems. Proliferation in chemokines, tumor necrosis factor (TNF-α), and systemic interleukins (ILs) has been observed during COVID-19 (Huang *et al*., 2020). All these modifications are in relation to cytokine release syndrome, most of the clinical characteristics are IL-6-linked. Now, a current retrospective multicenter study has focused on the influence of IL-6 in COVID-19 patients. (Ruan *et al*., 2020), presenting that circulating IL-6 level was increased in patients of COVID-19 in comparison with those who have been discharged. These findings demonstrate that that therapeutic predictor of fatal outcome in these patients might have been the "cytokine storm syndrome," that was triggered due to viral infection.

On behalf of inflammatory procedure, clotting and vascular changes are responsible for oxidative stress, especially ROS derived from NADPH oxidase 2 are concerned with an activation of platelets, clotting, and thus helpful in stimulating the production of thrombin or weakening of artery dilatation. According to these findings, nutraceuticals are defined as constituents that include herbal products, isolated nutrients, and dietary supplements that could take part in the prevention of anti-inflammatory as well as antioxidant processes. Most common nutraceuticals enlisted are vitamin E, carotenoids, vitamin C, minerals (Se, Cu, Mn), and polyphenols (lignans and phenolic acids) that deliver promising health effects through a synergistic process and preserve apposite redox homeostasis. Moreover, a combination of three nutrients obtained from plants like vitamin C, glycyrrhizic acid, and curcumin endorse production of interferons (IFs) and thus control the inflammatory response, signifying that all these natural molecules are useful to regulate immune response and are also involved in fighting against infections due to SARS-CoV-2 (Chen *et al*., 2020).

A study integrating molecular docking and target receptors along with receptor-binding domain (RBD) of virus spike glycoprotein, ACE2's protease domain, and SARS-CoV-2 protease, are intended to take a part in viral infection (Shanmugarajan *et al*., 2020). Finally, Runfeng *et al*., (2020) verified *In vitro* antiviral activity of Chinese nutraceutical comprising of almost 13 different herbs, named as Lianhuaqingwen, and concluded that this can inhibit replication of SARS-CoV-2 by noticeable reduction in mRNA's level especially of pro-inflammatory cytokines including CXCL-10/IP-10 and TNF-α (Runfeng *et al*., 2020). It is determined that nutraceuticals employ beneficial effects counteracting oxidative stress and COVID-19 (Table 5). Certain preclinical revisions on influenza conducted in mice, and Respiratory Syncytial Virus (RSV) suggested an optimistic comeback to therapies involved in anti-TNF (Hussell *et al*., 2001). A recorded Randomized Controlled Trial (RCT) assessment of adalimumab for treatment of COVID-19 is under progress.

Vaccines and Nanobiotechnology for the Treatment of SARS-CoV-2

Vaccines: After emergence of SARS-CoV-2 virus, scientific communities put in an unprecedented effort and its genome identified, resulting in the introduction of over 300 vaccine programs. More than 40 are currently undergoing clinical trials, with ten in Phase III and three accomplished Phase III with promising results. Some of these experimental vaccines have received emergency approval. Data indicates that potential vaccine candidates could aid in the protection of individuals and the containment of a pandemic. New findings from research study of Phase III indicates the vaccines are dependent on nucleic acids coding for Spike protein, transmitted by way of liposomes or adenoviruses, may provoke a defensive reaction (Koirala *et al*., 2020). Several techniques are being used to develop and produce SARS-CoV-2 vaccines. Physical and chemical methods such as, UV light, β-propiolactonean, and formaldehyde might be used to produce inactivated virus vaccines (Ita, 2021). virus vaccines, in comparison to wild-type SARS-CoV-2, can be produced with a virus that has less pathogenic features that would be higher anti-inflammatory cytokine levels, lower neutrophil release, and minimal lung injury. Surface-exposed spike (S) glycoprotein is the target for most of vaccines. A number of researchers have used vaccine modeling strategies that are based on expression in VLP (viral like particles), DNA, or viral vectors, entire S protein, the S1 receptor-binding domain (RBD), or combinations of these. According to some hypothesis, involvement of spike protein-based vaccines may result in development of antibodies to inhibit receptor binding and viral genome uncoating. Production of a universal Coronavirus vaccine is possible because T-cell epitopes of SARS-CoVs and MERS are similar and may cause cross-reactivity. Because SARS-CoV-2 shares a high genetic similarity with SARS-CoV, the SARS-CoV vaccine can induce cross-reactivity with SARS-CoV-2. According to a study of their S protein sequences, S1 subunits in both forms of viruses had highly varying amino acid residues. Vaccines that provide a prophylactically significant immunological response opposing SARS-CoV may not be effective against SARS-CoV-2 due to this variability (Dhama *et al.*, 2020).

During production of SARS-CoV-2 vaccine, various vaccine prototypes were tested by various groups (Table 6) summarizes all the phase III SARS-CoV-2 vaccines with virus type, vaccine strategy and efficiency, including those with late-stage clinical outcomes and others have been authorized for use.

Vaccination remains the most important approach for ending the pandemic. Although an emergence of various SARS-CoV-2 strains with decreased disease susceptibility and vaccine-induced immunity poses a threat to improve the current situation, the effectiveness of SARS-CoV-2 vaccinations gives hope for the future.

Nanotechnology: Nanotechnology is a highly multidisciplinary and translational-focused field of science and technology, that offers maximum outcomes and minimum side effects. Nanomedicine has tremendous potential in prevention, early diagnosis, imaging, and treatment of various diseases.

Since the size of viruses is in nanometer range, nanotechnology-based therapeutics for treating viral infection fits well here (Bezbaruah *et al.*, 2022). Nanovaccines and nano antiviral agents are two major therapeutic approaches of nanobiotechnology against coronaviruses as shown in (Fig. 5). Nanovaccines are expected to boost up immune response while nano antiviral drugs would manipulate viral mechanism of action. Research has looked at the using nanoparticles as a disease therapy to fight against malaria, cancer, AIDS, and certain other infectious diseases. It has also been possible to use "green nanotechnology" to create therapeutic nanoparticles exploiting the medicinal plant extract.

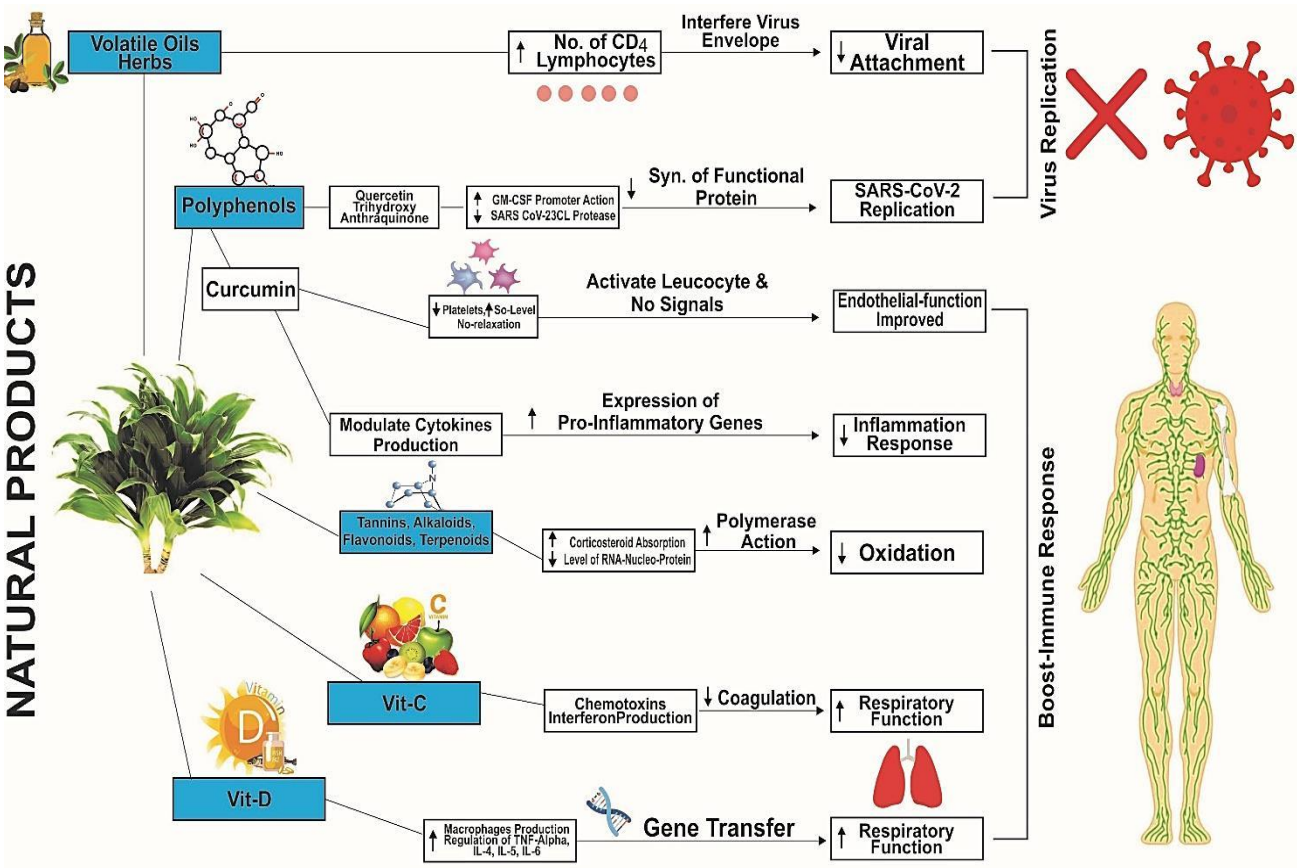

Fig. 4. Intervention of natural products in COVID-19 management.

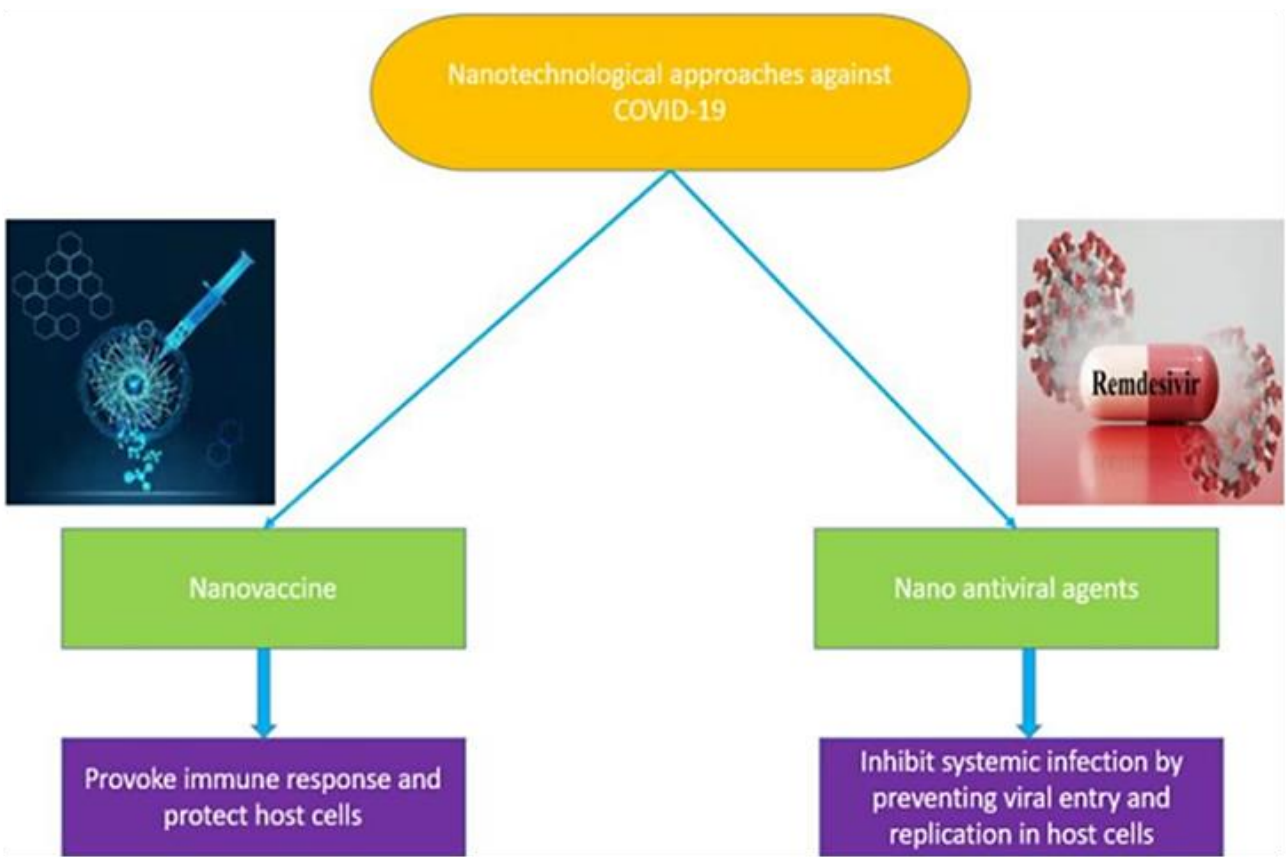

Fig. 5. Proposed nanobiotechnological approaches for treating SARS-CoV-2 infection. Nano vaccines are anticipated to strengthen the immune response whereas nano antiviral drugs would manipulate viral mechanism of action.

Table 5. Nutraceuticals with impending role in counteracting with COVID-19.

No.	Leading Nutraceuticals	Pathway postulated against COVID-19	References
1.	Minerals, Vitamin E, Polyphenols, Vitamin C, and Carotenoids	Hyper-coagulation and inflammatory cascade by involvement of antioxidant and anti-inflammatory response (in pathway of COVID-19, targets of endothelium may be significant)	(Loffredo *et al*., 2016)
2.	Polyphenols (flavonoids, lignans, phenolic acids, stilbenes,)	NO-dependent relaxation; pro-inflammatory genes expression and cytokines production modulates, antiviral response against a number of viruses (not proven for SARS-CoV-2)	(Cangemi *et al*., 2016)
3.	Curcumin	Binding with targeted receptors of SARS-CoV-2	(Shanmugarajan *et al*., 2020)
4.	Lianhuaqingwen	Replication of SARS-CoV-2; pro-inflammatory cytokines (CCL-2/MCP-1, IL-6, TNF-α, and CXCL-10/IP-10)	(Runfeng *et al*., 2020)

Table 6. SARS-CoV-2 vaccines.

Vaccine type	Mode of action	Vaccine name	Company and country	Dose	Storage conditions	Efficacy	References
Whole inactivated virus SARS-CoV-2	SARS-CoV-2 is inactivated by exploiting different chemical techniques. All these candidate vaccines are injected intramuscularly	Sinovac Biotech (China)	CoronaVac	2 doses	2-8°C; Lifespan unknown	Phase III data not published. In Brazil, its efficacy is 50.38% in mild cases and 78% in mild to severe cases. In Indonesia it is 65% and in Turkey it is 91.25% 14 days after second dose	(Creech *et al.*, 2021).
		Sinopharm (China)	BBIBP	2 doses	2-8°C; Lifespan unknown	Phase III data not published. Unpublished reports of 86% effective	(Isakova-Sivak & Rudenko, 2021)
Spike protein mRNA carried by lipidic microparticles.	mRNA vaccines are transferred by several ways for entry to human cell. Once entered, mRNA vaccine for the time being effect cell to generate antigen protein encoded mRNA	Moderna (US)	mRNA-1273	2 doses	-30 to -80°C; 2 to 8°C for 30 days	92.1% efficacy is reported 14 days after first dose and 94.1% efficacy is reported 14 days after second dose	(Forni & Mantovani, 2021)
		Pfizer-BioNTech (US)	BNT162b2	2 doses	-30 to -80°C; 2 to 8°C for 5 days	52% efficacy is reported 14 days after first dose and 94.6% efficacy is reported 14 days after second dose	(Forni & Mantovani, 2021)
		CureVac/ GlaxoSmith Kline (Germany)	CVnCoV	2 doses	2-8°C for up to 3 months	Unknown efficacy; Phase III clinical trials ongoing	(Forni & Mantovani, 2021)
Viral vectors	DNA coding for Spike protein can be transmitted to cells by viral vectors. When DNA is inserted into virus, possibility of exploiting virus's remarkable capability to infect and distribute mRNA within human cells is created	Gamaleya Res Inst, Russia	Sputink V	2 doses	-18°C; 2-8°C for up to 6 months in freeze dried form.	87.6% efficacy is reported 14 days after first dose and 91.1% efficacy is reported 14 days after second dose	(Creech *et al.*, 2021).
		Johnson & Johnson, US	Ad26COVs1	1 dose	-20°C; 2-8°C for up to 3months	85% after 28 days; 100% after 49 days.	(Pang *et al*., 2020)
		Astra Zenca/ Oxford (US)	ChAdOx1	2 doses	2-8°C for up to 6 months	64.1% efficacy is reported 14 days after first dose and 70.4% efficacy is reported 14 days after second dose	(Pang *et al*., 2020)
Protein subunit	Spike proteins play critical role in docking mechanism of SARS-CoV-2 to human cells. Spike protein or its fragments or nucleoprotein (N) are main targets of vaccines. To activate immune reaction, most often these vaccines exploit adjuvants	Novavax, Inc (US)	NVX-CoV2373	2 doses	2-8°C for up to 6 months	In UK 89.3% after second dose. In South Africa 60% after second dose	(Creech *et al.*, 2021), (Pandey *et al*., 2020).
		Medicago, canada, GSK and Italy	CO-VLP	2 doses	2-8°C for up to 6 months	Unknown efficacy; Phase III clinical trials ongoing	(Pandey *et al.*, 2020), Creech *et al*., 2021)

However, it has been assumed that nano vaccines would be more potent in comparison with conventional antigen-based vaccines and turning this imagination in to reality would be very beneficial for the world via host cell protection. The therapeutic effect of SARS-CoV-2 vaccines could be enhanced by means of nanotechnology. Since nanoparticles boost up the immunogenicity, the delivery of nanoparticles along with the vaccine making nano formulations would cause stimulation of immune system by the targeted delivery of molecules to the specific host site. It would also increase the viral antigen uptake by APCs. mRNA-based vaccines have recently been suggested in which synthetic mRNA of the virus would be delivered to the respiratory tract so that the host cells would produce viral proteins themselves (Talebian *et al.*, 2020).

Nano antiviral drugs seems more effective approach for SARS-CoV-2 treatment as compared to nano vaccines because vaccines for every virus are mostly specific while antiviral drugs could be broad-spectrum in action. Viral attachment, entry, replication, and shedding could be prevented by this approach. Such antiviral studies have been performed *In vitro* and have been proved successful, but more investigation needs to be conducted *In vivo* in animal models and humans. Moreover, these drugs could use nanoparticulate RNA interference (RNAi) mechanism via small interfering RNAs (siRNAs) to prevent viral progression. Gold (Au), silver (Ag), titanium dioxide (TiO_2), and graphene have been efficaciously utilized in concentration-dependent manner to achieve the objective of applying nanomaterials for viral therapeutics (Nikaeen *et al.*, 2020).

In July 2021, it was disclosed that Pfizer and BioNTech would begin producing COVID-19 mRNA vaccines in 2022 at a rate of around 100 million doses annually in collaboration with South Africa's Biovac Institute, that already participates in vaccine manufacturing (Dube *et al*., 2021). Gene-based or protein-based nano vaccines are available, some of these are in clinical trial phases, one of the COVID-19 vaccines that have recently started phase 2/3 clinical trials is the CoVLP vaccine, manufactured by Medicago. Another is J&J (Ad26.COV2.S) developed by Janssen Research & Development, Inc., USA, and Convidicea (Ad5-nCoV) developed by the CanSino Biologics, China. J&J's vaccine is an Ad26 vector encoding full-length S protein of SARS-CoV2 and is currently in (phase 4) clinical trials. In Australia, nanoemulsion SARS-CoV-2 vaccine MF59C (contains MF59 as adjuvant along with the SARS-CoV-2 Sclamp antigen) developed by Seqirus has recently entered in clinical trials.

Another two lipid nanoparticles-based vaccines developed by Novavax, Gaithersburg, Maryland, and CureVac N.V, Germany encode the Spike protein. The S protein of SARS-CoV-2 is translated by novel LNPs that are currently being evaluated as vaccines. These novel platforms include LNP-nCoVsaRNA (Imperial College London, UK), which boosts antigen production at lower doses by using self-amplifying RNA (Helmy *et al*., 2022).

Now, nano vaccine and nano antiviral drugs are available in the market to combat COVID-19. COVOVAX™ (manufactured by Serum Institute of India Pvt Ltd) and Nuvaxovid (manufactured by Novavax) are marketed and available SARS-CoV-2 rS Protein (COVID-19) as nanovaccine (Kudlay *et al*., 2022).

It seems an unprecedented potential in the field of nanotechnology not only for the treatment but also for the prevention and diagnosis of COVID-19 and other coronaviruses. In fact, nano detection of coronaviruses via nano biosensors would be a rapid and cost-efficient alternative to RT-PCR-based analysis (Nikaeen *et al.*, 2020). Long lasting immunity to fight against SARS-CoV-2 could only be provided by exploring novel therapeutics such as the combinational aspects of nanobiotechnology.

Conclusions and Perspectives

The SARS-CoV-2 pandemic is one of the largest world public health issues of this generation, and potentially since influenza outbreak of 1918. In this review, we recapitulate all possible COVID-19 infection therapies, based on previous SARS-CoV-1 and MERS treatment. There are some vaccines which have been authorized by national regulatory authorities among these, Pfizer-BioNTech, Sinopharm- BBIBP, Pak Vac, Oxford-AstraZeneca and SinoVac have received WHO authorization. However, many potential COVID-19 vaccine candidates are currently under development stage. Moreover, numerous strategies and molecule-based synthetic drugs have been predicted to inhibit the virus pathways and are considered potentially useful for COVID-19 prevention. Host immune system susceptibility to RNA viral infection has been revealed to be significantly improved by conventional therapies. Immune system response has often been proven to be weekend by nutrient deficiency in many model organisms including human studies. Natural phytochemicals are enriched with a significant and effective source of chemical compounds having antiviral properties. In addition, coronavirus-specific therapies and antiviral drugs have also been found to be very efficacious for the cure of SARS and MERS. They can also be suggested as alternative therapies for infection with SARS-CoV-2. Besides, scientific reports significantly support the phenomenon that phytochemicals and secondary metabolites exert an intense boost to immune system response against few classes of respiratory viruses. Presently, only limited allopathic drugs are effective against COVID-19, however, by investigating the elucidation of SARS-CoV-2 mechanism, further development of new vaccines and drug design is needed in future. Recent literature offers obvious suggestions to support herbal medicines with diet supplementation as possible effective remedy against SARS-CoV-2 and preventive mediators in fight against COVID-19. Hence, these promising and less time-consuming alternatives are urgently required for the speedy recovery of COVID-19 patients until the vaccines or synthetic drugs could pass the undergoing clinical trials. Based on the evidence of viral proteins, a number of research groups are designing drugs and vaccines.

Clinical trials are currently in progress on some of these medicinal and prophylactic agents. It is predicted that vaccines and medicines will be developed to improve worldwide public health affected by this virus. Consequently, based on all these findings, we can say that proper diet therapy along with operative herbal medicines may serve as a COVID-19 preventative measure. However, all these possible hypotheses necessitate a rationalized experimental authentication in COVID-19 infected models, with a development of novel vaccines and drugs such as the emerging nanobiotechnological-based products (nano vaccines and nano antiviral agents) that could be prepared to obtain better outcomes than the conventional antiviral remedies.

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