ISSN:0976-4933
Journal of Progressive Science
A Peer-reviewed Research Journal
Vol.16, No.02, pp 117-131(2025)
https://doi.org/10.21590/jps.16.02.06

Review Article: COVID-19: Strategies to Combat- Current and Impending targets

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Abstract

At the end of year 2019, suddenly everyone is started talking about the Wuhan city of China, where a contagious virus SARS-CoV-2 jumps from bats to humans. It is one of the fastest spreading viruses, which spread around the globe in very few months. No country has been left untouched by this virus. Although there are number vaccines and preventive measures are available today. They check its spreading speed but it remains a great threat even today due to its properties of changing strains. According to covid tracker there are 482,551 confirmed deaths as on April 2026 in India alone and at world level it reaches to 7,114,028 . The most striking feature of all coronaviruses is that they transcribe and translate a polyprotein via ribosomal frameshifting. The spike protein (P). club-like, pear-shaped, or petal-shaped structures that are projected from the virus body envelope is the potential target for strategies to develop a vaccine or drug to combat with this deadly virus. The TMPRSS2, another gene supposed to help the fusion process, may also be the other potential target. A protein known as cathepsin L, which holds the key for binding between the endosome and vesicle containing virus, necessary for virus activation. The other targets for therapeutic development are RNA dependent RNA polymerase and Protease. Chloroquine, remdesivir, protease inhibitor and Aptamer are also the molecules of choice. Reverse vaccinology as a technique to deal with it is also being considered. Moreover, we need to learn from its reservoir, how to cope with such deadly viruses and study their immunological and biochemical changes.

Keywords Covid-19, SARS-Co-2, RNA Vaccines, and Immunotherapy

Introduction

Starting from the December of 2019, in Wuhan city of China, SARS-CoV-2 emerged to be one of fastest spreading viruses around the globe. Today there is no country has been left untouched by this virus. The disease caused by this virus is COVID-19. On March 12, 2020, WHO listed COVID-19 as world pandemic. According to covid tracker there are 482,551 confirmed deaths as on April 2026 in India alone and at world level it reaches to 7,114,028 Naveed et al. (2026). The mortality was recorded with delta variant of covid.

The covid-19 virus originates from the fruit bats, which carry a plethora of viruses (> 200). Out of these viruses, seven are known to cause infection to humans. Four viruses- 229E, OC43, NL63, and HKU1 are associated with common influenza like symptoms in immunocompetent individuals (Su et al., 2016) while the other three are: severe acute respiratory syndrome associated coronavirus (SARS-CoV-1) which caused an epidemic in 2003, Middle East respiratory syndrome coronavirus (MERS-CoV) also known as camel flu (2012) and Severe acute respiratory syndrome associated coronavirus2 (SARS-CoV-2) associated with current pandemic (COVID-19). SARS-CoV-2 is an enveloped, positive-sense single-stranded RNA virus with nucleocapsid of helical symmetry Zumla et al. (2016). The virus genome consists of 30 kb RNA bases, consist of 15 genes, including the S gene, which encodes for a surface protein located on the surface of virus and spikes and it help in recognition and binding with host. Genetically the SARS-CoV-2 virus is very close to the SARS CoV virus and placed in class: β-coronaviruses. The most striking feature of all coronavirus is that they transcribe and translate a polyprotein via ribosomal frameshifting. All SARS-CoVs contains two chief types of proteins: those related for maintaining cell shape and size known as structural proteins like Spike (S), Envelope (E), Membrane (M) and those help in maintaining integrity of genome is known as nucleoproteins. The proteins name as 3a, 3b, 6, 7a, 7b, 8a, 8b and 9b are specific to SARS-CoV family (Nieto-Torres et al., 2014).

The surface spikes (P) proteins are club-like, pear-shaped, or petal-shaped structures that are projected from the virus body envelope. The spike consists of S glycoprotein, which have specific proteins to interact with host cell membrane and help in fusion of virus membrane to host cell membrane.

The root of zoonotic trace back to fruit bats of family Pteropodidae , which work like a reservoir of SARS CoV-2 Zhou et al. (2020). The human-to-human, surface to human, secretion are the main reasons for the quick spread of the virus. It required a incubation time 2-16 days, that may be symptomatic and non-symptomatic. It was estimated that virus spread from human to human, at the time of sneezing and coughing in the form of droplet, and these droplets may cover up to 6 feet of aerial distance Zhou et al. (2020). The first case of this SARS-CoV-2 coronavirus was reported in Wuhan, China. So, sometimes it is also referred to as Wuhan virus. The disease caused by the virus is known as COVID-19.

There are reports available which demonstration that this virus can remain for three hours in air, four hours on copper surfaces, up to twenty-four hours on cardboard while on stainless steel, plastic for two to three days and stool samples for 4 days Kampf et al. (2020).

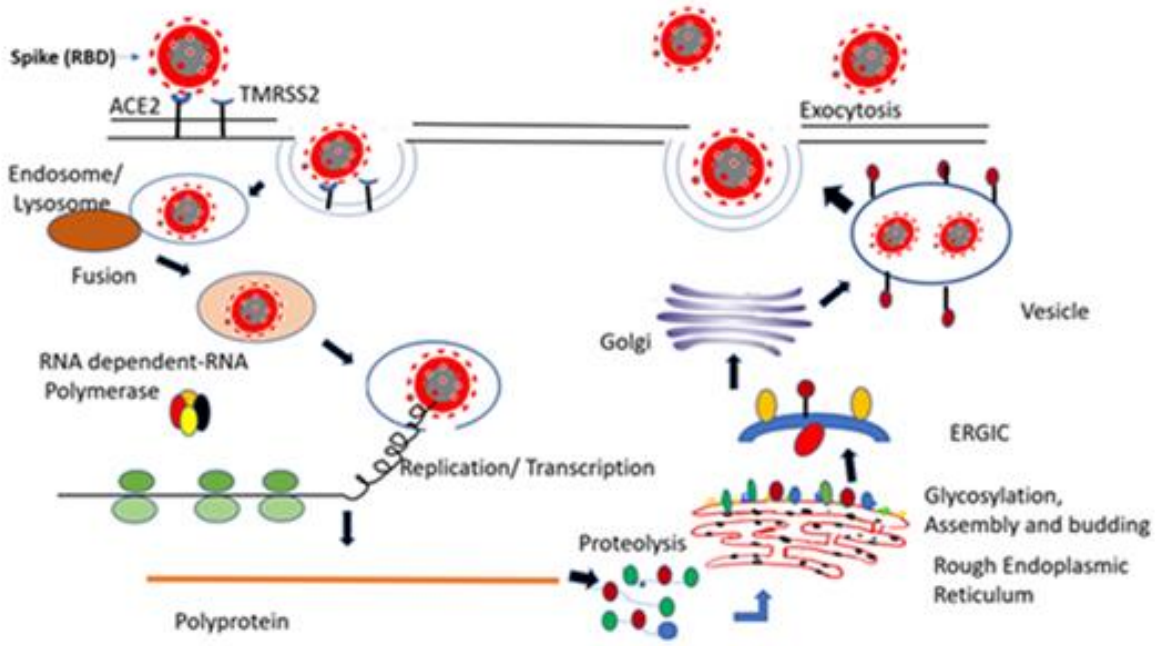
Based on phylogenetic tree analysis the strain of covid can be categorised as: Pre-Omicron variant of corona includes Alpha, Beta, Gamma, Delta and were very severe. These strains are displaced by Omicron and its descendants and are now rarely seen. In year 2021 mutation in pre-Omicron strains lead to development of Omicron strains. These strins highly transmissible and have greater capacity immune escape but usually lower severity than early Delta. Omicron (B.1.1.529) is a highly mutated SARS-CoV-2 variant with multiple subvariants that continue to evolve globally Dhawan et al. (2026). There are more than 30 distinct SARS-CoV-2 lineages (strains) are currently tracked and circulating globally, with Omicron-related strains (XFG-cluster, JN.1-cluster, LP.8.1, NB.1.8.1, etc.) forming the bulk.

Forster et al, (2020) suggests that immunological & environmental factors may play an important role in development of variant forms of SARS CoV-2 strains.

Mechanism of SARS-CoV-2 Infection

The exact mechanism of how SARS CoV2 virus jumps from bats to humans is still not clear. However, structural analysis suggests that coronaviruses have receptor binding domain (RBD) present in its spikes. The RBD recognised angiotensin-converting enzyme 2 (ACE2) receptor & a sialic acids link gangliosides of epithelial cell surface, which facilitates its entry in epithelial cells, like SARS CoV-1(Fantini et al., 2020). The ACE2 is type I transmembrane glycoprotein and consists of 805 amino acids along with an extracellular catalytic domain. ACE2 has two domains: the amino-terminal catalytic domain and the carboxy-terminal domain. The catalytic domain consists of a regulatory site for zinc metallopeptidase and the non-catalytic part of proteins might be help in amino acid re-absorption and perhaps a role in exocytosis . The RBD domain of SARS CoV-2, and SARS CoV-1 vary in multiple sites of amino acid residues that make it more compactable for binding with ACE2 receptor, and hence enhance its binding capacity Shang et al. (2020). The binding of RBD to the ACE2 receptor on the host cell lead to conformational changes, which initiates the fusion of host cell membrane and viral membranes. Apart from membrane fusion SARS CoV2 may enter in the cell through clathrin-dependent and independent endocytosis Kuba et al. (2010), Wang et al. (2008).

Fig.1 : Mechanism of Infection and Life Cycle of SARS-CoV-2



After entering the host cell, the virus starts fusing the neighbour cells forming a syncytium and now the viral RNA genome is translated into a polyproteins and structural proteins in cytoplasm of host cell; after which the viral genome starts replicating. Binding with receptor is one of the vital steps for a pathogen infectivity, pathogenesis, and host range Li (2016), Perlman & Netland (2009). The virus utilised fusion strategy to enter and starts replicating inside host cells as shown in Fig-1. Binding and entry step may represent a potential target for vaccine development and antiviral therapies Xia et al. (2020).

The N- terminal of Spike protein is introduced into the Endoplasmic reticulum, where the glycosylation of S protein and several amino acids of N-terminal take place. The process of glycosylation adds an additional mass of 30- 50 k Da to it. In later stages, the glycosylated Spike protein is splits into two parts

i.e. S1 and S2, by cellular proteases. Which cleaved S, the plasma membrane of host cell fuses with viral cell. The S1 provide the binding site for host cell receptor and S2 for viral membrane fusion site.

Besides the spike protein and its domain, envelope proteins are also formed; these proteins enters into endoplasmic reticulum or Golgi complex, where the process of glycosylation takes place and on interaction with RNA and nucleocapsid protein they form nucleocapsid. The viral particles are arising from endoplasmic reticulum-Golgi intermediate compartment (ERGIC). In the final step the vesicles containing the virus particles fuse with the plasma membrane to release the virus de Wit et al. (2016).

Neutralization of Virus in Affected Areas

The virus can be efficiently inactivated with the help of disinfectants which contain 62–71% ethanol plus 0.5% hydrogen peroxide or 0.1 % sodium hypochlorite added < 1 minute time. Other less effective but necessary components to be added are 0.05–0.2% benzalkonium chloride & 0.02 % chlorhexidine digluconate Kampf et al. (2020).

Strategies to combat

Paxlovid and its Mechanisms

Antiviral drugs such as Paxlovid (nirmatrelvir/ritonavir, oral for adults/children 12+), remdesivir (Veklury, IV for 3 days), and molnupiravir (Lagevrio, oral for adults) are recommended from mild-to-moderate cases in high-risk patients. These drugs reversible inhibits the SARS-CoV-2, protease (Mpro) protein, which is essential for viral replication. This binding prevents the virus from processing its polyproteins, halting the production of essential viral components and stopping replication Saindane & Pathania (2025). Apart from these drugs, some immune modulators like tocilizumab may use as additive for hospitalized patients.

Inhibition of SARS-CoV-2 RNA polymerase

The replication and transcription machinery of COVID-19 is governed by the RNA-dependent RNA Polymerase (nsp12). The RNA-dependent RNA Polymerase contains a “right hand” RdRp domain and a nido-virus RdRp-associated nucleo-tidyltransferase (NiRAN) Alves et al. (2025), which is unique to coronaviruses. Like other RNA polymerases, the active site containing domain (RdRp) is formed by motifs A-G domains and configuration. The RdRp remains the target of choice for the treatment of several viral diseases, including chronic liver disease (Hepatitis C), caused by hepatitis C virus infection Gao et al. (2020). The two important domains are domain A and C. The domain A contains a site for divalent-cation-binding and is most conserved part of viral polymerases. The Motif C contains a catalytic site, in the turn between two β-strands

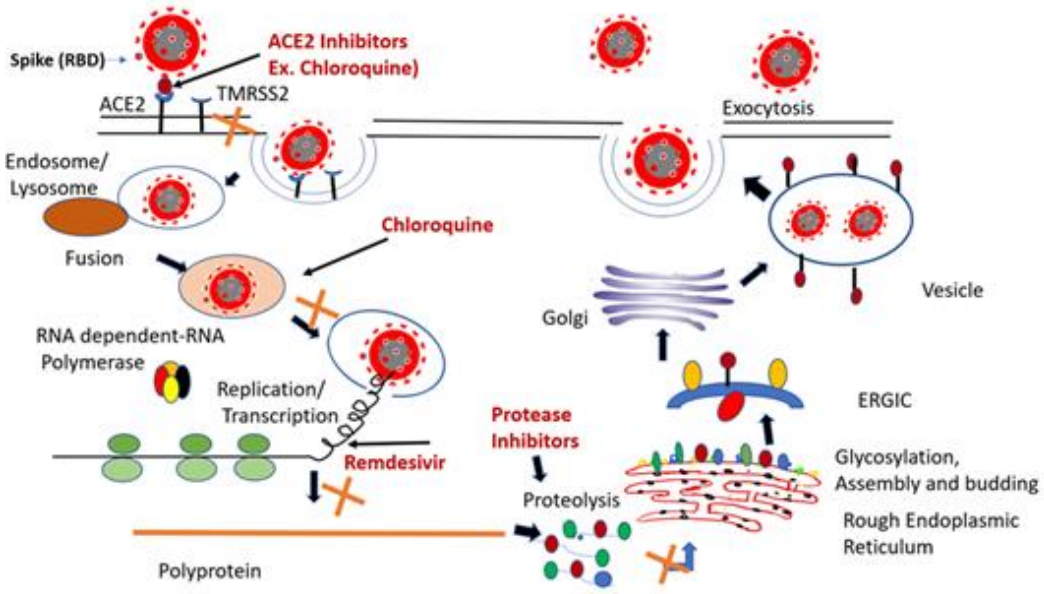
These active site motifs and catalytic sites may be the potential targets for drug screening. Recently discovered drug can be targeted with some drug or inhibitory molecule, which specifically binds and inactivates them by forming stable molecules or terminates the RNA synthesis chain.

The most promising molecules in this regard are nucleotide analogues / nucleotide prodrugs / metabolic products, which competes with endogenous nucleotides as substrates for the viral RdRp. Mostly of them are active 5'- triphosphate form (5'-TP) of molecules. The RNA dependent RNA Polymerase incorporates the newly formed RNA chain and ultimately leads to termination of RNA synthesis Shannon et al. (2020). It was also reported that combinational therapy (two or more nucleotide analogous) with

Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. They reported that remdesivir or combination of remdesivir and emetine reduced the viral yield approximately by 65% in vitro Choy et al. (2020).

Bioinformatic analysis of SARS-CoV-2 genome revealed that it genes have <80% nucleotide identity and 90% nucleotide similarity with SARS-CoV genes. SARS-CoV-2 genome produces approximately 750-800 kDa polyprotein on complete transcription of genome. This polyprotein is further sliced into smaller protein by papain-like protease (PLpro) and 3-chymotrypsin-like protease (3CLpro). The 3-chymotrypsin-like protease (3CLpro) produces 12 different proteins by cleaving the polyprotein at least 11 distinct sites, through a process initiated by the enzyme's own autolytic cleavage from pp1a and pp1ab. and generates various non-structural proteins which play important role in viral replication. Therefore, it is a potential target for protease inhibitors which stop or inhibit such autocatalysis.

Fig. 2 : Sites of Drug targets in SARS-CoV-2



The RNA Drug Remdesivir

The RNA as drug Remdesivir inhibit RNA Dependent RNA polymerase, The Remdesivir is nucleotide analogues, which is artificially design molecules that used by a RNA Dependent RNA polymerase as their substrate molecules such as nucleotides (A, U, G & C). The binding and accumulation of nucleotide analogous results in accumulated mutations and chain terminations, which further disrupt genomic replication. Presently they are either (i) adenine analogues (3-deazaneplanocin A, galidesivir, GS-6620 and remdesivir) or (ii) guanine analogues containing the carboxamide entity (ribavirin, EICAR, paradoxurine and favipiravir).

Most of nucleoside analogues are C- nucleosides, where sugar is attached to the carbon atom in place of N- atom in. This makes them resistance to hydrolysis; examples are galidesivir, GS-6620, remdesivir and pyrazofurin etc. Some of them contain phosphoramidate which is a phosphate that lost his all three OH groups to NR2 group and gives the phosphoric triamides (O=P(NR2)3). These phosphoric triamides are

commonly referre as phosphoramides and are known to be an essential part for its antiviral activity. The acyclovir, used for the treatment of herpes simplex virus infections and chickenpox, contains an open-chain structure in place of sugar De Clercq (2019), Elfiky (2020) and Lelyveld et al. (2020).

Remdesivir is a broad-spectrum drug with antiviral properties, competitively inhibiting viral RNA dependent RNA polymerases just like acyclovir and ganciclovir. Remdesivir-TP (adenosine analogue) inserts into viral RNA chains with similar efficiency as nucleotides and stops addition of more RNA subunits there by- stops transcription/ replication o viral genome.

Another interesting fact about the Remdesivir is that its metabolic product phosphoramidate (GS-441524), interferes with the action of viral RNA-dependent RNA polymerase and evades proofreading by viral exoribonuclease (ExoN), thus decreases viral RNA production Al-Tawfiq et al. (2020), Iannetti et al. (2025), Kupferschmidt & Cohen (2020), Rouhana El Feghali et al. (2026), Yamana et al. (2026).

Wu et. al (2020) attempted to utilise plasminogen activator (PA) system for the treatment of COVID-19. Plasminogen activator is a serine protease found on endothelial cell line of blood vessels. It breaks the zymogen plasminogen to active plasmin and helps in formation of fibrin in extra cellular matrix. They found, that plasminogen may work as an accessory component in effective and efficient treatment of critically ill COVID-19 patients as it help in healing lung lesions and hypoxemia during COVID-19 infections Abudouleh et al. (2025), Sharma et al. (2026). Recently a synthetic G4 DNA 20 mer, were confirmed that inhibited the replication of various SARS-CoV-2 variants in human lung cell cultures. GQ20-PTO bound to NSP13 and inhibited its helicase and ATPase activity Bojkova et al. (2026).

Immunotherapy for COVID-19

Convalescent plasma therapy (CPT) is recently approved as treatment method for COVID-19. In this method the antibodies are taken from the recovered patient and administered to the critically ill patients having poor chances of survival. The steps involved during the CPT process are collection of whole blood or plasma, administration to the patients and in the final step; this may lead to elicitation of patient immune system to produce more antibodies Elalouf & Maoz (2026) and Etienne et al. (2026).

Immunotherapeutic treatment of COVID-19 was established by scientists from Israel based company. They have utilised placenta-based cell-therapy approach for treatment of COVID-19. They have treated six critically ill coronavirus patients in Israel with Pleurite's placenta-based cell-therapy product, and found wonderful results, all treated patients were survived. The therapy also gets FDA node for larger clinical trials. In this placenta-based stem cell-therapy, the stem cells were isolated from the umbilical cord of caesarean section born babies to avoid the contamination of virus and bacteria, that may occur during normal delivery. The stem cells do not have any antigens, so they are not recognized as foreign by the immune system Maguire et al. (2023). The company has named these stem cells as Placental expanded (PLX) cells and are placenta-derived, mesenchymal-like adherent stromal cells that are designed to be administered to patients without the need for tissue or genetic matching. Pleurite's PLX cells have immunomodulatory properties, which induce the immune system's natural regulatory T cells and M2 macrophages, which release the cytokines, chemokines and growth factors. These biomolecules work as paracrine or endocrine factors, and facilitate healing of damaged tissue by stimulating the body's own regenerative mechanisms Larijani et al. (, 2021) and Sarangi et al. (2024).

Stem Cell therapy

Stem cells are pluripotent cells that have capability of self-renewal and can differentiate into many types and multifunctional cells. These are inserted into damaged areas of lung tissue where they replace the damaged bronchial epithelial cells and clear the virus infected cell. Till date more than four types of stem cells have got the nod from FDA for clinical trials English et al. (2026) and Rea-Moreno et al. (2026).

In silico studies for selection of therapeutic agents

There are enormous number of in-silico studies available, which suggest the potential drug targets of COVID-19. Very recently Gupta e.t al. (2020) suggest that the viral envelop protein (E protein) may be a potential drug target as it is known to play an important role in assemblage of the viral genome Gupta et al. (2020). Hyun-Jung and Koohy proposed two vaccine candidates (i) 28 nCoV peptides identical to SARS CoV), immunogenic and known to activate T cells (ii) 48 nCoV, also an immunogenic peptide and recently deposited in The Immune Epitope Database (IEDB) Dutta et al. (2026), Hyun-Jung Lee & Koohy (2020).

Using homology modelling approach, Elmezayen et. al. (2020) generated the 3D structure of human TMPRSS2 and, by molecular docking studies, four potential inhibitors against TMPRSS2- Rubitecan and Loprazolam are available drugs, and two are novel drug like compounds ZINC000015988935 and ZINC000103558522 Elmezayen et al. (2020). A group of researchers suggested that Nimesulide, Fluticasone Propionate, Thiabendazole, Photofrin, Didanosine and Flutamide are among possible drug candidates against SARS-CoV-2 Cava et al. (2020).

A Team of researchers from India found approximately 300 molecules as potential drug targets by screening the CHEMBL database, ZINC database, FDA approved drugs and molecules under clinical trials. They also noted that Cobicistat, ritonavir, lopinavir, and darunavir are the top screened molecules from FDA approved drugs Chhetri et al. (2026).

The number of drugs emerged through in-silico studies needs to be considered with caution as the results are inconsistent and have different target molecules and strategies. Recently FDA approve use of Many regulatory bodies, including the U.S. FDA, have authorized Remdesivir (RD) RD for the treatment of COVID-19. The other potential molecules Baloxavir Marboxil (BM), Dexamethasone (DM may be used under emergency Chhetri et al. (2026).

Reverse Vaccinology

The reverse vaccinology approach can be applied to identify the vaccine candidate's genes. In this approach the total genome of pathogen is screened to identify antigenic genes that code the extracellular proteins, signal peptides and B cell epitopes Kanampalliwar (2020). Using the reverse vaccinology approach, Enayatkhani et. al. (2020) have designed and introduced a multi-epitope vaccine against 2019-nCoV which is able to generate both CD4+ and CD8+ T-cell immune responses .

COVID-19 vaccines primarily prevent infection and severe disease rather than serving as direct treatments post-infection, working by training the immune system to recognize and combat the SARS-CoV-2 virus via its spike (S) protein Saravanan et al. (2025). A team of researchers from Oxford University developed an adenovirus vector vaccine (ChAdOx1) as an appropriate vaccine technology for a SARS-CoV-2 vaccine. They inserted the also inserted the surface spike protein genomic sequence in ChAdOx1 vector. The production of spike protein further prepared the body, for upcoming infection.

A single dose of ChAdOx1 can generate a strong immune response. Furthermore, the ChAdOx1 vector is not a replicating virus, so it can not cause additional infection in the vaccinated individual. Furthermore it don't have any age limit Deng et al. (2026), Hlaváč et al. (2026) and Saravanan et al. (2024).

Protein Subunit Vaccines

Examples like Novavax contain purified S protein pieces plus an adjuvant to boost immunity. Immune cells recognize the antigen, producing targeted antibodies and memory cells for rapid defence against COVID-19 Gröhn et al. (2026), Wang et al. (2026). A Maryland, based Novavax company produce first recombinant protein vaccine (Covovax), which targeting JN.1 protein (Spike protein). It was approved by European Union in year 2020 and in Canada it gets approval in 2021. This vaccine recently also got approval from FDA .

mRNA vaccines

mRNA vaccines are synthetic messenger RNA molecules, which introduced into the cells, produced harmless viral proteins and illicit the immune system like an live virus. The companies like Pfizer-BioNTech and Moderna produce mRNA vaccines, which showing high efficacy and rapid production Okechukwu Paul-Chima et al. (2026) and Straus (2026).

Medicinal Plants

There are a number of medicinal plants whose extracts or ingredients are known to have immunomodulatory or antiviral properties. These plant extracts have bioactive compounds that can be used to develop proper drugs against several diseases with no or minimal side-effects. Table 1.0 shows the name of plants, their bioactive compounds and their effects on immune system Adunlin et al. (2020) and Sharma (2017). In a study, Muhammad Tahir ul Qamar et al (2020), bioinformatically screened 32,297 bioactive compounds against COVID 19 and found 9-10 promising bioactive compounds that have a potential to inhibit SARS-CoV-2, 3CLpro activity and hence inhibit replication Tahir ul Qamar et al. (2020) . Lisboaeflavanonol A (LFA) is a novel glycosyl flavonoid isolated from a amazons plant Eugenia lisboae leaves, inhibit the SARS-CoV-2 proteins 3-chymotrypsin-like cysteine protease (3CLpro) and RNA-dependent RNA polymerase (RdRp) Grosche et al. (2026). Recently Malik et al. (2026) found the Inhibitory potential of Morus alba leaf extract and its phytoconstituent against SARS-CoV-2 main protease Malik et al. (2026) Table 1.

Table: List of some Immunomodulators and Antiviral Medicinal Plants

S. No.	Name of plant	Bioactive compound	Properties
1.	Vitex trifolia	Casticin	Immunomodulatory & Anti-inflammatory effect on lungs
2.	Tinospora cordifolia	Alkaloids and steroids	Immunostimulant, macrophase chemotaxis
3.	Ocimum Sanctum	Eugenol, rosmarinic acid, β–sitosterol	Enhances the production of RBC, WBC and haemoglobin
4.	Allium sativum	Allicin	Proteolytic and hemagglutinating activity and viral replication
5.	Andrographi paniculata	Andrographolid	Antiviral potential
6.	Sphaeranthus indicus	Tartaric acid	Inhibition of Mouse corona virus and Herpes virus -Bronchodilation
7.	Clitoria ternatea	Delphinidin-3-O-glucoside	Antiviral properties
8.	Hyoscyamus niger	Hyoscyamine	Viral Inhibition and Bronchodilator
9.	Eugenia jambolana	Ellagic acid	Protease Inhibitor
10.	Capparis zeylanica	E-octadec-7-en-5-ynoic Acid	Immunomodulatory activity, Phagocytosis
11.	Panax ginseng	Saponins and steroids	Immunomodulator. Activates macrophages.
12	Allium asativum	Organosulfur compounds	Activates macrophages, Immunomodulator
13.	Nigella sativa	Thymoquinone	immunomodulatory and anti-inflammatory

Conclusion

Most of drugs developed or proposed to treat COVID-19 are either in preclinical stage or some of them have crossed the first clinical stage. Today some of them gets approval from FDA and other agencies, but still, we need to couscous, because of its rapidly changing variants. Some of its variants are more dangerous than previous ones. Enthusiasm for such a treatment is premature. We need big clinical trials of the drugs against COVID-19.

Some sites are good vaccine candidates such as club-shaped spikes (S) protein present on the outer surface of coronavirus. Spike (S) protein is a potential target for developing a COVID-19 therapeutic.

Drug targets spike (S) protein as well as other targets needs deep understanding of fusion mechanism, sequence of events taking place in fusion process.

TMPRSS2 other gene which is suppose help in fusion process may also be the other potential target but the knockout for TMPRSS2 mice leads to severe immunopathological conditions. Moreover, the deletion of TMPRSS2 does not able to check the spread of SARS-CoV in the lung alveoli of knockout mice Iwata-Yoshikawa et al. (2019).

Other potential drug target includes are cathepsin L, which hold the key for binding between the endosome with vesicle containing virus, necessary for virus activation Tang et al. (2020). Out of two proteases, 3CLpro enzyme a major component of viral replication and infection may be potential target for antiviral therapy. This may be achieved by using the selection of RNA aptamer and peptides. The vigorous search is need to more effective and efficient nucleoside analogues for the treatment of SARS-CoV-2 infection. The use of quantum dots (CQDs) against SARS-CoV-2 may be an effective may check the entry of pathogen in host cells. The CQD are derived from carbon hence they are non-immunogenic Łoczechin et al. (2019). The development of Peptide or subunit vaccines, which consist of non-immunogenetic components or epitopes of the SARS-CoV-2 may be considered. Whatsoever may be the drugs or vaccines it should be evaluated before taking into consideration for safety and efficacy. As we know the disease is spreading day by day, it necessitates to prepare for the next step of clinical trials, the stock must be ready for next level. Moreover, we need to learn from its reservoir, how to cope with such deadly viruses and study their immunological and biochemical changes.

Conflict of Interest

Authors declare no conflict of Interest

Funding

The is thankful to Council for Science and Technology-Uttar Pradesh (CST-UP) for their financial assistance.

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Received on 09.11.2025 and accepted on 28.12.2025