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Review Article

Available drug therapies on COVID-19 and its side effects: An overview

Namrata Malik[1], Umesh Pravin Dhuldhaj[2,*]

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ABSTRACT

The sudden outbreak of coronavirus turned into a pandemic and resulted in huge socio-economic and human losses becoming a public health emergency. It took just 3-4 months to spread and encroach all over the world and not even a single country is left was unaffected by the coronavirus. WHO started clinical, epidemiological, and laboratory investigations in response to this outbreak to control the further spread of the virus. The coronaviruses are enveloped and pleomorphic. The spike proteins present on the virus surface mediate its entry into host cells. The vaccines recommended have been shown to reduce COVID-19 illness symptoms but somehow their role in the transmission of the disease is unclear. By contrast, immunomodulatory therapy has also benefitted patients. As long as SARS-CoV-2 spreads in the population there are chances of its mutation as RNA viruses mutate over time and its upcoming variants. The previous Delta variant and the latest Omicron variant may cause much more serious deaths and health issues. Variants reduce the effectiveness of monoclonal antibodies or antibodies generated by previously administered vaccines. This review focuses on the pathogenicity of coronavirus and various drug therapies available to date to cure the disease. The present study also highlights the target sites and side effects of available drugs for treating COVID-19.

1. Introduction

The Covid-19 pandemic caused by the novel Coronavirus destroyed the routine of normal people outbreaks in China in December 2019 and gradually in March 2020 spreads all over the Globe. Coronavirus is a large family of viruses infecting both humans and animals. Humans can develop respiratory infections which can be as simple as the common cold or severe such as MERS (Middle Eastern Respiratory Syndrome) and SARS (severe acute respiratory syndrome) [1-3].

The very first coronavirus was detected in birds in the year 1937 and after 20 years of span i.e. in 1960 was again detected in human beings. To date, the known strains of coronaviruses are HCoV-229E, HCoV-OC43, HCoV-NL63, SARS-CoV, MERS-CoV, HCoVHKU1, and SARS-CoV-2. Among these, people get more often exposed to 229E, NL63, OC43, and HKU1, these four coronaviruses are responsible for MERS, SARS, and very recent notorious infectious diseases [4, 5].

But the history of the coronavirus infection dates to the year 2002 when hundreds of cases of severe pneumonia were reported in Guangdong Province of China. Similar infection cases were also reported in Hong Kong, Vietnam, and Canada in February and

[1]*Department of Life Sciences and Biotechnology, Chhatrapati Shivaji Maharaj University, Panvel, Navi Mumbai Maharashtra 410206, India*
[2]*Department of Biotechnology, School of Life Sciences, Swami Ramanand Teerth Marathwada University, Nanded 431606, Maharashtra, India*
***Corresponding Author**: Umesh Pravin Dhuldhaj (umeshpd12@gmail.com)*

March in the year 2003. Then the World Health Organization (WHO) designated the causal virus as "SARS-CoV". In 2012 another coronavirus case was reported from Jeddah, Saudi Arabia. The patient was detected with acute pneumonia and renal failure. Similar cases were also reported in Jordan and UAE where the patients developed acute respiratory conditions with a mortality rate of around 60% [6].

The clinical features of this virus resembled SARS-CoV. The Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses decided to call the virus MERS-CoV [7]. On 11 February 2020, WHO named the new coronavirus infection Coronavirus Disease 2019 or COVID-19.WHO on March 10, 2020, reported 113702 confirmed cases of COVID-19 with 4012 total death cases worldwide. The infection of coronavirus is more prone to people having a weak immune system and also are already suffering from other diseases [8]. Approximately 20-51% of COVID-19-infected people are reported to have other diseases like heart and cerebrovascular diseases (7–40%), diabetes (10–20%), and hypertension (10–15%). Patients with weak immunity, respiratory failure, or weak lungs are more prone to death because of infestations of influenza, SARS-CoV and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and COVID-19 [9, 10].

Infections and transmissions of COVID-19 are highly contagious, within a short span it became a pandemic and within 3 months 165 countries got infected. At the site of origin, that is in China among the total number of infected cases of coronavirus with approximately 3.9 % of death cases registered. Globally among total cases of coronavirus infections, around 4.06 % of death cases are registered [11].

2. Taxonomy of Coronavirus

Order Nidoviralesconsists of three RNA virus families Coronaviridae, Roniviridae (pathogen of insects), and Arteriviridae (pathogen of birds). The Coronaviridae family comprises of two subfamilies, Coronavirinae and Torovirinae [12]. Coronavirinae comprises enveloped and spherical viruses pathogenic to humans and animals whereas, Torovirinae consists of kidney or rod-shaped viruses causing enteric infections of horses, pigs, cattle, and goats. Coronavirinae can further be genotypically and serologically divided into four groups: alpha-coronavirus, beta-coronavirus, gamma-coronavirus, and delta-coronavirus [13]. Human infections are caused by alpha and beta-coronavirus. Alpha-coronavirus contains human viruses HCoV-229E, HCoV-NL63, porcine transmissible gastroenteritis coronavirus (TGEV), PEDV, and porcine respiratory coronavirus (PRCV). Beta-coronavirus includes mouse hepatitis virus (MHV), SARS-CoV, MERS-CoV, HCoV-OC43, HCoV-HKU1, bat coronavirus HKU4, bovine coronavirus (BCoV), and various other animal pathogens. Their infestations result in multiple organ failures such as heart, kidney, liver, central nervous system, and gastrointestinal system [14] Gamma-coronavirus infects whales and birds including avian infectious bronchitis coronavirus (IBV), and delta-coronavirus infects pigs and avian species including porcine delta-coronavirus (PdCV).

During electron microscopy, the coronavirus appears to have spikes around it. These rings of spikes around the viruses help them to bind or adhere to host surfaces. In Latin, Corona means crown or halo, which indicates its morphological appearance as a crown or sort of solar radiation around the virus particles which appears as club-shaped and measures around ~20 nm[15]. The genome of coronavirus is made of positive-sense single-stranded RNA that weighs around 27 to 34 kb with helically symmetric nucleocapsid [16].

3. Genome of COVID-19

COVID-19 is pleomorphic, enveloped viruses. They have the largest positive-sense RNA genome typically ranging from 27 to 32 kb. COVID-19 is around 79% genetically similar to viruses belonging to the group SARS-CoV [17]. The genome of SARS-CoV is 29727 nucleotides in length and it has 11 open reading frames. These virions contain major structural proteins: the transmembrane (M) glycoprotein, the spike (S) glycoprotein, the envelope (E) protein, and the internal phosphorylated nucleocapsid protein (N) (See

Figure 1) [18]. The nucleocapsid of the virus is composed of genomic RNA and N proteins, buried inside phospholipid bilayers. The spike proteins S cover the phospholipid bilayer mediating virus entry into host cells. Some coronaviruses contain another envelope protein with both hemagglutinations, and esterase functions called hemagglutinin-esterase protein (HE). They have distinctive morphology having club-shaped glycoprotein projections at their envelope. These projections give coronavirus the appearance of crowns and hence their name; *corona* in Latin means crown.

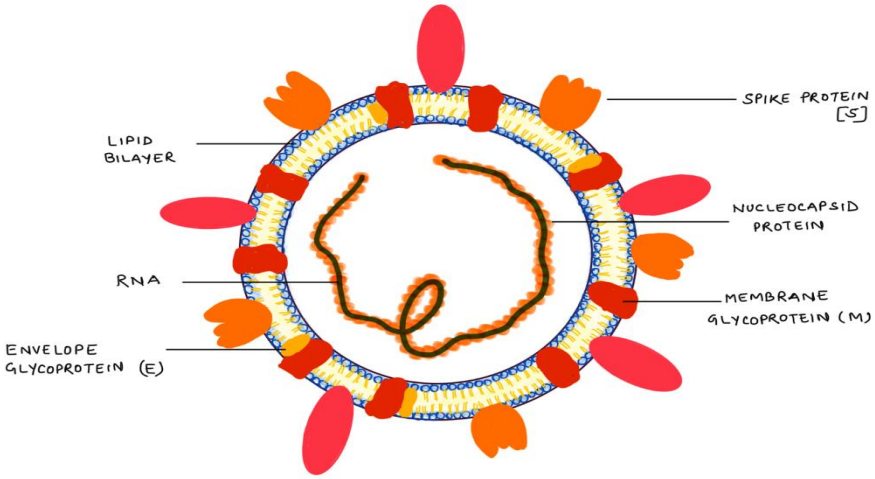

Fig. 1. A structure of Severe Acute Respiratory Syndrome (SARS) coronavirus

4. Molecular basis of pathogenicity

The COVID-19 infection begins with viral entry into the host cells via its binding to the host cell receptors ACE2, angiotensin-converting enzyme 2 [19]. Both the virion and host cells' membrane fuses giving a passage for the coronavirus to enter inside the host cell. The viral genome which is positive-sense single-stranded RNA enters into the host cells and highjacks the host's translation machinery, by attaching itself to the host's ribosomes producing structural and nonstructural polyproteins (nsp). These nsps are further lysed by conserved proteases of the virus, like the main protease (MPro), chymotrypsin-like protease (3CLpro), and papain-like protease (PLpro) [20]. The viral proteinase PLpro acts as deubiquitinase, which brings about immune suppression by de-ubiquitination of interferon factor 3 and NF-κB, etc. This coronavirus genome encodes RNA-dependent RNA polymerase RdRp (nsp12) a replicase that further generates negative-stranded RNA templates to make multiple copies of viral genomic RNA.[15]RdRp can also be a drug target for antiviral therapy. The negative-strand RNA further forms 3′ co-terminal nested genomic mRNAs. The virus once inside the host cells will take 10-12 hours to replicate. Newly synthesizing virions are grown into rough endoplasmic reticulum with the localizations of M proteins and concentrate at intracytoplasmic vesicles. Through the Golgi apparatus, the newly formed virions are released by exocytosis from plasma membranes. Infection of these viruses causes the formation of syncytia i.e., fusion or lysis of cells [21]. All these fragments formed help in the formation and packaging of new virions and hence spread the viral infection at a large scale.

The adherence of coronaviruses occurs in the host cells through S proteins or Spike proteins. S proteins are transmembrane glycoproteins present in coronavirus; they form homotrimers over the virus surface giving the virus its characteristic crown-like appearance [22]. These proteins are essential for viral entry into target cells and are thus important in therapeutic studies. S glycoprotein monomer contains two subunits S1 and S2. The S1proteinsubunit helps in virus attachment to target cell receptors and the S2 subunit helps in the fusion of both membranes [23]. S proteins play a crucial role in the tropism of coronaviruses; deletions in some portions of S proteins turn Transmissible Gastroenteritis Coronavirus (TGEV) into Porcine Respiratory Coronavirus (PRCV), leading to a change in tropism from

gastrointestinal to the respiratory tract. Group 1 coronaviruses bind to metalloproteases such as 229E adhere to human aminopeptidases N and NL63 binds to angiotensin-converting enzyme 2 (ACE-2). Group 2 coronaviruses on the host surface through the attachment of 9-O-acetylated neuraminic acid and SARS coronaviruses also binds to ACE-2 for entry into host cells.

5. Assay of Corona detections

The coronavirus (SARS-CoV2) genetically varies from SARS-CoV and MERS-CoV, but it shows 85% similarity with bat SARS-like coronaviruses (bat-SL-CoVZC45). Assay of corona detections is firstly done by screening existing antiviral molecules that could be of help in treating the disease. SARS-CoV2 infects upper respiratory tract epithelial cells and lungs in humans. COVID-19 when cultured in vitro in African green monkey kidney (Vero) cells E6 and human hepatoma cell line clone Huh-7 cell lines take around 6 days to reach a detectable limit, once infected it can be found in respiratory epithelial cells after 4 days [24].

The diagnosis of infected patients cannot be directly done on the basis of symptoms as the symptoms are non-specific and also asymptomatic infection is also observed in some of the patients. The confirmations and validations of coronavirus can be done by the Reverse transcription-polymerase chain reaction (RT-PCR) or Next-generation sequencing (NGS)by using the samples taken from patients such as nasopharyngeal swabs, sputum, lower respiratory tract secretions, blood, feces, etc by detecting nucleic acid of coronavirus. The samples taken from lower respiratory tracts are more accurate for the confirmation of the coronavirus [24]. The severity of SARS-CoV-2 is directly linked to the unpredictable nature of COVID-19 leading to further deadly complications. The RT-PCR performs amplifications and reverses transcriptions simultaneously henceforth there are more chances for the generation of lower molecular weight amplicons.

Biomarkers are important for categorizing patients and then proceeding with their proper line of treatment. Biomarkers such as hematological (lymphocyte and neutrophil count), inflammatory CRP (C-reactive protein), ESR (erythrocyte sedimentation rate), PCT (procalcitonin), immunological IL-6 (interleukin-6), biochemical such as D-dimer, troponin, CK (creatine kinase) AST (aspartate aminotransferase), and also ARDS (acute respiratory distress syndrome) are taken into account for the same [25]. The manifestation of coronaviruses leads to leukopenia (decrease in the leukocyte count) while this count may or may not be affected during the initial stages, critical patients have elevated WBC levels [26]. Another symptom is lymphopenia in which the total number of lymphocytes, $TCD4^{+}$, $TCD8^{+}$, B cells, and Natural killer cells (NK cells) decreases [27]. The physiological response to infections of coronaviruses varies from patient to patient, in some cases, the liver enzymes are increased such as lactate dehydrogenase (LDH), muscle enzymes, and myoglobin. Normal cases have increased levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and normal procalcitonin, and in serious cases, the D-dimer and peripheral blood lymphocytes spontaneously decrease and increased inflammatory factors. 2019-nCov can also be detected through the IgG antibody titers; it takes around 3 to 5 days after onset.

6. Modes of Transmission

The glycosylated spike (S) proteins can induce an immune response in human beings. The S protein priming to the ACE2 receptoriscatalyzed by the proteolytic enzyme serine protease TMPRSS211 of host cells. This also facilitates the invasion of coronaviruses into host cells [15]. Interaction between S protein and ACE2 initiates the infections and invasion of coronavirus. The affinity of the S protein belonging to SARS-CoV2 to ACE2 is very much higher in comparison to that of the SARS-CoV S protein [28]. Hence, the transmission rate of SARS-CoV2 is greater compared to SARS-CoV [29].

The infections and transmission of human coronaviruses occur through the respiratory tract. Experimentally the coronaviruses 229E and OC43 were observed in the intranasal inoculations of adult human samples [30]. The people coming in close contact with the infected patients can also be infected through the aerosol or airborne zoonotic droplets released during their coughing and sneezing

actions. COVID-19 became a pandemic in the current situation and globally in each country; researchers are trying to find out their different routes of transmission and methods of prevention [31]. Coronaviruses infect the ciliated epithelium through binding domains i.e. virus spikes and enter inside the human cells through exopeptidase (Angiotensin-converting enzyme, ACE2) present in the membrane receptors of the lungs [32]. Coronaviruses damage the sites of infections with their replications [33]. Initial reports for coronavirus infections were only for rats, mice, cats, dogs, horses, turkeys, cattle, and pigs and after some time these viruses are transmitted to human beings similar way as that SARS-CoV. Proteolytic enzymes which break at the S2 position of the S protein of SARS-CoV lead to infections and fusion to the host membranes [34]. The human enteric coronaviruses (HECoV) can be successfully cultured in human embryonic intestinal organ culture and prone to endemic in developing countries and western countries having large migrants from developing countries and low socio-economic groups, also the greater transmission of this virus is observed in homosexual males in comparison to normal peoples [35].

7. Pathogenicity and Symptoms of COVID-19 associated with some organs

In several studies, it is found that the pathogenesis of SARS (caused by SARS-CoV), results in the tremendous release of a pro-inflammatory cytokine such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and IL-12 [36]. Similarly, MERS (caused by MERS-CoV) causes a notable increase in the IL-6, IL-1β, and IL-8 but it has shown delayed induction of proinflammatory cytokine release [37]. Like that of SARS and MERS, the infection caused by SARS-CoV2 (in severe cases) also induces an increase in cytokines in plasma-like IL-6, IL-2, IL-7, IL-10, granulocyte-colony stimulating factor, interferon-γ (IFN-γ) inducible protein, monocyte chemo-attractant protein, macrophage inflammatory protein 1α, and TNF-α [38]. COVID-19 associated with SARS-CoV-2 is responsible for lower respiratory tract infections and in adverse conditions can also lead to Acute Respiratory Distress Syndrome (ARDS), sepsis and septic shock and multi-organ failure, including acute kidney injury and cardiac injury.

7.1. Lungs

SARS-CoV2-associated COVID-19 is primarily targeted at the respiratory tract which majorly involves the lungs. In diseased conditions, the lung's alveoli get fluid and fibrin-filled and form hyaline membranes. The alveolar exudates contain several syncytial cells including macrophages. Viral invasion and its presence can be detected in Type II pneumonocytes and macrophages. Also, the alveolar septum can have edema and congestion resulting in the infiltrations of monocytes and lymphocytes. In adverse viral infection cases, the lungs can be affected by hemorrhage, necrosis, and over-hemorrhagic infarction [24].

7.2. Spleen, hilar lymph nodes, and bone marrow

COVID-19 infections lead to a decrease in the number of lymphocytes and the spleen becomes atrophic and the malfunctioning of bone marrow resulting in decreased Myelopoiesis is observed. Spleen also shows necrosis, focal hemorrhages, the proliferation of macrophages, and phagocytosis. Focal necrosis and a decrease in the number of lymphocytes are also observed in lymph nodes. With the analysis of the immune-histochemistry of CD4+ and CD8+, it was revealed that both the spleen and lymph nodes are having a loss in the number of T cells [24].

7.3. Heart and blood vessels

Infections of coronaviruses along with the lower respiratory organs will also damage the heart and myocardial cells. In diseased persons having damaged myocardial cells, infiltrations of monocytes and neutrophils are observed in the cardiac interstitium. Blood cells are also affected because of viral infections and loss of endothelial cells, endovasculitis, and thrombi are observed [8].

7.4. Liver and gall bladder

COVID-19 infections cause liver enlargement with dark-red colorations and liver dysfunction in critically ill patients. This virus directly targets the liver as the receptor

of SARS-CoV-2 i.e., ACE2 is greatly expressed in cholangiocytes [39], hence disintegrated viral particles can also be observed in stool samples [40]. Hepatocytes are damaged and neutrophil infiltrations and congestions of sinusoids are also observed in coronavirus infections. Major symptoms of viral infections are the presence of microthrombi, infiltrations of lymphocytes and histiocytes, and gall bladder showing marked swellings [24]. Persons with comorbidity like COVID-19 infections and liver cirrhosis are prone to major chances of acute-on-chronic liver failure (ACLF) [41]. The viral invasion in the liver is enough to make people sicker [42].

7.5. Kidneys

Along with the heart, liver, and lungs, remarkable damage is also observed in kidneys like the destruction of renal tubules, epithelial cells, hyaline cells, and the occurrence of proteinaceous exudates in Bowman's capsule around glomeruli. The interstitium of the kidney shows the presence of microthrombi and fibrotic foci [24].

7.6. Other organs

SARS-CoV-2 infects and damages other organs also, like the central nervous system, stomach and bowel, and esophagus. Severe infections and invasion of COVID-19 lead to the destruction of neurons along with cerebral hyperemia and edema and marked focal necrosis in adrenal glands. The Epithelial mucosae of the esophageal, stomach, and bowel are destructed at variant levels [24].

8. COVID-19 Pandemic

The disease COVID-19 is the most notorious disease of this century caused by SARS-CoV-2. In a short span, this disease spread globally and harmed human beings potentially socio-economically and medically, hence on March 11, 2020, World Health Organization (WHO) declared COVID-19 as pandemic and as of April 12, 2020, globally 1,696,588 people were infected with 105,952 reported death cases [43]. The notable coronaviruses which cause harm to human beings are SARS-CoV, MERS-CoV, and SARS-CoV-2, which have originated from other mammals like bats, civet cats, camels, and pangolins [44]. COVID-19 or 2019-nCoV belongs to a group of enveloped positive-sense RNA viruses. In comparison to DNA viruses, RNA viruses can mutate faster and there are more chances of strain modifications as mutations are negatively related to their genome [45]. Coronaviruses HCoV 229E, OC43, and NL63 are often detected in serology testing for mild to severe pathogenicity. Very fewer reports are available on HKU1, but its occurrence is reported worldwide, once it is infected there are more chances of its reinfection within a short span like a month [46, 47].

9. Available treatment therapies for COVID-19

The treatment policies and regulatory guidelines for the prevention of COVID-19 are somewhat different in each country. The guidelines as given by the WHO are accepted worldwide for the management of symptoms, and suggestions of caution to different patients like pediatric patients, pregnant women, and patients with co-morbidities. Initially, there were no approved treatment methods and general treatments were advised for the general and supportive management concerning requirements of patients, such as antipyretics for fever, oxygen therapy for respiratory distress, hydration maintenance, antibiotic treatments for bacterial infections, and ventilation for respiratory support. Medicine like hydroxychloroquine, chloroquine phosphate, remedesivir, and lopinavir/ritonavir are now globally recommended [48]. In the initial stages of a pandemic, ribavirin is thought to be having a synergistic effect along with interferon-alpha, and mycophenolic treatment is supposed to be monotherapy for recovery [49].

9.1. Allopathic

For the disease conditions and invasion of coronaviruses, the prior treatment suggestions are allopathic drugs. The drugs advised to COVID-19 patients i.e., Tocilizumab can significantly improve the health of patients and minimize the destruction. This could be one of the therapeutic strategies for the treatment of COVID-19 patients [39]. The emergence of this disease has occurred in China, the Chinese National Health Commission (NHC) for the prevention,

diagnosis and treatment of COVID-19 suggested several groups of antiviral drugs including interferon α (IFN-α), lopinavir/ritonavir, chloroquine phosphate, ribavirin, and arbidol [5].

9.1.1. Hydroxychloroquine

As the Chinese NHC suggest allopathic drugs, among them Hydroxychloroquine (HCQ) is an important drug, which is a derivative of chloroquine (CQ), and after the declaration of the pandemic this drug is in high demand as it is having potential activity against SARS-CoV-2, in comparison to CQ [15]. The combinations of HCQ with azithromycin possess potent activity against SARS-CoV-2 in comparison to HCQ alone [50]. But these therapies have several issues and are dropped out as the HCQ causes QT prolongation [51] while azithromycin showed pro-arrhythmic activity. As per the safety precautions concerns, ICMR (Indian Council of Medical Research) doesn't recommend HCQ to common people, this drug is only suggested for critical cases and frontline workers like healthcare workers who are directly exposed to COVID-19-positive populations. For the healthcare workers exposed to household personnel, the ICMR suggested they be isolated and home-quarantined even after treatment with the HCQ [52]. Some authors also suggested the HCQ treatment can also lead to radiological progression [53].

9.2. Ayurvedic and Yoga

Ayurvedic and Yoga are ancient Indian well-known therapies without any side effects. For the effective prevention of COVID-19, several local decoctions and kadha have been suggested and in some Indian regions were found to be very effective with no cases of COVID-19. Ayurveda and Yoga played a major role in immunity booster's and a healthy lifestyle instead of the treatment of therapies and prescriptions of medicine [54].

9.2.1 Local Prophylaxis

The points of human beings that are directly linked to organs like the eyes, nose, and mouth will act as the major entry points for SARS-COV-2 and invade the human body. Once the SARS-COV-2 enters the respiratory tract through the mouth and nose, it stays to some extent in the throat. SARS-COV-2 having fatty acid covers can easily attach to mucosal layers and take access inside the body through cell receptors. Ayurveda therapies target these mucosal entry points to prevent the entry of COVID-19 and improve innate immunological responses. Ayurveda mentions general measures such as hot water, hot food, and herbal decoctions, gargling with medicated water, steam inhalation acts as a barricade or frontline of inhibitors for the entry of the virus and also recover the patients with mild cases [54].

9.2.2. Medicated water

Ancient therapies and Ayurveda recommends hot water and household spices in drinking hot water for the relief of mild symptoms of COVID-19 like sneezing, cough, and bodyache.[49]The popular spices that can be used as medications along with the hot water are dry ginger (*Zingiber officinale*), yashtimadhu (*Glycyrrhiza glabra*), and nut-grass (*Cyperus rotundus*) rhizomes; khus (*Vetiveriazizanioides*), and Indian sarsaparilla (*Hemisdesmus indicus*) roots; coriander (*Coriandrum sativum*) and fennel seeds (*Cuminum cyminum*); and cinnamon (*Cinnamomum verum*) and catechu (*Acacia catechu*) barks [55].

9.2.3. Mouth rinse and gargle

To wash and clean the mouth, recommended ayurvedic formulations are Gandusha and Kavala [54]. The major components used for the preparations of medicated water are turmeric (*Curcuma longa*) rhizome, yashtimadhu or liquorice (*Glycyrrhiza glabra*) stem, neem (*Azadirachta indica*) and catechu (*Acacia arabica*) barks, and natural salt, etc. The secondary metabolites or active components present in liquorice e.g., glycyrrhizin is having significant potential in the prevention of viral attachment and penetrations and help in inhibiting viral replications in comparison to viral drugs for SARS coronaviruses [56]. Also in Yoga therapy, salt water is recommended for nasal clearance and washing as Jala Neti [57].

9.2.4 Nasal oil application

For the prevention of viral entry and protection of the respiratory tract, ayurvedic

oils are effective. In Ayurveda, medicated oil such as vegetable and butter oil was prepared from sesame and coconut and administered through the nostrils [54].

9.2.5. Steam inhalation

Steam inhalations are a routine method in Ayurveda and Allopathy for disease treatment. The hot water steam along with the aromatic oils prepared from menthol extract is effective in the treatment of nasal and throat congestion, broncho-constriction, headache, and sinusitis [54].

9.2.6. Rasayanas as Immunomodulators

Ayurvedic formulations like Rasayana are very much effective in the treatment of SARS-COV-2. These formulations are also helpful in the curing of immune hemostasis and immunomodulation [58]. SARS-COV-2 infections are faced by the defensive mechanism of the human body in which the adaptive immune response acts as the protective phase which helps in the elimination of viral infection [59]. The Rasayana formulations prepared from medicinal plants help in strengthening immunity and immunomodulation. The major plants used are Ashwagandha, Guduchi, Shatavari, Amalaki, and Yashtimadhu [54].

9.3. Homeopathy

Homeopathic therapeutics is recommended for chronic and communicable diseases and also helps in immune modulations. With the symptoms of the diseases, often recommended medicines are *Aconite napellus*, *Arsenicum album*, *Bryonia alba*, *Gelsemium sempervirens*, *Rhus tox*, *Eupatorium perfoliatum*, *Ipeca caucunha*, *Belladonna, Camphora*.

9.4. Immune system booster

The best strategy to fight against diseases is the prevention and enhancement of the immune system. The human body has a great immune system and with the maintenance of perfect body health, it gets better to fight against diseases. Good health and good nutrient supplement in their daily intake of food and ignorance of junk food enhance the immunity of human beings [5].

9.5. Convalescent plasma

Convalescent plasma is the plasma collected from the B cells of recovered patients infected with Covid-19, which has pathogen-specific active antibodies. These recovered patients are presumed to have developed an efficient antibody response. This slowly responding antibody therapy with the aid of convalescent plasma helps in the prevention of pathogen infection, minimizing pathogenesis. With the varying symptom severity, antibody therapy is recommended for the treatments. The well-known antiviral therapy is a passive antibody treatment, used more than a hundred years ago [60]. In this therapy, antibodies directly target the pathogen of interest. Passive antibody therapy is primarily based on the pooling of immunoglobulin as it contains major concentrations of antibodies. When prophylactically administered, this passive antibody treatment has also shown effective recovery in patients [61]. Plasma therapies are nowadays recommended when the subject is unable to generate antibodies. Plasma is the major source for the generations of immunoglobulins and this therapy has significant recovery after post-exposure prophylaxis. Convalescent plasma therapy is recommended for the treatment of hepatitis, mumps, polio, measles, rabies, influenza, Argentine hemorrhagic fever, SARS-CoV, MERS, and Ebola and is also effective in viral loads, cytokine responses [62].

9.6. Vaccines on trials

To control pandemic situations, the administrations of novel vaccines are the most sought-after approach for the prevention of pathogenic diseases. Indian firms in collaboration with foreign laboratories launched several vaccines against coronavirus such as Covishield (Launched by Serum Institute Pune), Covaxin (Launched by Bharat Serum, Hyderabad), and Sputnik (Gamaleya Research Institute). Other than this DNA vaccine has been produced against four MERS coronavirus, whose phase I clinical trials started in September of 2019 [63] and one of the firms Moderna Inc. launched the first batch of mRNA vaccine against SARS-CoV-2 for phase I trials in the USA in February of 2020.

9.7. Mechanism of actions of some drugs and Side effects

Drugs tested to treat COVID-19 can be categorized as those that target the viral replication cycle and others controlling symptoms of the disease. Various steps in the viral lifecycle can act as targets for potential drugs to be used for treating COVID-19. Nonstructural proteins such as 3CL-pro, PL-pro, RdRp, entry pathways for SARS-CoV2, and immune regulation pathways act as drug targets for various medicines [64]. Figure 2 shows a schematic representation of the SARS-CoV2 life cycle and various drug targets at different steps. Because of the serious effects of SARS-CoV-2 on human lives, it is of utmost importance to develop antiviral drugs effective against COVID-19. To stop the intrusion and proliferation of SARS-CoV-2 a combination of drugs or drugs with multiple targets can be employed.

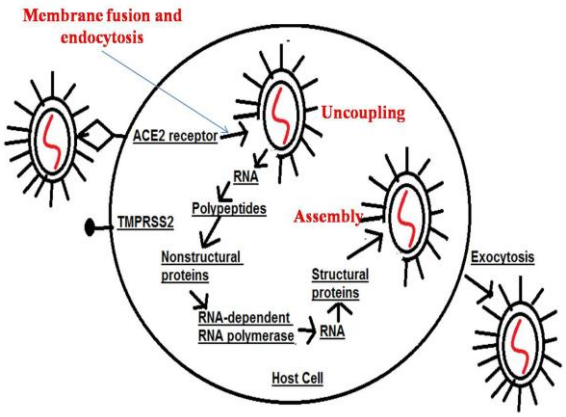

Fig. 2. SARS-CoV2 life cycle and drug targets; ACE2: angiotensin-converting enzyme 2; and TMPRSS2: type 2 transmembrane serine protease

9.7.1. Antimalarial Drugs

During the initial period of SARS infection, based on symptoms, antimalarial drugs were recommended in most countries, and even India exported chloroquine to several other countries. These drugs have shown significant effects in the prevention of SARS and MERS virus replications. Chloroquine and its derivative hydroxychloroquine help in raising the pH of cellular organelles and lysosomes resulting in the enhancement of phagocytic degradations. These drugs are bits of help in the enhancement of the immune system against the pathogen, in combination with cell contents produced during phagocytosis. The drug can be administered solely or in combination with azithromycin [65].

Quinine was initially used as an antimalarial drug which is now taken over by chloroquine and its derivative hydroxychloroquine. They both are polymerase inhibitors targeting heme polymerase which kills the malarial parasite by accumulating toxic heme. These drugs are also used to treat rheumatoid arthritis and SLE (systemic lupus erythematosus) [66]. They can also be used as an antiviral drug in cases of Borna disease, hepatitis A and AIDS [67]. A decrease in viral load is also observed in SARS-CoV-2 patients [68]. Drugs cause inhibition of glycosylation of host cell receptors, and also inhibition of endosomal acidification which leads to the stoppage of viral protein production. Glycosylation inhibition results in the prevention of the binding of ACE2 receptors to the S protein and stops further viral replication, assembly, and release into the host cells. Inhibition of endosomal and lysosomal acidification prevents viral assembly and its re-release in the host cytoplasm [69]. The immunomodulatory effects of the administration of these drugs are attenuation of cytokine production, inhibition of autophagy, and lysosomal activity in host cells [70].

9.7.1.1. Chloroquine

Chloroquine helps in the enhancement of the immune system raising the pH of cell organelles like lysosomes leading to phagocytosis of entering pathogens. It also checks the enzyme metabolism of viruses which includes viral polymerase (both DNA and RNA), glycosylations of viral protein, assembly and transport of viral particles, and finally its release. Chloroquine is also involved in the inhibitions of cellular receptors like ACE2, acidification of the cell surface for the prevention of attachment of viruses, and release of cytokine by immunomodulation [71].

9.7.3. Hydroxychloroquine

Similar to chloroquine, hydroxychloroquine also inhibits viral

metabolism-like enzyme processes and is also involved in raising the pH of cellular membranes to avoid viral attachments. The administration of hydroxychloroquine is involved in the prevention of viral assembly, transport, and release; it also inhibits the polymerizations of RNA and DNA [68].

9.7.4. Antiviral Drugs

In these pandemic conditions, the recommended antiviral drugs are those which are mostly used for the treatment of HIV such as Lopinavir and Ritonavir. Other recommended antiviral drugs which are involved in the inhibition of RNA synthesis areFavipiravir, Ribavirin, Remdesivir, and Galidesivir [70].

9.7.4.1. Remdesivir (GS-5734)

The most recommended antiviral drug is Remdesivir, which is involved in the inhibition of viral RNA polymerization by preventing the activity of RNA-dependent RNA polymerases (RdRps). It is a monophosphoramidate prodrug of a nucleotide analog. Remdesivir-triphosphate (RDV-TP) is similar to ATP which competes to incorporate into polymerizing viral RNA. Once it is incorporated into RNA, it blocks RNA synthesis at the +3 position. Inhibition of RNA synthesis immediately occurs after the addition of three more nucleotides, and then the chain is terminated. Remdesivir incorporation is not proofread by exoribonucleases and remains in the RNA till it blocks further RNA synthesis [71].

9.7.4.2. Lopinavir; Ritonavir

Lopinavir is a protease inhibitor used along with ritonavir as a booster and an antiviral drug. It acts against the virus's main protease (MPro), chymotrypsin-like protease (3CLpro). These drugs bind to the catalytic site of the protease enzyme which is responsible for the replications of the virus and suppress the cleavage of viral polyprotein precursors into mature functional proteins [15].

9.7.4.3. Favipiravir

Like Lopinavir and Ritonavir, another recommended drug in the coronavirus pandemic is Favipiravir which inhibits viral replications by inhibiting RNA synthesis. It is a synthetic prodrug and the active form of this drug is favipiravir-RTP formed by phosphoribosylation. This activated drug principally acts as an RNA-dependent RNA polymerase (RdRp) substrate and gets incorporated into the growing polypeptide chain in place of a purine nucleotide halting further extension. This leads to the termination of viral protein synthesis [71].

9.8. Immunomodulatory

9.8.1. Azithromycin

Azithromycin belongs to the macrolides group of antibiotics. It is having antibacterial, antiviral, and immunomodulatory activities. The immunomodulatory properties present in Azithromycin are preventing pulmonary inflammatory disorders, down regulation of cytokine production, and maintaining and stabilizing the epithelial cell membrane. The action of this drug on viral mitigation is not clear; the principal mechanism which controls viral infection is by reducing cytokine production, respiratory viral infections, and also downregulation of inflammatory responses. The other mechanism involved in the immunomodulation includes inhibition of IL-8 cytokines leading to a reduction in chemotaxis of neutrophils in the lungs, reduction in reactive oxygen species production, enhancement in apoptosis caused by neutrophils, inhibitions of the nuclear transcription factor, activation and reduction in hypersecretions of mucus [67].

9.8.2. Interleukin-1 (IL-1) Antagonists

Anakinra and canakinumab act as Interleukin-1 receptor antagonists which prevent interleukin-1 binding to its IL-1 receptors. Interleukin-1 is responsible for several immunological responses like activations of IL-6. Anakinra competitively prevents the binding of IL-1 alpha and IL-1 beta to IL-1 receptors. Similarly, Canakinumab prevents the binding of IL-1 beta to IL-1 receptors by neutralizing it with the help of human monoclonal antibodies[72].

9.8.3. Interleukin-6 (IL-6) Receptor Antagonists

Interleukin-6 (IL-6) receptor antagonists bind to soluble and membrane-bound IL-6 receptors and inhibit IL-6-mediated signaling.

IL-6 is involved in major immunological and physiological responses, helps in the T-cell activation, induction of antibody secretions and initiation of synthesis of acute-phase proteins, stimulation for the cell differentiation, and cell proliferation of hematopoietic precursors. The production of interleukin-6 is done by fibroblasts, monocyte, and T and B-cells [73]. Improvement in respiratory and hemodynamic parameters is reported in patients after IL-6 blockade [74]. Activation of T-lymphocytes and macrophages in COVID-19 patients results in the release of proinflammatory cytokines including IL-6 which bind to IL-6 receptors present on the target cells causing hyperinflammation [75]. Blocking the IL-6 receptor by IL-6 receptor antagonists in these patients results in weakened immune damage to target cells and inflammatory responses [76].

9.8.4. Janus Kinase (JAK) Inhibitors

Janus kinase (JAK)/ signal transducers and activators of transcription (STATs) act as the mediator for the signal transmission between interactions of membrane receptors of cells and growth factors with cytokines. Many cytokines are regulated by this mode of signal transduction. Janus kinase is involved in the modulation of intracellular activity (e.g., gene expression) by phosphorylation and activation of STAT. The cytokine receptors are expressed in several cells of the immune system, hence JAK-mediated signaling plays a vital role in the pathogenesis of immune-mediated diseases. The STATs activation (latent cytoplasmic transcription factors) and prevention of phosphorylation are modulated by JAK inhibitors. These JAK inhibitors prevent phosphorylation and bring about downregulation of the JAK/STAT signal-transduction pathway causing a significant reduction in cytokine release and hence decreased inflammation. Reports are there stating that JAK inhibitors can be used for COVID patient's treatment[77].

9.9. Side effects of available drugs

9.9.1. Remdesivir

The antiviral drugs administered during the infection of COVID-19 come along with several side effects. These side effects are reported in 66% of patients approximately; the major caution is observed in renal impairment when remdesivir is formulated with sulfobutyl ether beta-cyclodextrin sodium (SBECD). The patients treated with remdesivir also show infusion-related reactions, enhancement of hepatic enzyme concentrations indicating possible liver damage, and hypersensitivity (Table 1)[78].

9.9.2. Chloroquine and Hydroxychloroquine

During the initial outbreak of coronavirus, the globally recommended drug was Chloroquine and Hydroxychloroquine as it helps in the recovery of infected patients. These drugs are not suggested to infected patients without a prescription of medical practitioners or in a nonhospital setting as after administration of this drug patients have to face several side effects like cardiac arrhythmias (e.g., QT prolongation) and several unnecessary drug interactions [79]. It is also suggested that during chloroquine treatment other drugs which are responsible for QT prolongations should be avoided [79]. Patients having comorbidity are at high risk during the treatment of chloroquine, as the drug may cause retinal damage, reduced visual acuity and bilateral loss of vision. Patients suffering from diabetes and G6PD deficiency are at high risk. HCQ is a less toxic and preferred drug when compared to CQ [80].

9.9.3. Lopinavir and Ritonavir

The recommended antiviral drugs next to Remdesivir are Lopinavir and Ritonavir. Administration of these drugs into coronavirus-infected patients shows several side effects like that of chloroquine and hydroxychloroquine such as cardiac arrhythmias (e.g., QT prolongation) [79]. These drugs are having significant drug interactions but are not recommended to patients with hepatic disease or hepatitis.

9.9.4. Favipiravir

Similar to the above-mentioned drugs, favipiravir is also used in antiviral therapy. This drug is not recommended in the case of pregnancy, during animal studies it was observed that this drug can lead to the death of embryos and causes teratogenicity [105].

Table 1. List of the drugs, their target sites, and side effects

Sr. No.	Name of Drug	Action	References
1	Brivaracetam	Binds to synaptic vesicle protein 2A (SV2A) influencing synaptic vesicle release	[81]
2	Carbamazepine	Induced Toxic Epidermal Necrolysis	[82]
3	Cannabidiol	PPARγ agonist, inhibits the development of pulmonary fibrosis and regulates activation of fibroblast/myofibroblast, and is effective in the progressivity of corona by downregulation of SARS-CoV2, also it has immunomodulatory and anti-inflammatory activity	[83]
4	Cenobamate	Anti-seizure medications	[84]
5	Clonazepam	Anxiety Management	[85]
6	Clobazam	Acute seizure management and ATV	[86]
7	Diazepam	Acute seizure management and ATV	[86]
8	Eslicarbazepine	CYP3A inducers	[84]
9	Ethosuximide	Seizure management	[77]
10	Gabapentin	Neuropathic pain reliever	[87]
11	Lacosamide	Antiepileptic drugs	[86]
12	Lamotrigine	Antiepileptic drugs	[81]
13	Levetiracetam	Reduce seizure threshold	[88]
14	Lorazepam	Antidepressant	[89]
15	Oxcarbazepine	Antiseizure management	[85]
16	Perampanel	Neuroprotector, antiviral	[90]
17	Phenytoin	Antiseizure management	[91]
18	Phenobarbital	Antiseizure management	[86]
19	Pregabalin	To control nerve pain from diabetes, shingles, spinal cord injury, and fibromyalgia	[92]
20	Primidone	The anti-epileptic drug, seizure management	[86]
21	Retigabine	Antiseizure drug	[77]
22	Rufinamide	Antiepileptic drug	[84]
23	Sulthiame	Antiseizure drug	[77]
24	Tiagabine	blocks GABA uptake into presynaptic neurons	[93]
25	Topiramate	Antiepileptic drug	[84]
26	Valproic acid	Reducing its receptor ACE-2 expression level	[94]
27	Hydroxychloroquine	Potent in vitro inhibitor of SARS-CoV-2	[95]
28	Chloroquine	Blocks viral entry by increasing endosomal pH and inhibiting viral fusion to the cell Membrane Decreases affinity of ACE2 receptor for SARS-Cov-2 by impairing terminal glycosylation of ACE2	[96]
29	Lopinavir/ritonavir	Lopinavir is a viral protease inhibitor that blocks viral replication Ritonavir blocks CYP3A4 thereby boosting concentration of lopinavir	[95]
30	Remdesivir	RNA-dependent RNA, polymerase inhibitor	[97]
31	Favipiravir	RNA-dependent RNApolymerase inhibitor	[97]
32	Angiotensin/RAS Blocking gents	Antiviral	[61]
33	Darunavir/cobisistat10	Antiviral	[98]
34	Interferons	Antiviral	[99]
35	Nitazoxanide	Potential against SARS-CoV-2	[97]
36	Oseltamivir	Neuraminidase	[100]
37	Ribavirin (oral)	Antiviral for MERS	[99]
38	Steroids	No effects	[101]
39	Tocilizumab	Antivirals	[36]
40	IL-6 inhibitors	Curbs cytokine release syndrome by inhibiting IL-6 receptors	[102]
41	Anti-GM-CSF	Reduce severity of cytokine release syndrome by inhibiting GM-CSF pathway	[103]
42	Convalescent plasma	Antibody neutralization of virus	[104]

9.9.5. Azithromycin

Similar to other drugs recommended during COVID-19 infection, this drug also has several side effects in the patients. This drug is having significant drug interactions but patients with comorbidity are at high risk for cardiac arrhythmias (e.g., QT prolongation) [79].

9.10. Interleukin-1 (IL-1) Antagonists and Interleukin-6 (IL-6) Receptor Antagonists

Interleukin-1 (IL-1) antagonists have a significant effect on the virus multiplication and recovery of patients, but treatment with these drugs is not recommended for patients with thrombocytopenia and neutropenia who are at high risk as it will cause infusion-related reactions (anakinra). Administrations of Interleukin-6 (IL-6) receptor antagonists in coronavirus-infected patients have a high risk of GI perforation and hepatotoxicity.

9.10.1. Janus Kinase (JAK) Inhibitors

Treatment of patients with Janus Kinase (JAK) inhibitors shows a reduction in viral infections, they also have a high risk of pulmonary embolism (PE), Thrombosis, including deep vein thrombosis (DVT), pulmonary embolism (PE), and GI perforation. This drug is not recommended for patients suffering from neutropenia, lymphopenia, and anemia.

10. Social impacts

Since March 23, 2020, after the outbreak of the COVID-19 pandemic, the social life of

human beings is completely disturbed. Not only normal routine is disturbed, but it also has a major impact on socio-economic life, people lost their job. During the corona pandemic, around 2.6 billion people, or more than that was completely put under strict lockdown and the pandemic has taken the lives of many people. The strict lockdown kept people away from social gatherings, meetings, and several other celebrations resulting in a major loss in businesses at local and global levels. National and International tourism is majorly affected as all national and international flights were canceled; only Japan and Indonesia alone estimated a loss of 2.44 billion dollars during this pandemic. Not only the tourism industry but all manufacturing units and factories were closed as transportation are restricted, workers were not allowed to work, and production in every sector has been stopped during this pandemic. To date, COVID-19 is not been completely eradicated socially, and we are facing often lockdowns and we will continue to suffer from economic loss and social complications.

11. Conclusion

After the plague pandemic in 1919, the major outbreak of COVID-19 occurred in 2019 by SARS-CoV-2 belonging to the coronavirus family. SARS-CoV-2 which is highly dangerous and contagious has hit the world with an unsolicited surprise causing COViD-19, a highly transmissible disease that shows variations in the clinical profile. A thorough study and investigation are needed to understand the efficacy and safety profile for the treatment of COViD-19. Several drugs are available for viral infections in the modern sciences, but most of the drugs have major side effects, hence the development of safe vaccines is mandatory during this pandemic. The outbreak of COVID-19 infections is a major challenge for the healthcare industry to reduce the chances of infection and transmission. For the development of long-term drugs for such pathogenic viruses, researchers should focus on the mode of replications and infections associated with COViD-19, not only symptomatic infections but asymptomatic infections should also be given special interest.

Conflict of Interests

All authors declare no conflict of interest.

Ethics approval and consent to participate

No human or animals were used in the present research.

Consent for publications

All authors read and approved the final manuscript for publication.

Availability of data and material and Code availability

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Authors' contributions

All authors had equal role in study design, work, statistical analysis and manuscript writing.

Informed Consent

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