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COVID-19 Infection: Targeting Possibilities for Treatment

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ABSTRACT: The outbreak of novel coronavirus (nCoV) or severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in December 2019 in Wuhan, China, has posed an international public health emergency worldwide and forced people to be confined in their homes. This virus is of high-risk category and is declared a pandemic by the World Health Organization (WHO). The worldwide researchers and various health professionals are working together to determine the best way to stop its spread or halt this virus's spread and circumvent this pandemic condition threatening millions of human lives. The absence of definitive treatment is possible to explore to reduce virus infection and enhance patient recovery. Along with off-label medicines, plasma therapy, vaccines, the researchers exploit the various plants/herbs and their constituents to effectively treat nCoV infection. The present study aimed to present brief and most informative salient features of the numerous facts regarding the SARS-CoV-2, including the structure, genomic sequence, recent mutation, targeting possibility, and various hurdles in research progress, and off-labeled drugs, convalescent plasma therapy, vaccine and plants/herbs for the treatment of coronavirus disease-2019 (COVID-19). Results showed that off-labeled drugs such as hydroxychloroquine, dexamethasone, tocilizumab, antiviral drug (remdesivir, favipiravir), etc., give positive results and approved for use or approved for restricted use in some countries like India. Future research should focus on these possibilities that may allow the development of an effective treatment for COVID-19.

KEY WORDS: COVID-19, genomic sequence, spike protein, SARS-CoV-2, ACE2

I. INTRODUCTION

A novel and alarming primary contagious atypical pneumonia was found in December 2019 at Wuhan in China, the cause of which was not known at the initial stage. The cause of this atypical pneumonia was then found to be a zoonotic coronavirus (CoV), which was similar to the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) CoV and named coronavirus disease-2019 (COVID-19).[1] COVID-19 infection includes the fever and respiratory symptoms in which cough followed by shortness of breath is most important and is fatal in about 10% of cases. The COVID-19 infection is transmitted from person to person, primarily by respiratory droplets and the things which come in contact with these droplets.[2] The reproduction

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of SARS-CoV-2 compared with SARS-CoV was much higher,[1] and COVID-19 was declared a pandemic by the WHO on March 11, 2020. The leading cause of this virus's spread risk to more than 200 countries was due to carriers moving abroad from China through commercial aircraft. Accordingly, the new CoV infection is roughly divided into three main stages. Stage I represents an asymptomatic incubation period with or without detectable virus, Stage II represents a non-severe symptomatic period with the presence of the virus, and Stage III represents a severe respiratory symptomatic stage with high viral load.[3]

This disease's outbreak is challenging as there are no specific therapeutics or vaccines available to cure and control, even in developed countries. Only non-pharmaceutical health measures like avoiding person-to-person contact through various means such as social distancing isolation and quarantine and community containment have been taken into account to control the spread and growth rate of this epidemic respiratory disease. These massive tools have played a vital role in the non-spreading of this disease when taken timely.[4,5] Many pharmaceuticals such as drugs and vaccines are in the developing stage and require many clinical trials and other regulatory formalities before entering the market.

As of June 15th, 2020, COVID-19 has been confirmed in 8,525,042 people worldwide, having 456,973 deaths[6] and increasing day by day, thus an urgent need to find out the effective and novel treatment. The current focus has been developing a proper and effective therapy for its management, including antiviral, vaccines, and other therapies. Here, targeting the possibility for the treatment of COVID-19 based on the structure composition and surface protein available on the SARS-CoV-2 surface and other aspects are reviewed.

II. STRUCTURE OF COV

CoV is spherical-shaped lipid bilayer enveloped particles, having 26.4 to 31.7 kb (kilobases) single-stranded RNA genome, which is longer than all other RNA genome-viruses. This largest or longer genome provides different gene modifying capacity to this family (family: Coronaviridae, sub family Coronavirinae, Order: Nidovirales) of the virus.[7,8]

Genetically SARS-CoV-2 is 76% similar to SARS-CoV and 50% to MERS-CoV. The length of non-structural proteins in SARS-CoV-2 is 29844 base pairs (bp) (7096 amino acids [aa]) while 29751 bp (7073 aa) and 30119 bp (7078 aa), respectively, found in SARS-CoV and MERS-CoV. The spike protein of SARS-CoV-2 contains 1273 aa while 21493 aa in SARS-CoV and 21493 aa in MERS-CoV.[8]

There are four types of structural proteins: membrane (M)-protein, spike (S)-protein, envelope (E)-protein, and nucleocapsid (N)-protein are encoded by the viral genome (Fig. 1A). These structural proteins have played their role individually in the replication of the virus.[9] Among these four proteins, M and E are the most essential small transmembrane proteins involved in developing virus structure.

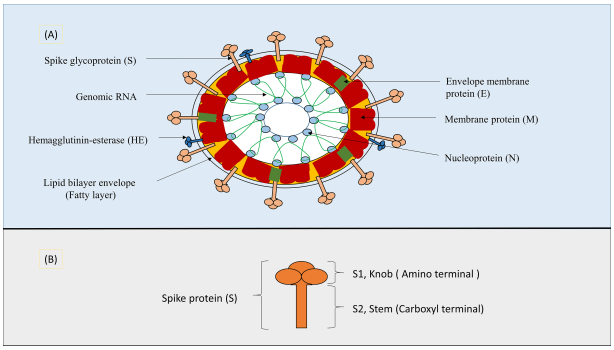

FIG. 1: Structures (A) Structure of SARS-CoV-2. (B) Structure of the S–protein.

The M-protein is a glycoprotein, plays a critical role in the intracellular formation of virus particles, and is responsible for the virus's shape.[9] It possesses four different domains, i.e., carboxylic acid or cytoplasmic domain, amino or luminal domain, transmembrane cluster, and amphiphilic domain.[10] Homotypic interaction between M and other viral proteins (E, S, and N) is most important for forming the virion envelope.[11] Interaction between the carboxyl domain of M-protein and N-proteins plays a crucial role in completing viral assembly by the stabilizing internal core and nucleocapsid of virions in the infected cells.[12] Assembly and release of virus-like particles (VLPs) and viral envelope development results from the interaction between the C-termini of M- and E-proteins.[13] The deletion of this M-E domain causes the reduction of VLPs.[9]

S-protein (Fig. 1B), also known as a fusion protein, is signal peptides containing type-1 glycoprotein, projected as spikes at the virus's surface and provides crown-like characteristics structure to the SARS-CoV-2.[7,14,15] S-protein is divided into two terminal S1 amino-terminal and S2 carboxyl-terminal, both S1 and S2 terminals are indispensable for attachment of virus and membrane fusion with the host cell.[16] S1 terminal formed a knoblike structure while S2 formed a stem. S2 terminal contains two heptad repeat regions (HR1 and HR2) and fusion peptide (FP) at the amino-terminal of the HR1 region.[10] The details about the S1 and S2 will be discussed in the section "S-protein of CoV."

The E-protein is the most mysterious smallest structural proteins of 8.4 to 12 kDa with 16–109 amino acids.[17] It passages an extended hydrophilic carboxyl terminus, hydrophilic amino-terminus (has 7–12 amino acids), and hydrophobic transmembrane domain (TMD; has 25 amino acids).[18] An amply amount of E-protein is expressed during the replication cycle of the virus in the infected cell. These expressed E-proteins remain localized in the Golgi body, endoplasmic reticulum (ER), and ER-Golgi intermediate compartment (ERGIC) for the assembly and budding of SARS-CoV-2, and only a small portion of E-proteins are involved in the formation of the virion envelope.[9]

Hemagglutinin-Esterase protein is a glycoprotein that is not found in the SARS-CoV genome, but it forms a smaller (5–7 nm) S-protein peplomers on the envelopes of some group II CoV.[18]

A. Genome Organization of CoV

CoV contains a positive-sense, unsegmented single-stranded RNA genome (genus Beta CoV) with a diameter of 80–120 nm.[19] Among all known RNA viruses, the largest genome (26.4–31.7 kb) makes the virus family more flexible to accommodate and modify genes with G + C content ranging from 32% to 43%. It is divided into four types: α-CoV, β-CoV, δ-CoV, and γ-CoV. Earlier, six CoV were known to cause human disease, and SARS-CoV-2 is the seventh member of the CoV family that infects humans after SARS-CoV and MERS-CoV.[20] The SARS-CoV-2 genome shows high sequence resemblance (89–96.3%) with two bat CoV, bat-SLCoVZC45 and bat-SL-CoVZXC21, and 79–82% with that of human SARS-CoV.[21] There are small open reading frames (ORFs) present in an uneven number between the different conserved genes (ORF 1ab, spike, envelope, membrane, and nucleocapsid) and downstream to the nucleocapsid gene in different CoV lineages.[15] CoV genomes are composed of short untranslated regions at both the 5′ and 3′ ends. The genome organization of all CoV has identical characteristic gene sequences for the coding region, i.e., 5′-replicase ORF1ab, S, E, M, N-3′.[22] The genome contains 14 ORFs encoding 27 proteins (Fig. 2). The longest ORF is located at the 5′ terminus encoding for 16 nonstructural proteins collectively involved in virus replication and possibly immune evasion. The 3′ terminus of the genome encodes structural proteins and accessory proteins. Hypervariable genomic hot spots have been detected in the spike gene and other ORFs for nonstructural proteins (nsps).[8] Interestingly, the unique aspects of SARS-CoV-2 were found in genes of spike glycoprotein, orf8, and orf3b. Intermediate frameshifts of ORF1a and ORF1b produced two polypeptides: pp1a and pp1ab that are processed into 16 nsps by virus-encoded chymotrypsin-like protease or main protease and one or two papain-like proteases.[23] Single guide RNA (sgRNAs) of CoV translate all structural and accessory proteins. One-third of the genome contains four essential structural proteins S-, M-, E-, and N-proteins near the 3'-terminus

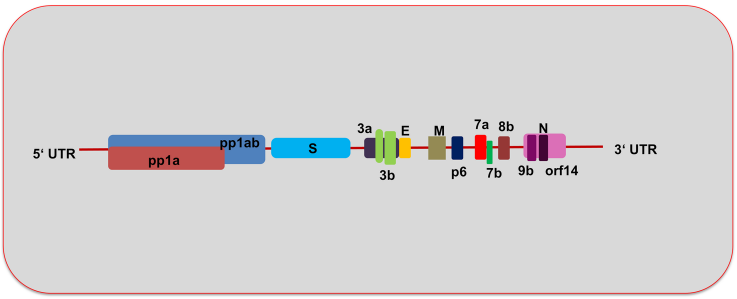

FIG. 2: Genome organization of SARS-CoV-2 showing that there are 14 ORFs. The genome comprises of 5′ untranslated region (5′UTR) with two ORFs coding for polyprotein (pp1a/ab) necessary for replication, followed by structural proteins including spike S–protein, E–protein, M–protein, and N–protein. Accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b and orf14) at 3′UTR. ORF, open reading frame; SARS-CoV-2, severe acute respiratory syndrome CoV.

encoded by ORFs 10 and 11. These nsps reposition the membranes derived from the rough endoplasmic reticulum (RER) into double membranous vesicles, where virus replication and transcription occur.[24] A transcriptional regulatory sequence (TRS) motif has existed at the 3′ end of the leader sequence that precedes most ORFs. The TRS motifs are thought to be necessary for the "copy selection" mechanism that mediates specific spontaneous template changes during RNA replication, leading to the high frequency of symmetric RNA recombination in CoV.[25]

B. Division/Multiplication Mechanism of COVID-19

The life cycle of a CoV in a host cell subdivided into four phases are (i) attachment of virus with the host cell and entry into the host cell, (ii) replicase protein expression, (iii) replication and transcription of viral protein in the host cell, and (iv) assemble and release the virus.

The angiotensin-converting enzyme (ACE) 2 is a crucial receptor for the subunit of S1 and S2 of S-protein for the CoV (Fig. 3) and expressed in cells of the lungs, heart, testis, liver, vascular endothelium, kidney, and intestine.[16] After binding the S1 terminal to

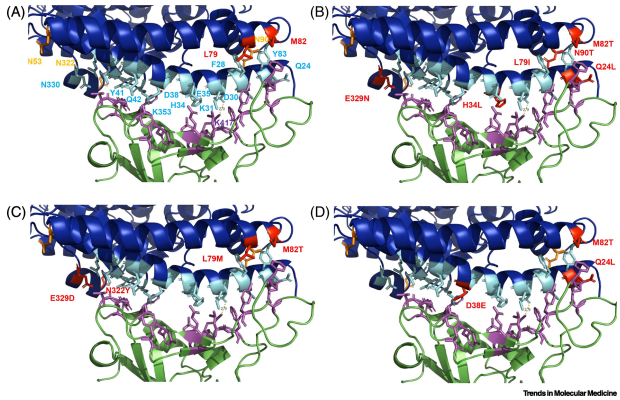

FIG. 3: Structure of the S-protein before and after membrane fusion. (A) Structure of the trimeric ectodomain of S from nCoV. The S2 subunit in one monomer is shown in green, the NTD of S2 is shown in magenta and the CTD of S2 is shown in blue. The CTD is in the "up-conformation," exposing the binding domain for the ACE2 receptor (cyan). The S1/S2 and S2′ cleavage sites are indicated in red (Figure was created with Pymol from Protein Data Bank [PDB] file 6VSB). (B) Structure of the HR domains of S from SARS-CoV. HR1 is labeled green and HR2 is labeled blue. The formation of this six-helix bundle is supposed to drive membrane fusion (Figure was created with Pymol from PDB file 1ZV8). (C) Structure of the HR1 of S from SARS-CoV (green) bound to the panCoV peptide inhibitor EK1 (blue). The amino acids in S essential for binding to EK1 are shown as magenta sticks in one helix. The amino acids in S from SARS-CoV-2 not conserved in S from SARS-CoV are shown as red sticks. Because the nonconserved amino acids are apparently not required for binding to EK1, the fusion inhibitor is likely to prevent cell entry of SARS-CoV-2 (Figure was created with Pymol from PDB file 5ZVM) (reprinted from Sun et al. with permission from Elsevier, copyright 2020).

the receptor, it triggers conformational changes that expose the fusion peptide for the fusion function of the S2 terminal. As a result, the two HR regions formed a heterotrimeric six-helix bundle (at the S2 terminal). This heterotrimeric six-helix bundle is responsible for the membrane fusion between the fusion peptide and the transmembrane domain.[26] This fusion mainly occurs in acidified endosomes. Then the viral genome is released into the cytoplasm of the host cell. After entry of the virus into the host cells' cytoplasm, the translation of polypeptides (pp) replicated the viral genome into negative-strand RNA and transcription of mRNAs.[27]

Firstly, two large polypeptide/polyproteins, such as pp1a and pp1ab, are translated using frameshift mechanism by ORFs, i.e., 1a and 1b at the 5′ end of the genome RNA. For this purpose, the virus utilizes an RNA pseudoknot and a slippery sequence (5′-UUUAAAC-3′). The polyproteins pp1a contain nsps 1–11 while pp1ab contains nsps 1–16. CoV family encoded 2–3 protease enzymes like the main protease or Mpro enzyme, Papain-like proteases (PLpro), and serine-type protease. These enzymes cleave polyproteins into individual nsp by acting at specific polyprotein sites, nsp3 encoded PLpro that cleave polyprotein into nsp1, nsp2, and nsp3, while nsp5 encoded Mpro for cleavage of remaining nsps in the polyprotein. Now cleaved nsps are gathered into replicase–transcriptase complex (RTC), which provides an ambient environment for RNA replication and transcription of the sub-genomic mRNAs.[4,18,27]

Synthesis of sub-genomic mRNAs is regulated by transcription-regulating sequences present at the transcriptional start sites in the genome RNA for each mRNA. mRNA translated individual viral proteins from its 5′ end.[28] Structural proteins M, S, and E-protein after translation were inserted into the ER. Then viral proteins move into endoplasmic reticulum–Golgi intermediate compartment (ERGIC) using secretory pathway and M-protein get to interact with N-protein and bud into membranes of the ERGIC which formed mature virions. These virions move to the cell surface and get released from the cell by exocytosis. Some S-proteins are also distributed on the plasma membrane, promoting syncytium by S-mediated cell-to-cell fusion.[29,30]

C. S-Protein of CoV

One of the CoV characteristics is a spiked club-shaped protein (~ 180 kD) present on the virus's surface. The S, which is a type I membrane glycoprotein, compose peplomers. Indeed, the primary inducer of neutralizing antibodies is S-protein. The S is the primary determinant of cellular tropism, therefore, the main determinant of interspecies transmission to host cells. The number of these S-proteins is a critical feature of virus risk. CoV infection can increase as the number of S-proteins increases per virion. In addition, adverse surroundings, for example, alterations in pH and temperature, make a wide range of virions relatively spike free.[31] The S-protein is a trimeric transmembrane protein with an N terminal cleavable signal peptide, one heavily and large ectodomain (60–90 carbohydrates per trimer), a single-pass transmembrane region, and a short cytoplasmic intracellular tail containing a cluster of S-acylated cysteine residues. Among these sections, the ectodomain is cleaved by proteases into two subunits, namely S1 of a single polypeptide and S2 of

highly conserved polypeptides.[8] The S1 subunit binds to receptors on the host cell surface (i.e., essential for CoV to enter host cells) and subsequent conformational changes in S2 facilitate the fusion of the cell membrane between the envelope and the plasma membrane, and it is the leading cause of virus-neutralizing antibodies.[32] Subunit S1 is again divided into terminal parts N and C into two independent domains and is known as the N-terminal domain (NTD) and C-terminal domain (CTD).[33] The NTD exhibits a structural fold like human galectins, galactose binding lectins, and therefore, in most CoV, sugars present on the cell surface can serve as binding factors. Although CTD is responsible for direct contact with the human receptor through ACE-2. The CTD contains two subdomains: the core structure (five-strand antiparallel β-sheet) and the actual receptor binding motif (RBM), which determines the binding specificity of the receptor (Fig. 4).[34,35]

During SARS-CoV-2 infection, RBM in the S1 subunit of S-protein binds directly to ACE2 in human or host cells. The RBM of SARS-CoV-2 contains a significant amino acid residue, i.e., Gln493, which is responsible for the binding and fusion of the viral S-protein with the ACE2 protein of human cells, mainly that is present in the lungs that cause human respiratory infections.[36] After virion RBM binding to targets ACE2 receptor to the target cell, HR1 and HR2 domains in the S2 subunit of the S protein combine with each other to form a six-helix bundle (6-HB) fusion core, and brings

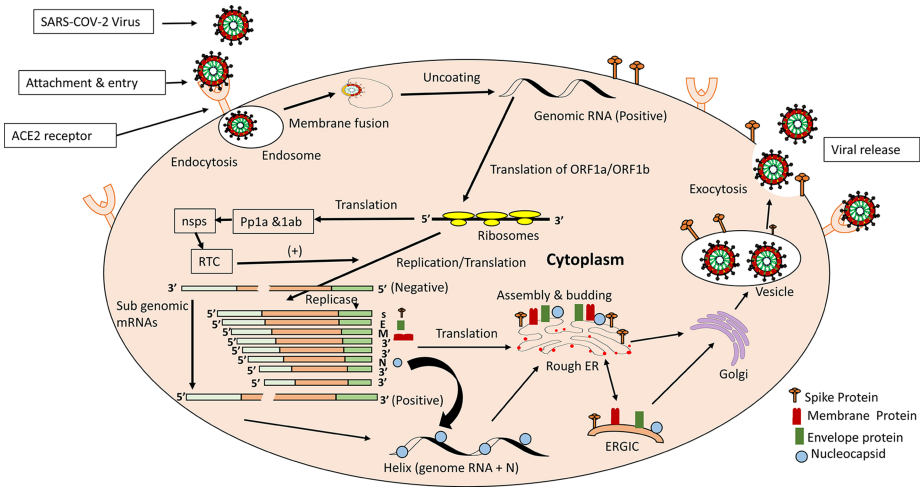

FIG. 4: SARS-CoV-2 attached with host cell using own S–protein and ACE2 cellular receptor of the host cell, and then it releases viral genome into the host cell cytosol by receptor–mediated endocytosis, polyproteins pp1a and 1ab are translated by the viral genome, pp1a and 1ab cleaved into small nsps (non–structural proteins) which forms an RTC. The RTC engages in the synthesis of genomic RNA as well as subgenomic mRNAs. mRNA translates viral proteins from the 5′ end. New virions are assembled by budding into intracellular membranes and used rough endoplasmic reticulum (RER), endoplasmic reticulum/Golgi intermediate compartment (ER/GIC) like cell secretory mechanisms for release from the host cell.

viral and cell membranes for fusion and infection. As a result, the 6-HB fusion core structure of SARS-CoV-2 was studied, and the structural basis of its S-protein-mediated membrane fusion laid the foundation for the rational design of CoV fusion inhibitors.[37] Significant research has been carried out for identifying antibody molecules directed against S-proteins that mediate the entry of virus and their potential to induce host immune responses and elicit protective antibody responses in infected individuals.[38]

III. MUTATIONS IN SARS-COV-2

SARS-CoV-2 has a particular mutation and cause unpredictable effects on COVID-19.[39] In the entire genome of SARS-CoV-2, 42 missense mutations were investigated, including structural and non-structural protein, except the E-protein. Besides, 29 missense mutations identified in ORF1ab polyprotein, 8 in the spike surface glycoprotein, 4 in the N-protein, and 1 in the matrix protein Notable, three mutations (F36, D354, and Y364) present in the spike surface glycoprotein receptor-binding domain (RBD) on ACE2 receptors.[40] Similarly, SARS-CoV-2 RNA-dependent RNA polymerase (RdRp; also known as nsp12) is the central part of the replication/transcription machinery and a vital targeting moiety for antiviral drug development. Mutations in critical residues, a significantly less binding affinity of therapeutic molecules with RdRp, may lead to drug resistance.[41]

IV. IMMUNE RESPONSE IN COVID-19 INFECTION

The initial infection site and pathogenesis of SARS-CoV-2 are still poorly understood and under investigation. The histopathological examination of COVID-19 showed acute respiratory distress syndrome (ARDS), bilateral diffuse alveolar damage, pulmonary edema, and normal syncytial cells in the alveolar lumen.[42,43] The pathology of COVID-19 is similar to SARS-CoV's finding in 2002–03.[44,45] Chu et al. performed a comparative study of the replication of immune activation between SARS-CoV and SARS-CoV-2. The result showed that the SARS-CoV-2 replication was faster than SARS-CoV in human lungs and produced more than three folds of infectious virus particles after 48 h. SARS-CoV-2 and SARS-CoV were similar in cell tropism, the two types of targeting I and II pneumocytes and alveolar macrophages. In contrast to SARS-CoV, SARS-CoV-2, even with the more efficient virus replication, did not significantly induce types I, II, or III interferons (IFNs) in the infected human lung tissues.[46]

The SARS-CoV-2 triggers lower levels of IFNs and pro-inflammatory cytokines/chemokines despite being capable of infecting and producing a significantly higher amount of virus in human lung tissue. Chu et al. studied the expression of pro-inflammatory cytokines/chemokines in SARS-CoV-2 and SARS-CoV. They found that the proinflammatory mediators such as interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), chemokine (C-X-C motif) ligand-1 (CXCL-1), CXCL-5, and CXLC-10 expression were upregulated, which are lesser than the SARS-CoV. The infection with SARS-CoV-2 did not significantly trigger an IFN response and only significantly activated lesser proinflammatory mediators than the SARS-CoV.[46] SARS-CoV-2 can

be infected and reproduced in a significantly higher yield in the human lung, and it has generally triggered significantly lower levels of IFN and pro-inflammatory cytokines/chemokines. The innate immune response in infected cells is our first line of defense against acute viral infection. Due to the lesser triggers of IFN and proinflammatory mediators' activation, the fever and pneumonia-like symptoms in the people positive with SARS-CoV-2 showed lesser than that SARS-CoV infection. SARS-CoV-2 may target and deplete the natural killer cells, which are the primary cell type, is responsible for the destruction and elimination of virus-infected cells.[47] The mild symptom and asymptomatic COVID-19 one of the severe problems to the community spread of SARS-CoV-2. A report confirmed that about 50% of positively tested healthcare workers in King County, Washington, were asymptomatic. A statement of the Indian Council of Medical Research confirmed that 69% of positive cases are asymptomatic out of 18,601 positive cases tested over four lack samples in India.[48] In the case of intensive care unit (ICU) and non-ICU COVID-19 patient's, it was found that their plasma contains a higher concentration of proinflammatory mediators such as IL-1B, IL-1RA, IL-7, IL-8, IL-9, IL-10, MCP-1, IFN-γ, basic fibroblast growth factors, granulocyte-colony stimulating factor (GCSF), colony-stimulating factor, granulocyte-macrophage, macrophage inflammatory protein 1A (MIP-1A), MIP-1B, platelet-derived growth factor, tumor necrosis factor-α (TNF-α), IFN-γ–induced protein 10 (IP-10), and vascular endothelial growth factor. While the plasma levels of IL-2, IL-7, IL-10, GCSF, IP-10, MCP-1, MIP-1A, and TNF-α was found to be more compared with the non-ICU patients.[49] Another study has been shown that a cluster of differentiation (CD) 4 T cells ICU patients with COVID-19 produced more IL-6 and GM-CSF than that of non-ICU.[50] Xu et al. investigated a seriously COVID-19 infected 50-year-old man and found that the number of peripheral CD4 and CD8 T cells decreases considerably when their states are over-activated. High concentrations of pro-inflammatory CD4 T cells and CD8 T cell cytotoxic granules were also determined, suggesting antiviral immune responses and T cell overactivity.[43] Several studies also suggested that lymphopenia is a common feature of COVID-19 and is a critical factor that decides severity and mortality.[51,52]

Host innate immunity acts as the first line of defense during virus attack or entry of any foreign particles like antigen in the host body. It activates when viral pathogen-associated molecular patterns (PAMPs) like viral surface glycoproteins, capsid, and the viral genome are recognized by host pattern recognition receptors (PRRs).[53] Toll-like receptors (TLRs) are present in the endosomal compartment or at the cell-surface to recognize viral motifs, known as non-cytoplasmic PRRs. The retinoic acid-inducible gene I (RIG-I) like receptors (RLRs), the nucleotide-binding domain-leucine-rich repeat-containing molecules (NLRs), novel DNA-binding factors, C-type lectin receptors, nucleotide-binding oligomerization domain (NOD)-like receptors, and cyclic guanosine monophosphate–adenosine monophosphate (cyclic GMP-AMP) synthetase for cytosolic DNA sensor is the cytoplasmic PRRs which plays chief roles in recognition of viral nucleic acid. Interaction between PAMPs and PRRs in the infected cell activates various signaling pathways through various adaptor proteins, such as stimulator of IFN genes (STING) and mitochondrial antiviral signaling protein (MAVS), which

cause the production of host defense molecules such as proinflammatory chemokines-2, cytokines, type-I and III IFNs. After the secretion, IFNs and cytokine activate Janus kinases (JAKs)/signal transducer and activator of transcription proteins (STAT) signaling cascade via autocrine and paracrine mechanisms, which inhibit the replication through activation of IFN-stimulated genes (ISGs) and also cause cellular apoptosis of the infected cell. Besides, viruses have various strategies to avoid the PAMPs detection by the host immune system, which include masking the specific molecular motifs of the viral genome that are recognized by cytosolic sensors and degradation of signaling molecules.[54,55]

V. MEDICINES/THERAPIES USED IN THE TREATMENT OF COVID-19

A. Off-Label Medicines

The use of licensed drugs for indications that have not been approved by a national drug regulatory authority is considered "off-label" use.[56] Currently, no drugs have been approved for COVID-19. However, some have been used to treat COVID-19 patients, including hydroxychloroquine (HCQ) by the President of Brazil on April 7, 2020 was called "Sanjeevani Booti." The following section has tried to compile the off-label medicines for COVID-19 in the scientific brief released by the WHO. The numbers of potential investigational therapies have been suggested and are in a clinical trial by various countries. The treatment strategies that attempt to interfere with different parts and stages in the CoV replication cycle (Fig. 5) are discussed here.

1. Chloroquine and HCQ

It is a 4-aminoquinoline antimalarial drug, which is a derivative of quinine. It is a weak base that increases the intracellular pH necessary for membrane fusion and blocks endosome maturation as acidic pH is not available, thus finally blocking the virions transport. This drug is effective due to the phagolysosome's alkalinization and has been reported in its effectiveness against CoV.[57] Wang et al. demonstrated that chloroquine plays a role in both the entry and post-entry stages of SARS-CoV-2 infection in Vero E6 cells. In addition to its antiviral activity, chloroquine also has immunomodulatory activity, which can synergistically enhance its antiviral effect of remdesivir *in vivo*. After oral administration, chloroquine is broadly distributed throughout the body, including the lungs. In Vero E6 cells, the EC_{90} value of chloroquine for SARS-CoV-2 is 6.90 μM, which can be demonstrated in the plasma of rheumatoid arthritis patients receiving 500 mg and is clinically achievable. Chloroquine is a cheap and safe drug that has been used for more than 70 years. Therefore, it may be clinically applicable to SARS-CoV-2.[58]

HCQ is a 4-aminoquinoline, an analog of chloroquine where one of the N-ethyl substituents of chloroquine is β-hydroxylated. It has been used as a drug for rheumatoid arthritis and malarial treatment. It is a weak base that increases the intracellular pH necessary for membrane fusion and blocks endosome maturation as acidic pH is not

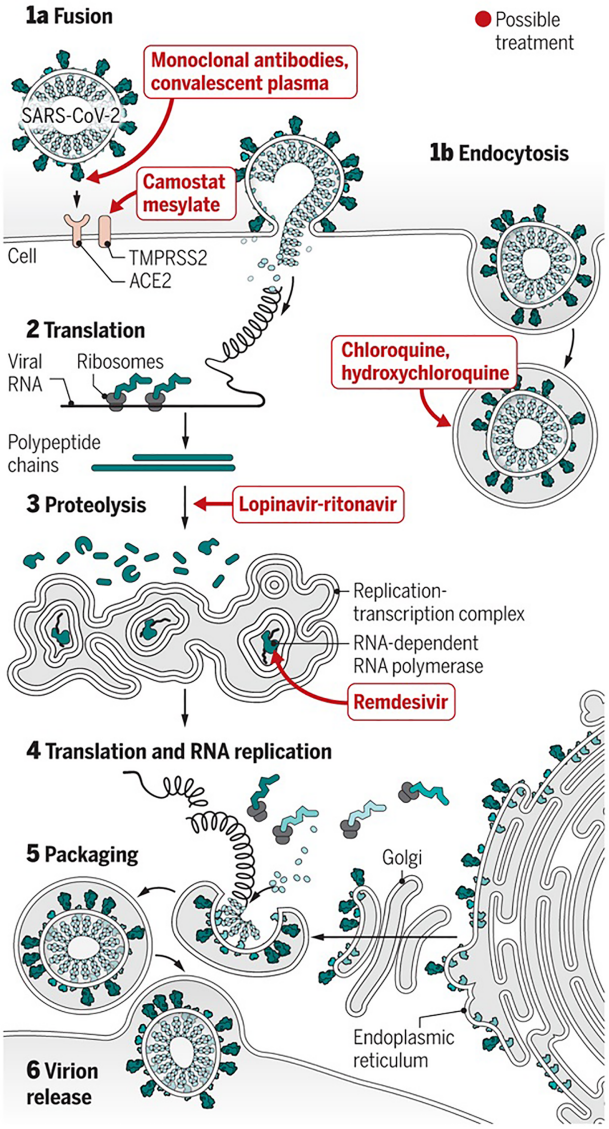

FIG. 5: Line of attack. Experimental treatment strategies attempt to interfere with different steps (numbers) in the CoV replication cycle (reprinted from Kupferschmidt and Cohen with permission from American Association for the Advancement of Science, copyright 2020).[59]

available, thus finally blocking the virions transport. These two drugs, i.e., chloroquine and HCQ, have been used as a prophylactic treatment to prevent the persons at risk of COVID-19.[57,60] The U.S. Food and Drug Administration (USFDA) has approved chloroquine and HCQ for use in the management of COVID-19. The detailed mechanism of action of chloroquine and HCQ are as follows.

Chloroquine in the deprotonated form gets diffuse into acidic vesicles, such as lysosomes, late endosomes, trans-Golgi network (TGN) vesicles across cell membranes. The protonated chloroquine does not diffuse out of these acidic vesicles and thus get trapped in the protonated form's vesicles. The drug gets accumulated inside these vesicles due to the difference in pH. The virus gets entrapped in the endoplasmic and TGN vesicles by modifying glycoproteins envelope by using the enzymes glycosyltransferases and proteases requiring low pH. Chloroquine and HCQ neutralize this acidic pH, causing the deactivation of these enzymes in the vesicles, which leads to inhibition of glycosylation (by inactivation of glycosyltransferases). Glycosylation inhibition causes the host to develop an adaptive immune response against the infection. This also weakens the cellular receptor enzyme called ACE2 required for the entry of SARS-CoV-1 into the host cell.[61]

Both chloroquine and HCQ help prevent viral entry into the host cells by inhibiting the biosynthesis of sialic acids, which have a critical role in virus-cell ligand recognition. This, in turn, causes the inhibition of viral attachment and its entry into the host cell.[62]

Chloroquine has also been reported to reduce the phosphatidylinositol binding clathrin assembly protein (PICALM) expression. PICALM is a cargo-selecting adaptor having its lead role in clathrin-coated pits regulating the cellular clathrin-mediated endocytosis, which is considered to be involved in SARS-CoV entry in human cells.[62]

2. Lopinavir/Ritonavir

Lopinavir and ritonavir are protease inhibitors that block viral cellular entry given at a dose of 400 mg twice daily, thus found to be effective against SARS-CoV studied in both *in vitro* and human studies and have been approved for human immunodeficiency virus-1 (HIV-1) infections.[63] It has been registered in a clinical trial and is in phase II.[64] Another clinical trial has been registered to compare the Lopinavir/Ritonavir or HCQ in COVID-19 patients and is in phase II.[65]

3. IFN Plus Lopinavir/Ritonavir

Type I IFN acts as an immunomodulator is the first cytokine produced during a viral infection. After secretion, type I IFN is attached with IFNAR receptors present in the plasma membrane of cells. Interaction between type I IFN and IFNAR stimulates phosphorylation and relocalization to the nucleus of transcriptional factors STAT1, where STAT1 activates IFN-stimulated genes (ISGs). Activated ISG inhibits or reduces the cytokine secretion, and metabolism of the cell causes hindered viral replication and spread.[66] Type I IFN also provides antiviral immunity through ISG genes, which reduce the cell membrane fluidity and prevent fusion with the virus. IFN-β1 is a more potent inhibitor of coronavirus than IFN-α, protects the lungs by maintaining the endothelial barrier, increases the secretion of anti-inflammatory adenosine through up-regulation of the cluster of differentiation 73 (CD73) in endothelial cells. The immunomodulator nature of type I IFN and the antiviral property of lopinavir/ritonavir enhance the efficacy of the

combination against viral infection.[67,68] IFNβ inhibits viral replication, which is based on the study for SARS-CoV-2 and MERS. IFN-β1a is safe and comfortable to be used against COVID-19 treatment in the early stages of infection. The combination of IFN plus lopinavir/ritonavir has been registered in clinical trials in China to assess the ability of lopinavir/ritonavir and IFN combination in COVID-19 (ChiCTR2000029387).[68]

4. Ribavirin

Ribavirin is a nucleoside analog that blocks the viral RNA synthesis and mRNA capping. This antiviral activity of ribavirin against SARS-CoV-2 through *in vitro* activity may be useful for its potency in developing treatment strategies based on its potential strategy developed during the prior MERS and SARS outbreaks.[69] In Hong Kong, the antiviral therapy of lopinavir/ritonavir alone or ribavirin and IFN-β1b has been tried for its treatment.[70] Ribavirin, in combination with IFN, works by inhibiting viral replication and has shown mixed results against MERS.[71] Ribavirin, in combination with steroids, has also been tried.

5. Lopinavir/Ritonavir, Ribavirin, and IFN-β1b

Lopinavir/ritonavir belongs to medication class HIV protease inhibitor blocking cellular entry. Lopinavir/ritonavir, ribavirin, and IFN-β1b are in phase II clinical trial[70] by SAME University of Hong Kong with a hypothesis that the said combination will accelerate recovery rate with decreased viral load and mortality in COVID-19 patients as compared with lopinavir/ritonavir alone.

6. Remdesivir

Remdesivir is small molecule GS-5734, an antiviral prodrug of adenosine, developed by Gilead Sciences in 2016 for the treatment of RNA-based viruses that is mostly responsible for a global pandemic such as Ebola virus disease caused by Ebola virus (Zaire ebolavirus; Family: Filoviridae), and Coronaviridae family viruses (MERS and SARS).[72,73] Remdesivir shows broad-spectrum antiviral activity against many RNA viruses, i.e., Ebola, MERS-CoV, SARS CoV, Nipah, and respiratory syncytial virus. Remdesivir acts as delayed chain termination of RNA synthesis. It metabolizes into active nucleoside triphosphate and converts into remdesivir triphosphate (RDV-TP) after entering the host cells. RDV-TP resembles ATP. RDV-TP competes with ATP for i-position (site for incorporation of ATP or RDV-TP) and acts as substrate for viral enzyme RNA- dependent RNA polymerase (RdRp). After attachment with i-position, RDV-TP formed phosphodiester bond with upcoming nucleotides, but terminate premature RNA synthesis at i+5 position due to steric clash between 10-CN substituent of the incorporated RDV-TP and an S861 specific residue of RdRp upon further chain elongation.[74,75]

Remdesivir prevents virus replication and shows its prospective in mild-to-moderate COVID-19 patients but is not found to be suitable for severe cases. It can be

added as therapy and improve clinical efficacy but no improvement in mortality in COVID-19 patients. Remdesivir is in multiple ongoing trials, including phase III trial by the for mild-to-moderate (NCT04252664) and severe (NCT04257656) patients by investigators in China. Another clinical trial is ongoing by American biopharmaceutical Gilead Sciences, Inc., and was in phase III for moderate (NCT04292730) and severe (NCT04292899) COVID-19 patients.[76] But this drug fails its first trial and is not found to show any remarkable effect in the COVID-19 patients. Some of the ongoing clinical trials are summarized in Table 1.

7. Favipiravir

Favipiravir has been approved for CoV by the National Medical Products Administration of China as the first CoV drug in China. This antiviral drug works by inhibiting RNA polymerase, which is required and necessary for viral replication. It is a broad-spectrum antiviral drug that shows its effectiveness against arenavirus, bunyavirus, filovirus, and influenza.[77] The clinical trial for the favipiravir has been registered in a clinical trial to evaluate efficacy in COVID-19 (NCT04336904 and NCT04349241 in phase III).[78,79] Recently, Glenmark Pharmaceutical Ltd. received regulatory approval for the oral favipiravir (FabiFlu®) in India. The favipiravir showed clinical improvements of up to 88% in COVID-19, with a rapid viral load reduction by 4 days. The result showed the clinical improvement in patients across age groups 20 to > 90 years, including in patients with diabetes and heart disease suffering from mild to moderate COVID-19.[80]

8. Ifenprodil

Ifenprodil, an N-methyl-d-aspartate (NMDA) glutamate receptor antagonist, has been reported for its efficacy to improve the survival rate in survivability in H5N1 infected mice.[81] The NMDA receptor plays a crucial role in glutamate signaling and shows its expression in neutrophils and T-cells. The NMDA receptor activation in T-cells leads to the release of cytokines, blocked by Ifenprodil. Algernon Pharmaceuticals has reported the new therapeutic potential of its brand NP-120 (ifenprodil) as a potential treatment COVID-19 and has submitted an application to Health Canada for its phase IIb/III Multinational Clinical Trial. The company is to submit the same to the USFDA and Australian regulatory authorities.[82]

9. Camostat Mesylate

Camostat nesylate is a protease inhibitor that blocks viral maturation and its entry into cells. A virus needs a living body for survival, so its survival requires our genes and proteins to replicate and survive in our body. This drug blocks the interactions between the virus and body proteins and genes; thus, the drug targets the host and not the virus and effectively block the entry of SARS-CoV-2 in lung cells. First, the S-protein on

TABLE 1: Ongoing clinical trials of Remdesivir

ClinicalTrials.gov ID	Title	Study design	Actual start date	Phase	No. of participants
NCT04292899	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS–5734™) in Participants with Severe Coronavirus Disease (COVID-19)	Randomized, open–label clinical trial	March 6, 2020	3	400
NCT04292730	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS–5734™) in Participants with Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment	Randomized, open–label clinical trial	March 15, 2020	3	600
NCT04252664	A Trial of Remdesivir in Adults with Mild and Moderate COVID-19	Randomized, Double–blind, Placebo–controlled clinical trial	February 12, 2020	3	308
NCT04257656	A Trial of Remdesivir in Adults with Severe COVID-19	Randomized, Double–blind, Placebo–controlled clinical trial	February 6, 2020	3	453
NCT04280705	Adaptive COVID-19 Treatment Trial (ACTT)	Adaptive, Randomized, Double–blind controlled trial	February 21, 2020	3	394
NCT04302766	Expanded Access Remdesivir (RDV; GS–5734™)	Expanded access	—	—	General (Intermediate–size Population)
NCT04315948	Trial of Treatments for COVID-19 in Hospitalized Adults (DisCoVeRy)	Adaptive, Randomized, Open–label clinical trial	March 22, 2020	3	3200

the viral surface gets attaché to the human cell receptor called ACE2. Then, transmembrane protease serine 2 (TMPRSS2), another human protein, cleaves the viral S-protein, which helps for the fusion of the virus with the cell and its replication inside the cell, allowing the virus to fuse with the cell and start to replicate inside it. camostat mesylate blocks TMPRSS2 protein and entry of virus in the cell.[83] The combined therapy of camostat mesylate (400 mg three times a day) with HCQ (400 mg twice on day 1, 200 mg twice on days 2–7) is under clinical trial for COVID-19 (NCT04338906) and is in phase IV.

10. Nafamostat

Nafamostat, a drug used for pancreatitis in Japan, can inhibit S-protein fusion with the cell membrane and stop virus entry in human cells when administered as an intravenous infusion. Both camostat and nafamostat have been used in pancreatitis treatment, and the University of Tokyo is planning for clinical trials in April 2020 to test the efficacy of these two drugs in COVID-19 treatment. The concentration of camostat is about 10 times more than that required for nafamostat administered orally. These drugs can be used alone or with other antiviral drugs that target RNA replication or viral protein processing.[84] A clinical trial (NCT04352400 in phase II/III and NCT04321096 in phase I/II) has been registered to find the efficacy of nafamostat (TMPRSS2 inhibitor) in COVID-19 patients.[85,86]

11. Darunavir/Cobicistat

Darunavir and cobicistat are protease inhibitors that block viral cellular entry and have found their applicability as anti-HIV medication. A clinical trial is under process to find the efficacy and safety of protease inhibitors darunavir and cobicistat by taking one tablet per day for 5 days in the COVID-19 treatment and is in phase III.[87]

12. Umifenovir (Arbidol)

Umifenovir, an antiviral fusion inhibitor drug, is used for influenza infection in Russia and China. It works by inhibiting the fusion of cellular and viral membrane, restrict the entry in cells, and may show its antiviral activity against other CoV. An interventional phase IV trial GDCT0378006 (NCT04246242) has been tried on 500 patients to explore the use of umifenovir in antiviral therapy. The two sets of experimental studies are planned by administering the 200 mg and 400 mg of umifenovir with conventional antiviral therapy in China.

13. Oseltamivir

Oseltamivir is a neuraminidase inhibitor approved by the USFDA in 1999 that inhibits viral replication and is recommended by the WHO for people at high risk of pandemic

influenza. Since then, it has played a vital role in treating influenza A and B. Atypical pneumonia caused by the SARS-CoV that broke out in Guangzhou, China, in 2003 linked oseltamivir to the coronavirus. Zhang et al. found that the active site of the Spike (S)1 protein of SARS is similar to that of neuraminidase, which indicates that neuraminidase inhibitors may be useful for the treatment of SARS-CoV.[88]

14. Oseltamivir, HCQ, and Azithromycin

The combination of these three drugs is registered as a clinical trial to test the effectiveness of oseltamivir (75 mg twice in a day for 5 days orally), HCQ (200 mg thrice in a day for 5 days orally), and azithromycin (500 mg daily or 250 mg twice in a day on days 2–5 orally) individually and in combination.[89] The combination of HCQ and azithromycin showed a favorable effect on COVID-19 patients,[90] but medications increased QT-interval prolongation.[91]

15. Baloxivir and Marboxil

It is a viral endonuclease inhibitor that inhibits the multiplication of influenza viruses and is approved for uncomplicated influenza when given by oral route. In China, a clinical trial is registered to check the efficacy and safety of baloxavir, marboxil, and favipiravir tablets in COVID-19 patients, which are detected positive with the current antiviral therapy (ChiCTR2000029544).

16. Tocilizumab, Sarilumab, and Eculizumab

Tocilizumab and Sarilumab are monoclonal antibodies which act as IL-6 inhibitor and blocks cytokine storm. Among these, tocilizumab reduces the fever and oxygen requirement in COVID-19 patients and is an approved drug for rheumatoid arthritis treatment. IL-6 plays a crucial role in the cytokine storm for patients severely infected with SARS-CoV-2 pneumonia, and blocking of IL-6 may provide a suitable therapeutic target for their treatment. It is under phase II clinical trial, where the use of all these three monoclonal antibodies against IL-6 receptor has been used.[92] Eculizumab is a distal complement inhibitor used to alter the distal complement activity, preventing the membrane attack complex formation. By adjusting this distal complement activity in immune response, the patient recovers from the virus, while the mortality can be arrested with medical care support.

17. Acetazolamide

It is a drug approved by the USFDA for the treatment of high-altitude sickness. Acetazolamide forces the kidneys to excrete bicarbonate, and bicarbonate excretion acidifies the blood's pH. Because the body matches the blood's acidity by its CO_2 concentration, artificial acidification of the blood makes the body feel excess CO_2. To compensate

for this situation, more profound and faster-breathing starts, resulting in increased body oxygen levels. This mechanism adjusts the body for high altitude,[93] and the same is used for COVID-19 treatment. High-altitude pulmonary edema and COVID-19 exhibits a decreased ratio of the partial pressure of arterial oxygen to fractionally inspired oxygen with hypoxia and concomitant tachypnea. Acetazolamide medication may significantly enrich COVID-19 respiratory symptoms.[94,95]

18. Dexamethasone

During the viral infection immune system activate the control virus replication. Still, in uncontrolled viral replication or an advanced stage of infection, the number of infected cells, debris, and epithelium cells increased, which caused a massive release of cytokine, called 'cytokine storm'.[96] A massive release of cytokine caused lung injury, decreasing the alveolar gas exchange by reducing the alveolar surfactant. Infected cell debris and epithelium cells also stimulate the release of inflammatory cytokines like IL-1, IL-6, and TNF-α, which causes shock, multi-organ failure, hypotension, disseminated coagulation, and death.[97] Dexamethasone (synthetic corticosteroid) mimics cortisol, a hormone that produces naturally from the adrenal glands.

Dexamethasone used for the immune modulation that downregulates cytokines' release reduces systemic inflammation, prevents alveolar diffusion, reduces the risk of respiratory failure, and accelerates clinical recovery in a severe case of COVID-19 requiring mechanical ventilator or artificial oxygen therapy.[97,98] Recently, an Oxford University researcher announced the dexamethasone trial result in 2104 enrolled patients. Administration of 6 mg dexamethasone for ten days in enrolled patients showed that less than a third of deaths were detected in ventilated patients and in one-fifth of patients who received only oxygen. The overall mortality rate was reduced by 17% in 28 days,[99] showing the high significance and great benefits among the patients requiring ventilation.

B. Convalescent Plasma Therapy

The convalescent plasma therapy is a preventive measure and simple immunized therapy in which antibodies from the blood of a patient recovered COVID-19 will be used to critically affect COVID-19 patients and help them get immunized against it. It is a passive immunization in which the particular antibodies developed from the blood of recovered COVID-19 patients are ingested into another person under treatment and help in fighting the second patient against CoV.[100] This therapy is useful for many diseases, like hepatitis B, hepatitis C, HIV, etc.[101] As suggested by immunologists John Hopkins study, the convalescent plasma therapy is associated with some of the risks, which include transmission of inadvertent infection to the patient, enhancement of infection on the failure of treatment in some therapy, and suppression of the body's natural immune response causing the re-infection in the COVID-19 patient.[102]

In India, a 49-year-old male in Max Hospital, New Delhi, received plasma therapy and found positive results and reported being out of danger by the hospital team.

C. Vaccine

Vaccines are essential and work by training and preparing the body's immune system to recognize and fight disease-causing germs, such as bacteria and viruses. When the body is exposed to these disease-causing germs, the body immediately prepares to destroy them and save the body from disease. According to the WHO, every year, 2–3 million deaths are prevented due to vaccination.

During the COVID-19 pandemic, the effective vaccine is excellent hope for the world's population, and the whole world is looking at the vaccine with hopeful eyes. The development of the vaccines is essential and superior to all therapy as it will stop the COVID-19. The first human trial for such vaccines in Europe has started in Europe by taking more than 800 people for the study by taking them into two groups. One group will be receiving the COVID-19 vaccine, and the second will act as a control receiving a vaccine against meningitis but not against the CoV without knowing who will get which vaccine. This vaccine, "ChAdOx1 nCoV-19," is developed by Professor Sarah Gilbert and the Jenner Institute, Oxford University, in three months and under the phase II clinical trial.[103] So far, two vaccines have been approved, i.e., Sputnik V was approved by the Gamaleya Research Institute in Moscow on August 11th by the Ministry of Health of the Russian Federation,[104] and there is another EpiVakCorona, also without registering phase III clinical, regulatory approval.[105] Experts have expressed considerable concern about the vaccine's safety and efficacy, given that it has not yet entered phase III clinical trials. Also given tests, the three vaccines, namely "BNT162" from Pfizer and BioNTech, "mRNA-1273" from Moderna and "AZD1222" from AstraZeneca and the University of Oxford, have been funded for phase III clinical trials by Operation Warp Speed (OWS) in collaboration with the United States Department of Federal Government.[106] The Chinese COVID-19 vaccine "BBIBP-CorV" is safe and effective in phase I and II trials, developed by researchers at the Beijing Institute of Biological Products Co. Ltd.[107] Sanofi, in collaboration with GlaxoSmithKline Plc. has been developing the vaccine and under the clinical trials phase II and ready to start phase III clinical trials before 2020. In collaboration with Translate, Sanofi developed another high level of protective neutralizing antibody, currently in an early animal study, and ready to go for the clinical trials in a later year.[108] Other vaccines have also been developed and under the pre-clinical and clinical trial stages. Hopefully, safe and efficacious vaccines will be approved for use, and the vaccination may reduce the infection of SARS-CoV-2 and deaths due to the COVID-19.

Genes for the S-protein present on the CoV surface were taken and added to the harmless virus for making the vaccine. This vaccine is then injected into the patients where on entering the cell, it will start producing S-protein for CoV and prompts the immune system to produce antibodies and activation of killer T-cells, thus helping in the

destruction of infected cells. If the patient reencounters the virus in the future, the T-cells and antibodies will trigger to fight against the virus.[109]

D. Anti-Coagulants as Lifesavers

In COVID-19-patients, it is generally diagnosed with thrombocytopenia, increased fibrinogen, and D-Dimer levels.[110] In the first stage of infection, SARS-CoV-2 uses the abundant expression of ACE2 in type II alveolar cells to enter vascular endothelial cells.[111] Then, platelet adhesion/aggregation and increased thromboembolism incidence, mainly in the microvasculature.[112] As outlined by Qin et al., the production of various pro-inflammatory cytokines and elevated levels of infection-related biomarkers contributes to a pro-coagulant state promoting platelets' activation and expression of tissue factor in COVID-19. They also characterized hyper-inflammation different levels of various cytokines, i.e., TNF-α, IL-6, and IL-1, which leads to an increase of plasma concentrations of fibrinogen and activation of T cells, CD4 and $CD8^+$ T cells and their essential role for controlling the viral replication, limiting the spread of virus, inflammation and cleaning the infected cells.[113] Currently, clinicians agree the coagulopathy is a common complication of the novel coronavirus SARS-CoV-2 and the use of anticoagulation in critically ill COVID-19-patients, reduced venous thromboembolism (VTE), and cerebrovascular accidents risk scores.[114] McGovern et al. investigated the therapeutic effect of low molecular weight heparin (LMWH) as an anticoagulant in COVID-19. They found that clinical trajectory was enhanced after the initial dose of LMWH. In resulting, platelet count, ECG was normal and showed no pulmonary embolism evidence.[115]

E. Traditional Use of Plants and Herbs for the COVID-19

There are numerous plant/herbal products, and their derivatives are used as traditional medicines and effective against various virus infections such as rabies virus, H1N1, HIV, Enterovirus, Japanese Encephalitis virus, etc.[116] There are several pieces of evidence that a large number of herbal medicines or their components have demonstrated possible antiviral activity to date. Nevertheless, there is a lack of substantial research on the development of anti-SARS-CoV-2 agents from such natural products to prevent and combat SARS-CoV-2. Based on previous research, the following section of the review aims to sketch the current possibilities of plants/herbs and herbal products to prevent and treatment against SARS-CoV-2 infection.

1. Plants and Herbs for Preventive and Prophylactic Treatment and Symptomatic Management

a. Tinospora cordifolia

Tinospora cordifolia (Guduchi) has active chemical constituents such as steroids, alkaloids, diterpenoid lactones, glycosides, aliphatics, etc., are extracted from the root, stem,

and whole plant.[117] The active constituents such as N-formylannonain, magnoflorine, 11-hydroxymustakone, cordifolioside A, N-methyl-2-pyrrolidone, syringe, and tinocordiside[118] have been documented to have possible cytotoxic and immunomodulatory effects.[119,120] These active constituents have been reported to work by boosting macrophages' phagocytic operations and generating reactive oxygen species (ROS) in human neutrophil cells.[121] The aqueous extract affects the cytokine production, mitogenicity, and stimulation of immune effector cells.[117] Guduchi's immunomodulatory activity attributed to the Synergistic effects of active constituents, cordifolioside A and syringin, which is well reported.[118] Hence because of positive effects like boosting phagocytic of macrophages and ROS in human neutrophil cells, cytokine production, mitogenicity, and stimulation of immunomodulator response, it can be used in combat against COVID-19.

b. Andrograhis paniculata

The extract of *Andrographis paniculata* is traditionally used as a medicine to treat various diseases globally. The main active constituents of *A. paniculata* are andrographolide, 14-deoxyandrographolide, and 14-deoxy-11,12-didehydroandrographolide.[122] Andrographolide is a diterpenoid lactone,[123] and it is used as an antiviral, anti-bacterial, and immunity regulator. It has a broad spectrum of antiviral properties and inhibits various viral infections such as influenza A virus, dengue virus, and human immunodeficiency virus.[124] Andrographolide may be a suitable drug for the treatment of COVID-19 because it can bond well with the key targets such as spike protein, 3CL.pro, ACE2, RdRp, and PLpro, and it has potential efficacy against such virus.[124]

c. Cydonia oblonga

Cydonia oblonga (quince) is a pome fruit that belongs to the family Rosaceae. Quince fruit is a good source of flavonoids, phenolic acids, cell-wall polysaccharides, fibers, organic acid, minerals (potassium, phosphorus, and calcium), and sugar.[125] Quince fruit extract with citrus juice reduces TNF-α, histamine, and IL-8 from mast cells induced by phorbol myristate acetate and Immunoglobulin-E (IgE) during allergic disorders, and inhibit the release of eotaxin from bronchial epithelial cells of human.[126] Hot water extract of quince fruit reduces the IgE, IL-13, and TNF-α expression and suppresses prostaglandin D2 and leukotriene C4 production in bone marrow-derived mast cells, Lipopolysaccharide of quince also inhibit the stimulation of pro-inflammatory cells.[127] The phenolic extracts of quince fruit exhibit better antioxidant properties than ascorbic acid and chlorogenic acid when DPPH (2,2′-diphenyl-1picrylhydrazyl) radical scavenging system and linoleic acid peroxidation system was used for comparison. Methanolic extracts of quince fruit and seed prevent the oxidative hemolysis of human erythrocytes by inhibiting 2,2′-azobis (2-amidinopropane) dihydrochloride (AAPH).[128,129] All these properties of quince fruit will help in the treatment of SARS-CoV-2 infections.

d. Zingiber officinale

Active components of *Zingiber officinale* (ginger) are isolated from their roots and rhizomes.[130] It contains many volatile and non-volatile oils (gingerol, zingiberene, β-sesquiphellandrene, bisabolene, farnesene, β-phellandrene, cineol, citral), enzymes (allinase, myrosinase, and peroxidase), and other Sulphur containing compounds (allicin, ajoene, and alliin).[131] Traditionally, it has been used to treat colds, bronchitis, indigestion, and antiviral agents. Gingerol, an active component of ginger, has been reported to give immunomodulatory and anti-inflammatory activity. The n-gingerol prevents T helper 2 cells mediated immune response and airway inflammation, whereas 6-gingerol suppresses eosinophilia[132] and inhibits TNF-α, IL-1β, and IL-12 production.[133,134] In a cell line study on human respiratory tract cells, it has been found that fresh ginger dose-dependently inhibited viral attachment and internalization. At high concentrations, it can stimulate mucosal cells to secrete IFN-β that possibly contributed to counteracting viral infection.[135] In an *in silico* study, it has also been reported that 8Gingerol and 10Gingerol are significantly active against COVID-19 with a significant Glide score more (−5.47) than currently used drug HCQ.[136]

e. Aloe barbadensis

Aloe barbadensis (*Aloe vera; A. vera*) gel contains a large number of bioactive ingredients, such as vitamins, amino acids, trace elements, polysaccharides, and anthraquinones; as such, it has antibacterial, anti-inflammatory, antioxidant, wound healing-promoting, and immunity-enhancing functions.[137,138] *A. vera* can function as nutritional support for patients who are infected with HIV in clinical trials and can simultaneously affect the viral capability of replication.[139] *A. vera* also shows antiviral activity may be due to indirect or direct effects. The indirect effect is due to stimulation of the immune system, and direct effect is due to anthraquinones. The anthraquinone aloin inactivates various enveloped viruses such as *Herpes simplex*, *Varicella zoster*, and influenza.[140] *A. vera* gel extracts are conducive to treating genital herpes in males.[141] Acemannan polysaccharide is a representative acetylated mannan extracted from *A. vera* gel and has been approved by the USFDA for the treatment of AIDS in humans.[142] Gauntt et al.[143] also reported that Aloe polymannose can increase the titers of specific antibodies in mice infected with coxsackievirus B3, thereby inducing antiviral effects. Therefore, it can be speculated that *A. vera* may have great potential to inhibit SARS-CoV-2 infection.

f. Azadirachta indica

Indian origin traditional medicinal plant *Azadirachta indica* (Neem) has been used to treat several acute and chronic diseases. The insecticidal, larvicidal, antimalarial, antibacterial, antiviral, and spermicidal effect of different plant parts, including flowers, leaves, seeds, and barks, helps to treat several microbial diseases.[144] Water extracted polysaccharides (pectic arabinogalactan) from Neem leaves were found to have antiviral

activity against bovine herpesvirus type-1.[145] Neem leaves derived polysaccharides were also observed to have an *in vitro* antiviral potential against poliovirus type 1.[146] Neem seed kernel, bark extract, and neem oil were observed to have *in vitro* antiviral effect against the duck plague virus,[147] herpes simplex virus type-1,[148] and polio,[149] respectively. Aqueous extract of neem leaves was found to have both *in vivo* and *in vitro* antiviral potential against dengue virus type-2.[150] Neem leaf crude extract and twig is a widely used Ayurvedic medicine to treat normal fever and malarial fever,[151] and cough and asthma, respectively.[152] Diarrhea is another commonly observed clinical symptom for COVID-19–infected patients. Neem leaves are used to treat gastrointestinal disorders like diarrhea in India's different parts as a traditional practice.[153] Neem leaves extract was reported to induce a cell-mediated and humoral immune response in the albino mice model.[154] Aqueous preparation of Neem leaf was also observed to enhance Th1 type immune responses against breast tumor-associated antigen in mice and rats.[155] Similarly, Neem leaf extract was found to enhance HIV/AIDS patients' immunity by increasing $CD4^+$ cell levels.[156]

g. Withania somnifera

Withania somnifera, widely known as ashwagandha, among the most important medicinal plants in the traditional ayurvedic medicinal system, is used in more than 100 ancient ayurvedic formulations, and is considered to be therapeutically similar to ginseng.[157] It is often used as an antiviral herbal medication to treat venereal diseases caused by the herpes simplex virus among African tribes[158] and has been reported to have anti-influenza properties.[159] The main active chemical constituents of *Withania somnifra* is withanolides and has a significant role in frequent stress, improve brain and cognitive function, sustain glucose and lipid metabolism within the normal range, and strengthen the immune system. In a recent molecular docking study on ashwagandha's active constituents, it was found that withanone was well docked in the binding domain of the AEC2-RBD complex and dramatically reduced the electrostatic binding energy component of the ACE2-RBD complex. Such disruption of electrostatic interactions involving RBD and ACE2 leads to an obstruction in the entry of SARS-CoV-2 and its eventual infectivity.[160]

h. Emblica officinalis

Emblica officinalis (embelic myrobalan or Indian gooseberry or amla) embraces a sacred position in the ayurvedic medicine system and is native to mixed tropical Indian deciduous forests.[161] It is stated to comprise phenolic constituents such as gallic acid and its derivatives, mucic acid, and its derivatives, corillagine, chebulagic acid, putrajivain A,[162,163] tannins such as pedunculagin, punigluconin, and emblicanin A and B,[164] flavonoid compound quercetin,[165] and alkaloids (phyllantin and phyllantidin).[166] It was also reported to have high levels of vitamin C and significantly high levels of amino acids, minerals, and proteins such as proline, lysine, cysteine, alanine, aspartic acid,

and glutamic acid. Fruits also contain glucose, sugar, phosphorus, iron, and calcium.[167] Numerous studies have shown that the fruit extract is highly immunomodulatory when chromium (VI) has been used as immunosuppressive medication. The fruit also possesses anti-apoptotic properties and prevents DNA degradation, thus counteracting the immunosuppressive activity of chromium (VI) on immune functions.

Moreover, the fruit significantly enhances the development of IFN-γ and IL-2. This helped restore antioxidant status against chromium (VI) by getting free radical production back under control.[168,169] In another study, the immunostimulatory function of the aqueous extract of *Emblica officinalis* has been shown to increase white blood cell count significantly and the percent distribution of lymphocytes in treated mice, indicating its potential to strengthen the hemolymphopoietic system.[169] All these findings revealed the stimulating effect of *Emblica officinalis* for both cell-mediated and humoral immune responses. Therefore, it may play a worthy role in the treatment of viral infection.

i. Ocimum sanctum

Ocimum sanctum (sacred basil or tulsi) was used as a demulsifier, stimulant, and potent expectorant since ancient times. It has also been used to treat respiratory tract infections, chest infections, and skin infections.[34] The leaf of *O. sanctum* is consumed with the common belief that it strengthens immunity. This argument was tested in laboratory animals. When rats administered with methanolic extract of *O. sanctum* were exposed to typhoid H-antigen and sheep erythrocytes, it triggered a noticeable improvement in antibody titer in each group in comparison to saline-treated controls. It was also observed that the propensity of erythrocyte rosette formation in tulsi-treated animals was more significant than the saline control group.[170] The fresh leaf extract of tulsi obtained from steam distillation stimulated humoral immune responses among laboratory rats. It was demonstrated by an improved count of anti-sheep erythrocyte hemagglutination titer and IgE antibody titer evaluated by passive skin anaphylaxis in rats. Antigen mediated histamine secretion from peritoneal mast cells of attuned rats *in vitro* was substantially blocked by fresh leaves extract of tulsi.[171] Along with this, humoral and cellular immunity was found to be potentiated in non-stressed and restrain-stressed laboratory rats after administering tulsi seed oil, which is again confirming its immunomodulatory capacity.[172]

j. Curcuma longa

Curcuma longa (turmeric) is used as a spice in India and is derived from the plant's rhizomes, which belong to the family Zingiberaceae. From ancient times, it is used as an Ayurvedic medicine for the treatment of inflammation.[173] It is used effectively in the coagulation of blood and immune stimulation.[174] An aqueous extract of Curcuma longa, along with honey and lemon juice, effectively treats the common cold, viral infections.[175] Curcumin is a principal active constituent of *C. longa*, and it is responsible for yellowish color. Demethoxycurcumin and bisdemethoxycurcumin are other active constituents of *C. longa*.[173] Curcumin is an antiviral agent and inhibits several viral

infections such as influenza A, Zika, HIV, hepatitis, etc. The mechanism of curcumin action includes- inhibition of entry of the virus into the cells, stimulation of IFNs and some cytokines, and suppression of viral replication. Curcumin also inhibits viral growth by binding with spike protein and ACE-2 receptors,[174] which means it is a natural ingredient that may help in treatment.

k. Allium cepa

Allium cepa (onion) contains quercetin, zalcitabine, allicin, ribavirin, and kaempferol as the main phytoconstituent strong inhibitory effect on virus multiplication.[176] These phytochemicals present in onion have been observed to block the formation of protein and genetic material in the virus.[177,178] Onion extracts effectively decreased the New Castle disease virus infection by blocking the virus's attachment with the cell[179] and reducing the infection of potato virus Y.[180] Quercetin is also associated with an anti-infective and anti-replicative effect on viruses such as poliovirus, hepatitis viruses, influenza type A virus (IAV).[177] Quercetin acts against the entry of the virus into the host cell. For example, hemagglutinin and neuraminidase are envelope glycoproteins responsible for the entry of the Influenza virus. This glycoprotein helps in membrane fusion of the virus to the host cell.[181] Quercetin was observed to interact with haemagglutinin protein, which resulted in the inhibition of virus entry into the cell.[182] Quercetin and its derivatives have been proved to inhibit the translation of poliovirus RNA,[177] inhibit the translation process of the hepatitis C virus,[183] inhibit the SARS-CoV protease in SARS-CoV[176] and disrupt the activation of RNA polymerase in Rhinovirus proteases.[184] Quercetin can change proinflammatory cytokine activities in dengue virus-infected cells[185] and blocks cleaving eukaryotic initiation factor (eIF)-4GI and eIF4GII in rhinovirus release protease which attack host cells by cleaving eukaryotic initiation factor (eIF)-4GI and eIF4GII,[186] by which minimize the formation of viral capsid protein. Quercetin 3-O-D-glucoside, a quercetin derivative, was demonstrated to target the Ebola virus's entry into the host cell.[187] Other components present in onion also affect the immune system during viral infections by inhibiting the release of pro-inflammatory cytokines such as IL-6 and TNF-α.[188] Allicin has a high amount of selenium and sulfur, which impart antioxidant effect by reacting with intracellular thiol compounds.[189] Therefore, onion's chemical constituents may help suppress SARS-CoV-2 viral infection via avoiding viral entry through interacting with haemagglutinin protein as well as by modulation of immunity.

l. Allium sativum

Allium sativum (garlic) is an herb grown around, and garlic is also considered to possess potent antiviral properties. The garlic is effective against cytomegalovirus,[190] rhinovirus, HIV, herpes simplex virus 1 and 2,[191,192] common cold virus,[193] infectious bronchitis virus,[194] and influenza A and B viral.[195] Phytochemicals such as azin, allele alcohol, and diallyl disulfide in garlic may work against HIV-infected cells.[194] Organosulfur compounds like allicin, diallyl trisulfide, and ajoene have antiviral properties.[192] In an

experimental study, compounds like diallyl disulfide, diallyl sulfide, and alliin considerably reduced inflammation during dengue virus infection.[196] The effects of garlic must be evaluated against the SARS-CoV-2 infection.

m. Glycyrrhiza glabra

Glycyrrhiza glabra (licorice) is an herbaceous perennial legume used as a medicinal remedy and flavoring agent from ancient times. The root of licorice has been widely used to treat cough.[197] Glycyrrhizic acid is a major active component isolated from licorice. Other active constituents of licorice are thymol and carvacrol, which have significant bactericidal and antiviral effects. Licorice has a protective effect on lung inflammation. SARS-CoV-2 has the receptor ACE2, and glycyrrhizic acid potentially binds to this receptor and has the potential to treat SARS-CoV-2.[124] Glycyrrhizic acid also plays an essential role in inhibiting immune hyperactivation.[124]

n. Lycoris radiata

The root and bulb of *Lycoris radiata* (red spider lily) are used to treat swellings and ulcers, and emetic and expectorant. The active constituents such as lycorine, crinine, galanthamine, tazettine, narciclasine, lycorenine, homolycorine, and montanine are present in herb red spider lily.[198] Recently, Islam et al.[199] reported that the extract of lycoris radiata and extracts of *Lycoris radiata* with *Rheum officinale Baill* and *Polygonum multiflorum Thunb*. are effective against SARS-CoV. Besides, compounds such as lycorine, homoharringtonine, silvestrol, ouabain, tylophorine, and 7-methoxycryptopleurine have potent inhibitory effects against CoV species by inhibiting the entry of the virus into host cells.[199]

o. Houttuynia cordata

The traditional Chinese medicine plant *Houttuynia cordata* has been used by scientists to treat various disorders, including SARS, although there is no high-quality clinical research to confirm such use is safe or effective. Lau et al.[200] reported that *Houttuynia cordata* inhibits two critical proteins of SARSCoV, such as 3-chymotrypsin-like protease (3CLpro) and RdRp. The extract also increased $CD4^+$ and $CD8^+$ cell counts in test animals, suggesting its immunostimulatory effect, which may be an added advantage and its role in slowing viral replication.[200] The phytoconstituents of *Houttuynia cordata,* such as quercetin, rutin, cinanserin (1 and 2 dpi), etc., are effective against murine CoV.[201]

p. Other Drugs

The various medicinal plants have great potential against the COVID-19 prophylaxis, treatment, and systemic relief. Some of the other plants/herbs that have the possibility

in the COVID-19 treatment are discussed. The herbal extract of *Rehum palmatum*[202] and *Litchi chinensis*[203] and root extract of *Isatis indigotica*[204] have the inhibitory effect of 3CLpro. The phytoconstituents such as sinigrin obtained from *Brassica nigra*, Indigo from *Indigofera tinctorial,* hesperetin from *Citrus reticulate*, quercitin from *Grevillea robusta*, epigallocatechin gallate, and gallocatechin gallate from *Grevillea robusta* have the inhibitory effect on 3CLpro.[204,205] Betulinic acid (obtained from *Z. jujube*) is a pentacyclic lupane-type triterpene that exhibits antimalarial, anthelmintic, anti-inflammatory, antinociceptive, anticancer, and antibacterial properties and also used in the treatment of HIV infection. Betulinic acid is extensively present in *Z. jujuba*. Lupane triterpenoids inhibit the reproduction of viruses and proteinase activity.[206] Eun et al. studied the antiviral activity of betulinic acid using influenza A/PR/8/34 virus as a sample and found that 98% antiviral activity at 50 μM concentration of betulinic acid and 30% at 10 μM concentration. Betulinic acid decreases the level of IFN-γ and reduces the inflammation related to the virus attack.[207] *Bryonia alba* is traditionally used in the treatment of frontal pain, cough, inflammation of serous tissues, typhoid, pneumonia, jaundice, rheumatism, and as heart tonic[208] and as a prophylactic agent for the treatment of chikungunya in India.[209] The fruits and seed oil *Cordia myxa* showed significant anti-inflammatory activity.[210] Another plant, *Toxicodendron radicans*, also known as *Rhus toxicodendron* (poisonous ivy), is diluted to make traditional preparations. The dilution used in homeopathic medicine is prescribed for many complaints, including chickenpox, back pain, colds, herpes, hives, flu, mumps, measles, sore throat, nerve pain, muscle strains and sprains, dermatitis, arthritis, and rheumatism.[211,212] Another plant, *Eupatorium perfoliatum*, is used to treat diseases like the common cold, influenza, malaria, and immune-stimulating agent.[213] Herbacetin is one of the essential active constituents and has antiviral activity. It has excellent oral bioavailability, and it is a potential candidate to treat SARS-CoV-2 infection. SARS-CoV-2 has the receptors main protease and spike protein, and herbacetin potentially bind to these receptors and have the potential to treat SARS-CoV-2.[214] Another plant, *Adhatoda vasica*, contains alkaloids such as vasicine, a bronchodilator, and respiratory stimulant.[215]

The current scenario is needed to explore various plants/herbs and their constituents for the effective treatment of COVID-19. Previously studied plants and phytoconstituents, including antiviral effects, immune boosters, a bronchodilator, and other systemic relief, should be studied exhaustively in the context of SARS-CoV-2 infection.

VI. CAN TARGETING POSSIBILITY FOR THE PROTEIN AVAILABLE OF THE SURFACE

There are currently various research and clinical studies in progress for the various therapeutic drugs and prophylactic vaccines, but none have been approved for specific SARS-CoV-2 infection. As already discussed, S-protein (consists of two subunits, S1 and S2) is responsible for interacting with host cell receptors and entering into the cells by binding to the ACE2 through the RBD enables the virus entry and replication inside the cells.[216–218] Therefore, S-protein may be one of the key targets to develop the prophylactic

vaccine and therapeutic drugs. *In silico* molecular docking studies of USFDA-approved LOPAC library drugs against S-protein and the ACE2 host cell receptor were performed by the researchers and revealed that KT185, KT203 GSK1838705A, BMS195614, and RS504393 were identified as binding to the RBD whereas eptifibatide acetate, TNP, GNF5, hydrochloride hydrate GR 127935 and RS504393 have been shown to bind to ACE2 receptor.[219] Similarly, Cavasotto and Filippo perform the *in silico* molecular modeling of drugs and compounds (USFDA approved; under clinical trials) against three S-protein and two proteases (3CLpro and PLpro), which process the two viral polyproteins encoded by ORFs orf1a and orf1b. The experiment findings showed the potential inhibition of the 3CLpro with drug ID DB02747, DB04692, DB04722, and DB03311, whereas inhibition of PLpro was associated with the drug ID CH3360203, DB13635, DB11871, DB01340, CH77517, DB05932, DB13327, DB01748, DB08656, DB02861, and DB02429. Additionally, the potential S-protein binding inhibitors with ACE2 receptors were DB06813, DB13553, DB12126, DB12631, DB11842, and CHEMBL 4297618.[220] These findings need further clinical research for better efficacy against the COVID-19 treatment. The antibodies that target the SARS-CoV-2 S-protein may be prominent tools to inhibit the virus's entry inside the cells. Walls et al. also suggested that the SARS-CoV S mouse polyclonal sera inhibiting the entry of SARS-CoV-2 S pseudotyped viruses and leads to neutralization of the virus.[221] Recent research focuses on the TMPRSS2 because it employs S-protein priming after the S-protein engaged ACE2 for entry.[82,222] In that respect, Hoffmann et al. demonstrated that the serine protease inhibitor (camostat mesylate) is active against TMPRSS2 and responsible for the partial blockage of their entry into Caco-2 and Vero-TMPRSS2 cells which were infected pseudotyped virus particles bearing SARS-Cov-2 S protein.[82] Additionally, TMPRSS2, the proprotein convertase furin, cleaved the S-protein at the S1/S2, an essential step for the activation of SARS-CoV-2 in the human air passage. It may provide promising drug targets for the SARS-CoV-2 infection. The combination of TMPRSS2 and furin inhibitors showed the potential antiviral activity against COVID-19.[223]

It is already discussed that the entry of SARS-CoV-2 dependent on the binding of the surface unit, i.e., S1and S2 of S-protein to a cellular receptor and virus fusion with the cellular membrane, respectively.[82] These S1 and S2 may be exploited to block ACE2 and S-protein interaction, leading to entering the viruses inside the cells. The docking analysis of some flavonoids-SARS-CoV-2 interaction showed that the C-terminal of S1 and S2 domain can bind with flavonoids like hamferol and curcumin pterostilbene, and HCQ.[224] Wang et al. developed a monoclonal antibody for the S1 targeting from the immunized transgenic mice expressing variable heavy and light chains of human Ig, which can cross-neutralize SARS-CoV and SARS-CoV-2, using a mechanism that is independent of inhibition of binding to SARS-CoV-2 and SARS-CoV receptors.[225] The blockage of SARS-CoV-2-RBD-ACE2 interaction may other valuable targets to neutralize the COVID-19. Chen X et al. cloned the two human blocking monoclonal antibodies using SARS-CoV-2 RBD-specific memory B cells isolated from recovered COVID-19 patients. These monoclonal antibodies can specifically bind to SARD-CoV-2 RBD, interfere with the interaction between the SARS-CoV-2 RBD and the ACE2 receptor,

and lead to effective neutralization of infection by SARS-CoV-2 S-protein pseudotyped virus infection.[218]

Other than the S-protein, the M-protein and E-protein may also be exploited to protect the SARS-CoV-2. These glycoprotein proteins (M and E) play a critical role in virus morphogenesis and assembly via their interactions with other viral proteins. The M-protein's active sites are Lys50, Leu51, Leu54, Leu93, and Ala98, which may need to be further evaluated with the novel antivirals as well as USFDA-approved drugs for repurposing against SARS-CoV-2 by rational design and docking studies.[226] E-protein may also be an essential virulence factor because it was reported to trigger lymphocytes' apoptosis and causes lymphopenia. Lymphopenia is one of the causes of mortality due to COVID-19. In recent report showed that the E-protein of SARS-CoV-2 has C-terminal Bcl-2 homology 3 like motif that could be a potential therapeutic target.[227]

VII. CONCLUSIONS AND FUTURE PROSPECTIVES

COVID-19 is a pandemic and has affected most of the countries in the world. By April 28, 2020, COVID-19 has nearly three million cases and killed more than 211 thousand people worldwide. Until recently, there have been no vaccines and therapeutics available for the treatment. Due to the high rate of community spreads, most of the countries have imposed lockdown to stop/slow down the virus's spread. The lockdown may also affect the world economy. There is a need to develop vaccines and therapeutics for the prevention and treatment against SARS-CoV-2 infection. The S-protein, E-protein, M-protein, SARS-CoV-2-ACE2 complex, serine protease inhibitor, TMPRSS2, S1, S2, RBD-SARS-CoV-2 interaction, etc., are identified as the potential target for the development of treatment against SARS-CoV-2 infection. The plasma convalescent therapy is under clinical trial for the treatment of COVID-19. The antibodies are under investigation, which can interact and neutralize the virus. The antiviral drugs and pre-existing drugs such as chloroquine, HCQ, etc., are under trial for treatment in COVID-19. Various plants/herbs and new molecules are under consideration for treatment possibility in COVID-19. All these will result in a successful treatment against the COVID-19 pandemic.

REFERENCES

1. Liu Y, Gayle AA, Wilder-Smith A, Rocklov J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med. 2020;27(2):taaa021.
2. Vogt TM, Guerra MA, Flagg EW, Ksiazek TG, Lowther SA, Arguin PM. Risk of severe acute respiratory syndrome-associated coronavirus transmission aboard commercial aircraft. J Travel Med. 2006;13(5):268–72.
3. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, Bucci E, Piacentini M, Ippolito G, Melino G. COVID-19 infection: The perspectives on immune responses. Cell Death Differ. 2020;27(5):1451–4.
4. Wilder-Smith A, Freedman DO. Isolation, quarantine, social distancing and community containment: Pivotal role for old–style public health measures in the novel coronavirus (2019–nCoV) outbreak. J Travel Med. 2020;27(2):taaa020.

5. Patel DJ, Patel V. A review of the current state of management and post–recovery rehabilitation of COVID-19. Crit Rev Phys Rehabil Med. 2020;32(2):97–109.
6. World Health Organization. Coronavirus disease (COVID-19) situation report 152 [cited 2020 Jun 20]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200620-covid-19-sitrep-152.pdf?sfvrsn=83aff8ee_2.
7. Woo PC, Huang Y, Lau SK, Yuen KY. Coronavirus genomics and bioinformatics analysis. Viruses. 2010;2(8):1804–20.
8. Mousavizadeh L, Ghasemi S. Genotype and phenotype of COVID-19: Their roles in pathogenesis. J Microbiol Immunol Infect. In press 2020.
9. Schoeman D, Fielding BC. Coronavirus envelope protein: Current knowledge. Virol J. 2019; 16(1):69.
10. de Haan CA, Te Lintelo E, Li Z, Raaben M, Wurdinger T, Bosch BJ, Rottier PJ. Cooperative involvement of the S1 and S2 subunits of the murine coronavirus spike protein in receptor binding and extended host range. J Virol. 2006;80(22):10909–18.
11. Neuman BW, Kiss G, Kunding AH, Bhella D, Baksh MF, Connelly S, Droese B, Klaus JP, Makino S, Sawicki SG, Siddell SG, Stamou DG, Wilson IA, Kuhn P, Buchmeier MJ. A structural analysis of M protein in coronavirus assembly and morphology. J Struct Biol. 2011;174(1):11–22.
12. Sturman LS, Holmes KV, Behnke J. Isolation of coronavirus envelope glycoproteins and interaction with the viral nucleocapsid. J Virol. 1980;33(1):449–62.
13. Mortola E, Roy P. Efficient assembly and release of SARS coronavirus-like particles by a heterologous expression system. FEBS Lett. 2004;576(1-2):174–8.
14. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronaviruses: Drug discovery and therapeutic options. Nat Rev Drug Discov. 2016;15(5):327–47.
15. Kaul D. An overview of coronaviruses including the SARS-2 coronavirus: Molecular biology, epidemiology and clinical implications. Curr Med Res Pract. 2020;10(2):54–64.
16. Cheng VC, Lau SK, Woo PC, Yuen KY. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. Clin Microbiol Rev. 2007;20(4):660–94.
17. Kuo L, Hurst KR, Masters PS. Exceptional flexibility in the sequence requirements for coronavirus small envelope protein function. J Virol. 2007;81(5):2249–62.
18. Weiss SR, Navas-Martin S. Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus. Microbiol Mol Biol Rev. 2005;69(4):635–64.
19. Wang L, Wang Y, Ye D, Liu Q. Review of the 2019 novel coronavirus (SARS-CoV-2) based on current evidence. Int J Antimicrob Agents. 2020;55(6):105948.
20. Abduljalil JM, Abduljalil BM. Epidemiology, genome, and clinical features of the pandemic SARS-CoV-2: A recent view. New Microbes New Infect. 2020;35:100672.
21. Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. J Med Virol. 2020;92(4):418–23.
22. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res. 2020;24:91–8.
23. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. Lancet. 2020;395(10224):565–74.
24. Decaro N, Lorusso A. Novel human coronavirus (SARS-CoV-2): A lesson from animal coronaviruses. Vet Microbiol. 2020;244:108693.
25. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020;10(2),102–8.
26. Ma J. Coronavirus (COVID-19): History, current knowledge and pipeline medications. Int J Pharm Pharmacol. 2020;4(1):1–9.

27. Fehr AR, Perlman S. Coronaviruses: An overview of their replication and pathogenesis. Methods Mol Biol. 2015;1282:1–23.
28. Jendrach M, Thiel V, Siddell S. Characterization of an internal ribosome entry site within mRNA 5 of murine hepatitis virus. Arch Virol. 1999;144(5):921–33.
29. de Haan CA, Smeets M, Vernooij F, Vennema H, Rottier PJ. Mapping of the coronavirus membrane protein domains involved in interaction with the spike protein. J Virol. 1999;73(9):7441–52.
30. Krijnse-Locker J, Ericsson M, Rottier PJ, Griffiths G. Characterization of the budding compartment of mouse hepatitis virus: Evidence that transport from the RER to the Golgi complex requires only one vesicular transport step. J Cell Biol. 1994;124(1-2):55–70.
31. Petrov D. Photopolarimetrical properties of coronavirus model particles: Spike proteins number influence. J Quant Spectrosc Radiat Transf. 2020;248:107005.
32. Robson B. COVID-19 coronavirus spike protein analysis for synthetic vaccines, a peptidomimetic antagonist, and therapeutic drugs, and analysis of a proposed achilles' heel conserved region to minimize probability of escape mutations and drug resistance. Comput Biol Med. 2020;121:103749.
33. Ou X, Liu Y, Lei X, Li P, Mi D, Ren L, Guo L, Guo R, Chen T, Hu J, Xiang Z, Mu Z, Chen X, Chen J, Hu K, Jin Q, Wang J, Qian Z. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross–reactivity with SARS-CoV. Nat Commun. 2020;11(1):1620.
34. Sun J, He W-T, Wang L, Lai A, Ji X, Zhai X, Li G, Suchard MA, Tian J, Zhou J, Veit M, Su S. COVID-19: Epidemiology, evolution, and cross-disciplinary perspectives. Trends Mol Med. 2020;26(5):483–95.
35. Vellingiri B, Jayaramayya K, Iyer M, Narayanasamy A, Govindasamy V, Giridharan B, Ganesan S, Venugopal A, Venkatesan D, Ganesan H, Rajagopalan K, Rahman P, Cho SG, Kumar NS, Subramaniam MD. COVID-19: A promising cure for the global panic. Sci Total Environ. 2020;725:138277.
36. Wang X, Xu W, Hu G, Xia S, Sun Z, Liu Z, Xie Y, Zhang R, Jiang S, Lu L. SARS-CoV-2 infects T lymphocytes through its spike protein–mediated membrane fusion. Cell Mol Immunol. 2020:17(8):894.
37. Xia S, Liu M, Wang C, Xu W, Lan Q, Feng S, Qi F, Bao L, Du L, Liu S, Qin C, Sun F, Shi Z, Zhu Y, Jiang S, Lu L. Inhibition of SARS-CoV-2 (previously 2019-nCoV) infection by a highly potent pan–coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion. Cell Res. 2020;30(4):343–55.
38. Kumar GV, Jeyanthi V, Ramakrishnan S. A short review on antibody therapy for COVID-19. New Microbes New Infect. 2020;35:100682.
39. Ahmed SF, Quadeer AA, McKay MR. Preliminary identification of potential vaccine targets for the COVID-19 coronavirus (SARS-CoV-2) based on SARS-CoV immunological studies. Viruses. 2020;12(3):254.
40. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. Nat Med. 2020;26(4):450–2.
41. Pachetti M, Marini B, Benedetti F, Giudici F, Mauro E, Storici P, Masciovecchio C, Angeletti S, Ciccozzi M, Gallo RC, Zella D, Ippodrino R. Emerging SARS-CoV-2 mutation hot spots include a novel RNA-dependent-RNA polymerase variant. J Transl Med. 2020;18(1):179.
42. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. J Thorac Oncol. 2020;15(5):700–4.
43. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420–2.
44. Nicholls JM, Poon LL, Lee KC, Ng WF, Lai ST, Leung CY, Chu CM, Hui PK, Mak KL, Lim W, Yan KW, Chan KH, Tsang NC, Guan Y, Yuen KY, Peiris JS. Lung pathology of fatal severe acute respiratory syndrome. Lancet. 2003;361(9371):1773–8.
45. Franks TJ, Chong PY, Chui P, Galvin JR, Lourens RM, Reid AH, Selbs E, McEvoy CP, Hayden CD, Fukuoka J, Taubenberger JK, Travis WD. Lung pathology of severe acute respiratory syndrome (SARS): A study of 8 autopsy cases from Singapore. Hum Pathol. 2003;34(8):743–8.

46. Chu H, Chan JF, Wang Y, Yuen TT, Chai Y, Hou Y, Shuai H, Yang D, Hu B, Huang X, Zhang X, Cai JP, Zhou J, Yuan S, Kok KH, To KK, Chan IH, Zhang AJ, Sit KY, Au WK, Yuen KY. Comparative replication and immune activation profiles of SARS-CoV-2 and SARS-CoV in human lungs: An ex vivo study with implications for the pathogenesis of COVID-19. Clin Infect Dis. 2020;71(6):1400–9.
47. Jewett A. Novel coronavirus SARS-CoV-2 target and disable natural killer cells: Core immune effectors for fighting the disease. Crit Rev Immunol. 2020;40(2):167–71.
48. Dey S. 69% of cases found positive were asymptomatic: ICMR [updated 2020 Apr 22; cited on 2020 Apr 23]. Available from: https://timesofindia.indiatimes.com/india/69-of-cases-found-positive-were-asymptomatic-icmr/articleshow/75282825.cms.
49. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Hang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
50. Nikolich-Zugich J, Knox KS, Rios CT, Natt B, Bhattacharya D, Fain MJ. SARS-CoV-2 and COVID-19 in older adults: What we may expect regarding pathogenesis, immune responses, and outcomes. Geroscience. 2020;42(2):505–14.
51. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727–33.
52. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK, Yuen KY. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person–to–person transmission: A study of a family cluster. Lancet. 2020;395(10223):514–23.
53. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol. 2020;38(1):1–9.
54. Lee HC, Chathuranga K, Lee JS. Intracellular sensing of viral genomes and viral evasion. Exp Mol Med. 2019;51(12):1–13.
55. Wilkins C, Gale M Jr. Recognition of viruses by cytoplasmic sensors. Curr Opin Immunol. 2010;22(1):41–7.
56. World Health Organization. Coronavirus disease 2019 (COVID-19): Situation report 72 [cited 2020 Apr 23]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200401-sitrep-72-COVID-19.pdf?sfvrsn=3dd8971b_2.
57. Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents. 2020;55(4):105932.
58. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019–nCoV) in vitro. Cell Res. 2020;30(3):269–71.
59. Kupferschmidt K, Cohen J. Race to find COVID-19 treatments accelerates. Science. 2020;367(6485):1412–3.
60. Singh B, Ryan H, Kredo T, Chaplin M, Fletcher T. Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19. Cochrane Database Syst Rev. In press 2020.
61. Tripathy S, Dassarma B, Roy S, Chabalala H, Matsabisa MG. A review on possible modes of actions of chloroquine/hydroxychloroquine: Repurposing against SARS-COV-2 (COVID 19) pandemic. Int J Antimicrob Agents. 2020;56(2):106028.
62. Roldan EQ, Biasiotto G, Magro P, Zanella I. The possible mechanisms of action of 4–aminoquinolines (chloroquine/hydroxychloroquine) against SARS-CoV-2 infection (COVID-19): A role for iron homeostasis? J Pharm Res. 2020;158:104904.
63. Singh AK, Singh A, Shaikh A, Singh R, Misra A. Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries. Diabetes Metab Syndr. 2020;14(3):241–6.

64. Tan D. COVID-19 ring–based prevention trial with lopinavir/ritonavir (CORIPREV–LR) [cited 2020 Apr 23]. Available from: https://clinicaltrials.gov/ct2/show/NCT04321174.
65. Kim SH. Comparison of lopinavir/ritonavir or hydroxychloroquine in patients with mild coronavirus disease (COVID-19) [cited 2020 Apr 23]. Available from: https://clinicaltrials.gov/ct2/show/NCT04307693.
66. Schneider WM, Chevillotte MD, Rice CM. Interferon-stimulated genes: A complex web of host defenses. Annu Rev Immunol. 2014;32:513–45.
67. Sheahan TP, Sims AC, Leist SR, Schafer A, Won J, Brown AJ, Montgomery SA, Hogg A, Babusis D, Clarke MO, Spahn JE, Bauer L, Sellers S, Porter D, Feng JY, Cihlar T, Jordan R, Denison MR, Baric RS. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020;11(1):222.
68. Sallard E, Lescure FX, Yazdanpanah Y, Mentre F, Peiffer-Smadja N. Type 1 interferons as a potential treatment against COVID-19. Antiviral Res. 2020;178:104791.
69. Khalili JS, Zhu H, Mak NSA, Yan Y, Zhu Y. Novel coronavirus treatment with ribavirin: Groundwork for an evaluation concerning COVID-19. J Med Virol. 2020; 92:740–46.
70. Hung IF. Lopinavir/ritonavir, ribavirin and IFN-beta combination for nCoV treatment [cited 2020 Apr 23]. Available from: https://clinicaltrials.gov/ct2/show/NCT04276688.
71. Mok CC. Rheumatology drugs and COVID-19. J Clin Rheumatol Immunol. 2020;20(1):1–3.
72. Saha A, Sharma AR, Bhattacharya M, Sharma G, Lee SS, Chakraborty C. Probable molecular mechanism of remdesivir for the treatment of COVID-19: Need to know more. Arch Med Res. 2020;51(6):585–6.
73. Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, Patnaik S, Hall MD. Remdesivir: A review of its discovery and development leading to emergency use authorization for treatment of COVID-19. ACS Cent Sci. 2020; 6:672–83.
74. Tchesnokov EP, Feng JY, Porter DP, Gotte M. Mechanism of inhibition of Ebola virus RNA-dependent RNA polymerase by remdesivir. Viruses. 2019;11(4):326.
75. Han JA, Kim JI, Ongusaha PP, Hwang DH, Ballou LR, Mahale A, Aaronson SA, Lee SW. P53-mediated induction of Cox-2 counteracts p53-or genotoxic stress-induced apoptosis. EMBO J. 2002;21(21):5635–44.
76. Castaneda R. Gilead's remdesivir better suited to mild-to-moderate COVID-19 patients [cited 2020 Apr 24]. Available from: https://www.pharmaceutical-technology.com/comment/gilead-remdesivir-COVID-19/.
77. Duddu P. Coronavirus treatment: Vaccines/drugs in the pipeline for COVID-19 [cited 2020 Apr 25]. Available from: https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/.
78. Rizzardini G. Clinical study to evaluate the performance and safety of favipiravir in COVID-19 [cited 2020 Apr 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT04336904.
79. Dabbous H. Efficacy and safety of favipiravir in management of COVID-19 (FAV–001) [cited 2020 Apr 25]. Available from: https://clinicaltrials.gov/ct2/show/NCT04349241.
80. Glenmark Pharmaceuticals. Glenmark becomes the first pharmaceutical company in India to receive regulatory approval for oral antiviral Favipiravir, for the treatment of mild to moderate COVID-19 [updated 2020 Jun 20; cited 2020 Jun 20]. Available from: https://www.glenmarkpharma.com/sites/default/files/Glenmark-becomes-the-first-pharmaceut-cal-company-in-India-to-receive.pdf.
81. Zhang C, Zhang Y, Qin Y, Zhang Q, Liu Q, Shang D, Lu H, Li X, Zhou C, Huang F, Jin N, Jiang C. Ifenprodil and flavopiridol identified by genomewide RNA interference screening as effective drugs to ameliorate murine acute lung injury after influenza A H5N1 virus infection. mSystems. 2019;4(6):e00431–19.
82. Algernon Pharmaceuticals. Algernon submits application to Health Canada for ifenprodil COVID-19 phase 2b/3 multinational clinical trial [updated 2020 Apr 22; cited 2020 Apr 25]. Available from: https://www.globenewswire.com/news-release/2020/04/22/2019882/0/en/Algernon-Submits-Application-to-Health-Canada-for-Ifenprodil-COVID-19-Phase-2b-3-Multinational-Clinical-Trial.html.

83. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Muller MA, Drosten C, Pohlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271–80.e8.
84. Drug Target Review. Nafamostat inhibits SARS-CoV-2 infection, preventing COVID-19 transmission [updated 2020 Mar 31; cited 2020 Apr 25]. Available from: https://www.drugtargetreview.com/news/58915/nafamostat-inhibits-SARS-CoV-2-infection-preventing-COVID-19-transmission/.
85. Østergaard L. The impact of camostat mesilate on COVID-19 infection (CamoCO-19) [cited 2020 Apr 25]. Available from: https://clinicaltrials.gov/ct2/show/NCT04321096.
86. Rossi GP. Efficacy of nafamostat in COVID-19 patients (RACONA Study) (RACONA) [cited 2020 Apr 25]. Available from: https://clinicaltrials.gov/ct2/show/NCT04352400.
87. Lu H. Efficacy and safety of darunavir and cobicistat for treatment of COVID-19 (DC-COVID-19) [cited 2020 Apr 25]. Available from: https://clinicaltrials.gov/ct2/show/NCT04252274.
88. Zhang XW, Yap YL. The 3D structure analysis of SARS-CoV S1 protein reveals a link to influenza virus neuraminidase and implications for drug and antibody discovery. Theochem. 2004;681(1):137–41.
89. Azhar S. Hydroxychloroquine, oseltamivir and azithromycin for the treatment of COVID-19 Infection: An RCT (PROTECT) [cited 2020 Apr 25]. Available from: https://clinicaltrials.gov/ct2/show/NCT04338698.
90. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Dupont HT, Honore S, Colson P, Chabriere E, La Scola B, Rolain JM, Brouqui P, Raoult D. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56(1):105949.
91. Chorin E, Dai M, Shulman E, Wadhwani L, Bar–Cohen R, Barbhaiya C, Aizer A, Holmes D, Bernstein S, Spinelli M, Park DS, Chinitz LA, Jankelson L. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. Nat Med. 2020: 26:808–9.
92. Henriksen M. Anti-IL6 treatment of serious COVID-19 disease with threatening respiratory failure (TOCIVID) [cited 2020 Apr 25]. Available from: https://clinicaltrials.gov/ct2/show/NCT04322773.
93. Farzam K, Abdullah M. Acetazolamide. Treasure Island, FL: StatPearls Publishing; 2020.
94. Solaimanzadeh I. Acetazolamide, nifedipine and phosphodiesterase inhibitors: Rationale for their utilization as adjunctive countermeasures in the treatment of coronavirus disease 2019 (COVID-19). Cureus. 2020;12(3):e7343.
95. Geier MR, Geier DA. Respiratory conditions in coronavirus disease 2019 (COVID-19): Important considerations regarding novel treatment strategies to reduce mortality. Med Hypotheses. 2020;140:109760.
96. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–20.
97. Singh AK, Majumdar S, Singh R, Misra A. Role of corticosteroid in the management of COVID-19: A systemic review and a Clinician's perspective. Diabetes Metab Syndr. 2020;14(5):971–8.
98. Remmelts HH, Meijvis SC, Biesma DH, van Velzen-Blad H, Voorn GP, Grutters JC, Bos WJ, Rijkers GT. Dexamethasone downregulates the systemic cytokine response in patients with community-acquired pneumonia. Clin Vaccine Immunol. 2012;19(9):1532–8.
99. University of Oxford. Dexamethasone reduces death in hospitalised patients with severe respiratory complications of COVID-19 [updated 2020 Jun 16; cited 2020 Jun 17]. Available from: http://www.ox.ac.uk/news/2020-06-16-dexamethasone-reduces-death-hospitalised-patients-severe-respiratory-complications.
100. Cohen I, Efroni S, Atlan H. Immune computation and COVID-19 mortality: A rationale for IVIg. Crit Rev Immunol. 2020;40(3):195–203.
101. Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, Ng MH, Chan P, Wong KC, Leung CB, Cheng G.

Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis. 2005;24(1):44–6.
102. Johns Hopkins Bloomberg School of Public Health. Johns Hopkins Gets FDA OK to Test Blood Therapies for COVID-19 Patients [updated 2020 Apr 03; cited 2020 Apr 26]. Available from: https://www.jhsph.edu/news/news-releases/2020/hopkins-gets-FDA-ok-to-test-blood-plasma-therapies-for-COVID-19-patients.html.
103. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, Bellamy D, Bibi S, Bittaye M, Clutterbuck EA, Dold C, Faust SN, Finn A, Flaxman AL, Hallis B, Heath P, Jenkin D, Lazarus R, Makinson R, Minassian AM, Pollock KM, Ramasamy M, Robinson H, Snape M, Tarrant R, Voysey M, Green C, Douglas AD, Hill AVS, Lambe T, Gilbert SC, Pollard AJ. 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. 2020;396(10249):467–78.
104. Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation. An open study of the safety, tolerability and immunogenicity of the drug "Gam-COVID-Vac" vaccine against COVID-19 [cited 2020 Oct 18]. Available from: https://clinicaltrials.gov/ct2/show/NCT04436471.
105. Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector." Study of the safety, reactogenicity and immunogenicity of "EpiVacCorona" vaccine for the prevention of COVID-19 (EpiVacCorona) [cited 2020 Oct 18]. Available from: https://clinicaltrials.gov/ct2/show/NCT04527575.
106. Craven J. COVID-19 vaccine tracker [updated 2020 Oct 18; cited 2020 Oct 18]. Available from: https://www.raps.org/news-and-articles/news-articles/2020/3/COVID-19-vaccine-tracker.
107. Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, Tan W, Wu G, Xu M, Lou Z, Huang W, Xu W, Huang B, Wang H, Wang W, Zhang W, Li N, Xie Z, Ding L, You W, Zhao Y, Yang X, Liu Y, Wang Q, Huang L, Yang Y, Xu G, Luo B, Wang W, Liu P, Guo W, Yang X. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: A randomised, double–blind, placebo–controlled, phase 1/2 trial. Lancet Infect Dis. 2020;21(1):39–51.
108. Loh T. Sanofi plans human trial for experimental Covid vaccine after positive animal test results India [updated 2020 Oct 15; cited 2020 Oct 18]. Available from: https://theprint.in/health/sanofi-plans-human-trial-for-experimental-covid-vaccine-after-positive-animal-test-results/524452/.
109. Walsh F. Coronavirus: First patients injected in UK vaccine trial [updated 2020 Apr 23; cited 2020 Apr 25]. Available from: https://www.bbc.com/news/health-52394485.
110. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061–9.
111. Ziegler CG, Allon SJ, Nyquist SK, Mbano IM, Miao VN, Tzouanas CN, Cao Y, Yousif AS, Bals J, Hauser BM. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. Cell. 2020;181(5):1016–35.e19.
112. Song JC, Wang G, Zhang W, Zhang Y, Li WQ, Zhou Z, People's Liberation Army Professional Committee of Critical Care Medicine, Chinese Society on Thrombosis and Haemostasis. Chinese expert consensus on diagnosis and treatment of coagulation dysfunction in COVID-19. Military Med Res. 2020;7:1–10.
113. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, Xie C, Ma K, Shang K, Wang W. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis. 2020; 71(15):762–68.
114. Cattaneo M, Bertinato EM, Birocchi S, Brizio C, Malavolta D, Manzoni M, Muscarella G, Orlandi M. Pulmonary embolism or pulmonary thrombosis in COVID-19? Is the recommendation to use high-dose heparin for thromboprophylaxis justified? Thromb Haemost. 2020;120(8):1230–32.
115. McGovern R, Conway P, Pekrul I, Tujjar O. The role of therapeutic anticoagulation in COVID-19. Case Rep Crit Care. 2020;2020:8835627.

116. Ganjhu RK, Mudgal PP, Maity H, Dowarha D, Devadiga S, Nag S, Arunkumar G. Herbal plants and plant preparations as remedial approach for viral diseases. Virusdisease. 2015;26(4):225–36.
117. Upadhyay AK, Kumar K, Kumar A, Mishra HS. Tinospora cordifolia (Willd.) Hook. f. and Thoms. (Guduchi) – validation of the Ayurvedic pharmacology through experimental and clinical studies. Int J Ayurveda Res. 2010;1(2):112–21.
118. Sharma U, Bala M, Kumar N, Singh B, Munshi RK, Bhalerao S. Immunomodulatory active compounds from Tinospora cordifolia. J Ethnopharmacol. 2012;141(3):918–26.
119. Subramanian M, Chintalwar GJ, Chattopadhyay S. Antioxidant properties of a Tinospora cordifolia polysaccharide against iron–mediated lipid damage and gamma-ray induced protein damage. Redox Rep. 2002;7(3):137–43.
120. Kapil A, Sharma S. Immunopotentiating compounds from Tinospora cordifolia. J Ethnopharmacol. 1997;58(2):89–95.
121. More P, Pai K. In vitro NADH-oxidase, NADPH-oxidase and myeloperoxidase activity of macrophages after Tinospora cordifolia (guduchi) treatment. Immunopharmacol Immunotoxicol. 2012;34(3):368–72.
122. Kumar RA, Sridevi K, Kumar NV, Nanduri S, Rajagopal S. Anticancer and immunostimulatory compounds from Andrographis paniculata. J Ethnopharmacol. 2004;92(2-3):291–5.
123. Handa SS, Sharma A. Hepatoprotective activity of andrographolide from Andrographis paniculata against carbontetrachloride. Indian J Med Res. 1990;92:276–83.
124. Huang F, Li Y, Leung EL, Liu X, Liu K, Wang Q, Lan Y, Li X, Yu H, Cui L, Luo H, Luo L. A review of therapeutic agents and Chinese herbal medicines against SARS-COV-2 (COVID-19). Pharmacol Res. 2020;158:104929.
125. Mir S, Masoodi F, Gani A, Ganaie S, Reyaz U, Wani S. Evaluation of anti–oxidant properties of methanolic extracts from different fractions of quince (Cydonia oblonga Miller). Adv Biomed Pharma. 2015;2(1):1–6.
126. Grundemann C, Papagiannopoulos M, Lamy E, Mersch-Sundermann V, Huber R. Immunomodulatory properties of a lemon-quince preparation (Gencydo(R)) as an indicator of anti-allergic potency. Phytomedicine. 2011;18(8-9):760–8.
127. Kawahara T, Iizuka T. Inhibitory effect of hot-water extract of quince (Cydonia oblonga) on immunoglobulin E-dependent late-phase immune reactions of mast cells. Cytotechnology. 2011;63(2):143–52.
128. Pacifico S, Gallicchio M, Fiorentino A, Fischer A, Meyer U, Stintzing FC. Antioxidant properties and cytotoxic effects on human cancer cell lines of aqueous fermented and lipophilic quince (Cydonia oblonga Mill.) preparations. Food Chem Toxicol. 2012;50(11):4130–5.
129. Fattouch S, Caboni P, Coroneo V, Tuberoso CI, Angioni A, Dessi S, Marzouki N, Cabras P. Antimicrobial activity of Tunisian quince (Cydonia oblonga Miller) pulp and peel polyphenolic extracts. J Agric Food Chem. 2007;55(3):963–9.
130. Gangal N, Nagle V, Pawar Y, Dasgupta S. Reconsidering traditional medicinal plants to combat COVID-19. Res Rev J Herb Sci. 2020;9(2):29–43.
131. Gyawali R, Paudel PN, Basyal D, Setzer WN, Lamichhane S, Paudel MK, Gyawali S, Khanal P. A review on ayurvedic medicinal herbs as remedial perspective for COVID-19. J Karnali Academy Health Sci. 2020;26(3)1–21.
132. Ahui ML, Champy P, Ramadan A, Pham Van L, Araujo L, Brou Andre K, Diem S, Damotte D, Kati-Coulibaly S, Offoumou MA, Dy M, Thieblemont N, Herbelin A. Ginger prevents Th2–mediated immune responses in a mouse model of airway inflammation. Int Immunopharmacol. 2008;8(12):1626–32.
133. Tripathi S, Maier KG, Bruch D, Kittur DS. Effect of 6-gingerol on pro-inflammatory cytokine production and costimulatory molecule expression in murine peritoneal macrophages. J Surg Res. 2007;138(2):209–13.
134. Chopra RN, Nayar SL, Chopra IC. Glossary of Indian medicinal plants. New Delhi: Council of Scientific & Industrial Research; 1956.
135. San Chang J, Wang KC, Yeh CF, Shieh DE, Chiang LC. Fresh ginger (Zingiber officinale) has

anti–viral activity against human respiratory syncytial virus in human respiratory tract cell lines. J Ethnopharmacol. 2013;145(1):146–51.
136. Rajagopal K, Byran G, Jupudi S, Vadivelan R. Activity of phytochemical constituents of black pepper, ginger, and garlic against coronavirus (COVID-19): An in silico approach. Int J Health Allied Sci. 2020;9(5):43.
137. Yagi A, Byung PY. Immune modulation of Aloe vera: Acemannan and gut microbiota modulator. J Gastroenterol Hepatol. 2015;4(8):1707–21.
138. Langmead L, Makins RJ, Rampton DS. Anti–inflammatory effects of aloe vera gel in human colorectal mucosa in vitro. Aliment Pharmacol Ther. 2004;19(5):521–7.
139. Radha MH, Laxmipriya NP. Evaluation of biological properties and clinical effectiveness of Aloe vera: A systematic review. J Tradit Complement Med. 2015;5(1):21–6.
140. Sydiskis RJ, Owen DG, Lohr JL, Rosler KH, Blomster RN. Inactivation of enveloped viruses by anthraquinones extracted from plants. Antimicrob Agents Chemother. 1991;35(12):2463–6.
141. Syed TA, Cheema KM, Ahmad SA, Unit AH. Aloe vera extract 0.5% in hydrophilic cream versus aloe vera gel for the management of genital herpes in males. A placebo-controlled, doubleblind, comparative study. J Eur Acad Dermatol Venereol. 1996;7(3):294–5.
142. Kahlon JB, Kemp MC, Carpenter RH, McAnalley BH, McDaniel HR, Shannon WM. Inhibition of AIDS virus replication by acemannan in vitro. Mol Biother. 1991;3(3):127–35.
143. Gauntt CJ, Wood HJ, McDaniel HR, McAnalley BH. Aloe polymannose enhances anti-coxsackievirus antibody titres in mice. Phytother Res. 2000;14(4):261–6.
144. Gupta SC, Prasad S, Tyagi AK, Kunnumakkara AB, Aggarwal BB. Neem (Azadirachta indica): An indian traditional panacea with modern molecular basis. Phytomedicine. 2017;34:14–20.
145. Kumar VS, Navaratnam V. Neem (Azadirachta indica): Prehistory to contemporary medicinal uses to humankind. Asian Pac J Trop Biomed. 2013;3(7):505–14.
146. Faccin-Galhardi LC, Yamamoto KA, Ray S, Ray B, Carvalho Linhares RE, Nozawa C. The in vitro antiviral property of Azadirachta indica polysaccharides for poliovirus. J Ethnopharmacol. 2012;142(1):86–90.
147. Xu J, Song X, Yin ZQ, Cheng AC, Jia RY, Deng YX, Ye KC, Shi CF, Lv C, Zhang W. Antiviral activity and mode of action of extracts from neem seed kernel against duck plague virus in vitro1. Poult Sci. 2012;91(11):2802–7.
148. Tiwari V, Darmani NA, Yue BY, Shukla D. In vitro antiviral activity of neem (Azardirachta indica L.) bark extract against herpes simplex virus type-1 infection. Phytother Res. 2010;24(8): 1132–40.
149. SaiRam M, Ilavazhagan G, Sharma SK, Dhanraj SA, Suresh B, Parida MM, Jana AM, Devendra K, Selvamurthy W. Anti–microbial activity of a new vaginal contraceptive NIM-76 from neem oil (Azadirachta indica). J Ethnopharmacol. 2000;71(3):377–82.
150. Parida MM, Upadhyay C, Pandya G, Jana AM. Inhibitory potential of neem (Azadirachta indica Juss) leaves on dengue virus type-2 replication. J Ethnopharmacol. 2002;79(2):273–8.
151. Al-Hashemi ZSS, Hossain MA. Biological activities of different neem leaf crude extracts used locally in Ayurvedic medicine. Pac Sci Rev A: Nat Sci Eng. 2016;18(2):128–31.
152. Biswas K, Chattopadhyay I, Banerjee RK, Bandyopadhyay U. Biological activities and medicinal properties of neem (Azadirachta indica). Curr Sci. 2002;82(11):1336–45.
153. Thakurta P, Bhowmik P, Mukherjee S, Hajra TK, Patra A, Bag PK. Antibacterial, antisecretory and antihemorrhagic activity of Azadirachta indica used to treat cholera and diarrhea in India. J Ethnopharmacol. 2007;111(3):607–12.
154. Ray A, Banerjee BD, Sen P. Modulation of humoral and cell–mediated immune responses by Azadirachta indica (Neem) in mice. Indian J Exp Biol. 1996;34(7):698–701.
155. Mandal-Ghosh I, Chattopadhyay U, Baral R. Neem leaf preparation enhances Th1 type immune response and anti-tumor immunity against breast tumor associated antigen. Cancer Immun. 2007;7(1):8.
156. Mbah AU, Udeinya IJ, Shu EN, Chijioke CP, Nubila T, Udeinya F, Muobuike A, Mmuobieri A,

Obioma MS. Fractionated neem leaf extract is safe and increases CD4+ cell levels in HIV/AIDS patients. Am J Ther. 2007;14(4):369–74.
157. Sangwan R, Chaurasiya N, Misra L, Lal P, Uniyal G, Sharma R, Sangwan N, Suri K, Qazi G, Tuli R. Phytochemical variability in commercial herbal products and preparations of Withania somnifera (Ashwagandha). Curr Sci. 2004;86(3):461–5.
158. Kambizi L, Goosen B, Taylor M, Afolayan A. Anti–viral effects of aqueous extracts of Aloe ferox and Withania somnifera on herpes simplex virus type 1 in cell culture. S Afr J Sci. 2007;103(9-10):359–60.
159. Cai Z, Zhang G, Tang B, Liu Y, Fu X, Zhang X. Promising anti–influenza properties of active constituent of Withania somnifera ayurvedic herb in targeting neuraminidase of H1N1 influenza: Computational study. Cell Biochem Biophys. 2015;72(3):727–39.
160. Straughn, AR, Kakar, SS. Withaferin A: A potential therapeutic agent against COVID-19 infection. J Ovarian Res. 2020;13(1):1–5.
161. Chopra RN, Nayar SL, Chopra IC, Asolkar LV, Kakkar KK. Glossary of Indian medicinal plants. New Delhi: Council of Scientific & Industrial Research; 1956.
162. Zhang YJ, Tanaka T, Yang CR, Kouno I. New phenolic constituents from the fruit juice of Phyllanthus emblica. Chem Pharm Bull. 2001;49(5):537–40.
163. Zhang YJ, Nagao T, Tanaka T, Yang CR, Okabe H, Kouno I. Antiproliferative activity of the main constituents from Phyllanthus emblica. Biol Pharm Bull. 2004;27(2):251–5.
164. Ghosal S. Active constituents of Emblica officinalis: Part I. The chemistry and antioxidative effects of two new hydrolysable tannins, emblicanin A and B. Indian J Chem. 1996;35:941–8.
165. Anila L, Vijayalakshmi NR. Flavonoids from Emblica officinalis and Mangifera indica: Effectiveness for dyslipidemia. J Ethnopharmacol. 2002;79(1):81–7.
166. Khanna P, Bansal R. Phyllantidine & phyllantine from Emblica officinalis Gaertn leaves, fruits & in vitro tissue cultures. Indian J Exp Biol. 1975;13:82–3.
167. Asolkar LV, Chopra RN. Glossary of Indian medicinal plants with active principles, Part 2. New Delhi: Publications & Information Directorate, CSIR; 1992.
168. Ganju L, Karan D, Chanda S, Srivastava KK, Sawhney RC, Selvamurthy W. Immunomodulatory effects of agents of plant origin. Biomed Pharmacother. 2003;57(7):296–300.
169. Suja R, Nair A, Sujith S, Preethy J, Deepa A. Evaluation of immunomodulatory potential of Emblica officinalis fruit pulp extract in mice. Indian J Anim Res. 2009;43(2):103–6.
170. Godhwani S, Godhwani JL, Vyas DS. Ocimum sanctum: A preliminary study evaluating its immunoregulatory profile in albino rats. J Ethnopharmacol. 1988;24(2-3):193–8.
171. Mediratta PK, Dewan V, Bhattacharya SK, Gupta VS, Maiti PC, Sen P. Effect of Ocimum sanctum Linn. on humoral immune responses. Indian J Med Res. 1988;87:384–6.
172. Mediratta PK, Sharma KK, Singh S. Evaluation of immunomodulatory potential of Ocimum sanctum seed oil and its possible mechanism of action. J Ethnopharmacol. 2002;80(1):15–20.
173. Jurenka JS. Anti–inflammatory properties of curcumin, a major constituent of Curcuma longa: A review of preclinical and clinical research. Altern Med Rev. 2009;14(2):141–53.
174. Roy A, Sarkar B, Celik C, Ghosh A, Basu U, Jana M, Jana A, Gencay A, Can Sezgin G, Ildiz N, Dam P, Mandal AK, Ocsoy I. Can concomitant use of zinc and curcumin with other immunity–boosting nutraceuticals be the arsenal against COVID-19? Phytother Res. 2020;34:2445–8.
175. Ali I, Alharbi OML. COVID-19: Disease, management, treatment, and social impact. Sci Total Environ. 2020;728:138861.
176. Chen CH, Chou TW, Cheng LH, Ho CW. In vitro anti-adenoviral activity of five Allium plants. J Taiwan Inst Chem Eng. 2011;42(2):228–32.
177. Castrillo JL, Carrasco L. Action of 3-methylquercetin on poliovirus RNA replication. J Virol. 1987;61(10):3319–21.
178. Vrijsen R, Everaert L, Van Hoof LM, Vlietinck AJ, Vanden Berghe DA, Boeyé A. The poliovirus–induced shut–off of cellular protein synthesis persists in the presence of 3-methylquercetin, a flavonoid which blocks viral protein and RNA synthesis. Antiviral Res. 1987;7(1):35–42.

179. Harazem R, Rahman S, Kenawy A. Evaluation of antiviral activity of Allium cepa and Allium sativum extracts against Newcastle disease virus. Alex J Vet Sci. 2019;61(1):108–18.
180. Mohamed E. Antiviral properties of garlic cloves juice compared with onion bulbs juice against potato virus Y (PVY). J Am Sci. 2010;6(8):302–10.
181. Takimoto T, Taylor GL, Connaris HC, Crennell SJ, Portner A. Role of the hemagglutinin-neuraminidase protein in the mechanism of paramyxovirus-cell membrane fusion. J Virol. 2002;76(24):13028–33.
182. Wu W, Li R, Li X, He J, Jiang S, Liu S, Yang J. Quercetin as an antiviral agent inhibits influenza A virus (IAV) entry. Viruses. 2015;8(1):6.
183. Gonzalez O, Fontanes V, Raychaudhuri S, Loo R, Loo J, Arumugaswami V, Sun R, Dasgupta A, French SW. The heat shock protein inhibitor quercetin attenuates hepatitis C virus production. Hepatology. 2009;50(6):1756–64.
184. Hellen CU, Kraeusslich HG, Wimmer E. Proteolytic processing of polyproteins in the replication of RNA viruses. Biochemistry. 1989;28(26):9881–90.
185. Sinha M, Bandyopadhyay S, Banerjee S, Chakraborty U, Bhattacharjee A, Nayak D, Khurana A, Manchanda RK, Sarkar D, Ray R. Quercetin alters pro-inflammatory cytokine changes in wild dengue virus challenged HepG2 cell line. 2018;7(15):1137–49.
186. Glaser W, Skern T. Extremely efficient cleavage of eIF4G by picornaviral proteinases L and 2A in vitro. FEBS Lett. 2000;480(2-3):151–5.
187. Qiu X, Kroeker A, He S, Kozak R, Audet J, Mbikay M, Chretien M. Prophylactic efficacy of quercetin 3-beta-O-d-glucoside against Ebola virus infection. Antimicrob Agents Chemother. 2016;60(9):5182–8.
188. Shin JH, Ryu JH, Kang MJ, Hwang CR, Han J, Kang D. Short-term heating reduces the anti–inflammatory effects of fresh raw garlic extracts on the LPS-induced production of NO and pro-inflammatory cytokines by downregulating allicin activity in RAW 264.7 macrophages. Food Chem Toxicol. 2013;58:545–51.
189. Pandurangan AK, Ismail S, Saadatdoust Z, Esa NM. Allicin alleviates dextran sodium sulfate– (DSS–) induced ulcerative colitis in BALB/c mice. Oxid Med Cell Longev. 2015;2015:605208.
190. Guo NL, Lu DP, Woods GL, Reed E, Zhou GZ, Zhang LB, Waldman RH. Demonstration of the antiviral activity of garlic extract against human cytomegalovirus in vitro. Chin Med J. 1993;106(2): 93–6.
191. Tsai Y, Cole LL, Davis LE, Lockwood SJ, Simmons V, Wild GC. Antiviral properties of garlic: In vitro effects on influenza B, herpes simplex and coxsackie viruses. Planta Med. 1985;51(5):460–1.
192. Weber ND, Andersen DO, North JA, Murray BK, Lawson LD, Hughes BG. In vitro virucidal effects of Allium sativum (garlic) extract and compounds. Planta Med. 1992;58(5):417–23.
193. Josling P. Preventing the common cold with a garlic supplement: A double-blind, placebo-controlled survey. Adv Ther. 2001;18(4):189–93.
194. Shojai TM, Langeroudi AG, Karimi V, Barin A, Sadri N. The effect of Allium sativum (garlic) extract on infectious bronchitis virus in specific pathogen free embryonic egg. Avicenna J Phytomed. 2016;6(4):458–67.
195. Fenwick GR, Hanley AB. The genus Allium: Part 1. Crit Rev Food Sci Nutr. 1985;22(3):199–271.
196. Hall A, Troupin A, Londono-Renteria B, Colpitts TM. Garlic organosulfur compounds reduce inflammation and oxidative stress during dengue virus infection. Viruses. 2017;9(7):159.
197. Gulati K, Rai N, Chaudhary S, Ray A. Nutraceuticals in respiratory disorders. In: Gupta RC, editor. Nutraceuticals. Cambridge: Academic Press; 2016. p. 75–86.
198. Ji Y, Wei C, Xin G, editors. The study of chemical composition and pharmacological action of the alkaloid from plants of Lycoris herb. IOP Conf Ser Earth Environ Sci. 2017;100(1):012045.
199. Islam MT, Sarkar C, El-Kersh DM, Jamaddar S, Uddin SJ, Shilpi JA, Mubarak MS. Natural products and their derivatives against coronavirus: A review of the non-clinical and pre-clinical data. Phytother Res. 2020;34(10):2471–92.
200. Lau KM, Lee KM, Koon CM, Cheung CS, Lau CP, Ho HM, Lee MY, Au SW, Cheng CH, Lau CB, Tsui

SK, Wan DC, Waye MM, Wong KB, Wong CK, Lam CW, Leung PC, Fung KP. Immunomodulatory and anti-SARS activities of Houttuynia cordata. J Ethnopharmacol. 2008;118(1):79–85.
201. Chiow KH, Phoon MC, Putti T, Tan BK, Chow VT. Evaluation of antiviral activities of Houttuynia cordata Thunb. extract, quercetin, quercetrin and cinanserin on murine coronavirus and dengue virus infection. Asian Pac J Trop Med. 2016;9(1):1–7.
202. Miraj S. Therapeutic effects of Rheum palmatum L.(Dahuang): A systematic review. Der Pharma Chemica. 2016;8(13):50–4.
203. Gong S, Su X, Yu H, Li J, Qin Y, Xu Q, Luo WS. A study on anti-SARS-CoV 3CL protein of flavonoids from litchi chinensis sonn core. Chinese Pharmacol Bull. 2008;24:699–700.
204. Lin CW, Tsai FJ, Tsai CH, Lai CC, Wan L, Ho TY, Hsieh CC, Chao PDL. Anti-SARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds. Antiviral Res. 2005;68(1):36–42.
205. Nguyen TTH, Woo HJ, Kang HK, Kim YM, Kim DW, Ahn SA, Xia Y, Kim D. Flavonoid-mediated inhibition of SARS coronavirus 3C-like protease expressed in Pichia pastoris. Biotechnol Lett. 2012;34(5):831–8.
206. Smirnova IE, Kazakova OB. Structure - Anti-influenza type a activity relationship among a series of nitrogen lupane triterpenoids. Nat Prod Commun. 2018;13(10):1267–70.
207. Hong EH, Song JH, Kang KB, Sung SH, Ko HJ, Yang H. Anti-influenza activity of betulinic acid from Zizyphus jujuba on influenza A/PR/8 virus. Biomol Ther. 2015;23(4):345–9.
208. Kumar S, Madaan R, Gahlot K, Sharma A. The genus Bryonia: A review. Pharmacogn Rev. 2008;2(4):392–401.
209. Nair K, Gopinadhan S, Kurup T, Aggarwal A, Varanasi R, Nayak D, Padmanabhan M, Oberai P, Singh H. Homoeopathic genus epidemicus 'Bryonia alba' as a prophylactic during an outbreak of Chikungunya in India: A cluster-randomised, double-blind, placebo-controlled trial. Ind J Res Homoeopathy. 2014;8(3):160–65.
210. Al-Awadi FM, Srikumar T, Anim J, Khan I. Antiinflammatory effects of Cordia myxa fruit on experimentally induced colitis in rats. Nutrition. 2001;17(5):391–6.
211. Castro M. The complete homeopathy handbook: Safe and effective ways to treat fevers, coughs, colds and sore throats, childhood ailments, food poisoning, flu, and a wide range of everyday complaints. New York: Macmillan; 1991.
212. Moerman DE. Native american ethnobotany: In: Selin H, editor. Encyclopaedia of the history of science, technology, and medicine in non–western cultures. Dordrecht: Springer; 2017.
213. Maas M, Petereit F, Hensel A. Caffeic acid derivatives from Eupatorium perfoliatum L. Molecules. 2008;14(1):36–45.
214. Tallei TE, Tumilaar SG, Niode NJ, Fatimawali F, Kepel BJ, Idroes R, Effendi Y. Potential of plant bioactive compounds as SARS-CoV-2 main protease (Mpro) and spike (S) glycoprotein inhibitors: A molecular docking study. Scientifica. 2020;2020;6307457.
215. Duraipandiyan V, Al-Dhabi NA, Balachandran C, Ignacimuthu S, Sankar C, Balakrishna K. Antimicrobial, antioxidant, and cytotoxic properties of vasicine acetate synthesized from vasicine isolated from Adhatoda vasica L. Biomed Res Int. 2015;2015:727304.
216. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270–3.
217. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science. 2020;367(6485):1444–8.
218. Chen X, Li R, Pan Z, Qian C, Yang Y, You R, Zhao J, Liu P, Gao L, Li Z, Huang Q, Xu L, Tang J, Tian Q, Yao W, Hu L, Yan X, Zhou X, Wu Y, Deng K, Zhang Z, Qian Z, Chen Y, Ye L. Human monoclonal antibodies block the binding of SARS-CoV-2 spike protein to angiotensin converting enzyme 2 receptor. Cell Mol Immunol. 2020; 17(6):647–9.

219. Choudhary S, Malik YS, Tomar S. Identification of SARS-CoV-2 cell entry inhibitors by drug repurposing using in silico structure-based virtual screening approach. Front Immunol. 2020;11:1664.
220. Cavasotto CN, Di Filippo JD. In silico drug repurposing for COVID-19: Targeting SARS-CoV-2 proteins through docking and consensus ranking. Mol Inform. 2020;40(1):2000115.
221. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020;181(2):281–92.e6.
222. Shulla A, Heald-Sargent T, Subramanya G, Zhao J, Perlman S, Gallagher T. A transmembrane serine protease is linked to the severe acute respiratory syndrome coronavirus receptor and activates virus entry. J Virol. 2011;85(2):873–82.
223. Bestle D, Heindl MR, Limburg H, Pilgram O, Moulton H, Stein DA, Hardes K, Eickmann M, Dolnik O, Rohde C, Klenk HD. TMPRSS2 and furin are both essential for proteolytic activation of SARS-CoV-2 in human airway cells. Life Sci Alliance. 2020;3(9):e202000786.
224. Pandey P, Rane JS, Chatterjee A, Kumar A, Khan R, Prakash A, Ray S. Targeting SARS-CoV-2 spike protein of COVID-19 with naturally occurring phytochemicals: An in silico study for drug development. J Biomol Struct Dyn. In press 2020.
225. Wang C, Li W, Drabek D, Okba NM, van Haperen R, Osterhaus AD, van Kuppeveld FJ, Haagmans BL, Grosveld F, Bosch BJ. A human monoclonal 1 antibody blocking SARS-CoV-2 infection. Nat Commun. 2020;11:2251.
226. Talukdar A. Compilation of potential protein targets for SARS-CoV-2: Preparation of homology model and active site determination for future rational antiviral design. ChemRxiv [cited 2020 Apr 23]. Available from: https://doi.org/10.26434/chemrxiv.12084468.v1.
227. Navratil V, Lionnard L, Longhi S, Hardwick M, Combet C, Aouacheria A. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) envelope (E) protein harbors a conserved BH3-like sequence. bioRxiv [cited 2020 Jun 17]. Available from: https://doi.org/10.1101/2020.04.09.033522.