Current Pharmaceutical Design, 2022, *28*, 948-968

REVIEW ARTICLE

Nanotechnology-based Approaches and Investigational Therapeutics against COVID-19

Md. Mominur Rahman[1], Muniruddin Ahmed[1], Mohammad Touhidul Islam[1], Md. Robin Khan[2], Sharifa Sultana[1], Saila Kabir Maeesa[1], Sakib Hasan[1], Md. Abid Hossain[1], Kazi Sayma Ferdous[1], Bijo Mathew[3], Abdur Rauf[4] and Md. Sahab Uddin[5,6,*]

[1]*Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, Dhaka, Bangladesh;* [2]*Bangladesh Reference Institute for Chemical Measurements, Dhaka, Bangladesh;* [3]*Department of Pharmaceutical Chemistry, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Sciences Campus, Kochi 682041, India;* [4]*Department of Chemistry, University of Swabi, Swabi, Anbar, Khyber Pakhtunkhwa, Pakistan;* [5]*Department of Pharmacy, Southeast University, Dhaka, Bangladesh;* [6]*Pharmakon Neuroscience Research Network, Dhaka, Bangladesh*

ARTICLE HISTORY

Received: December 04, 2020
Accepted: April 30, 2021

DOI:
10.2174/1381612827666210701150315

Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the novel coronavirus responsible for the current global pandemic, which first emerged in December 2019. This coronavirus has affected 217 countries worldwide, most of which have enacted non-remedial preventive measures, such as nationwide lockdowns, work from home, travel bans, and social isolation. Pharmacists, doctors, nurses, technologists, and other healthcare professionals have played pivotal roles during this pandemic. Unfortunately, confirmed drugs have not been identified for the treatment of patients with coronavirus disease 2019 (COVID-19) caused by SARS-CoV2; however, favipiravir and remdesivir have been reported as promising antiviral drugs. Some vaccines have already been developed, and vaccination is ongoing globally. Various nanotechnologies are currently being developed in many countries for preventing SARS-CoV-2 spread and treating COVID-19 infections. In this article, we present an overview of the COVID-19 pandemic situation and discuss nanotechnology-based approaches and investigational therapeutics for COVID-19.

Keywords: COVID-19, SARS-COV-2, antiviral drugs, nanotechnology, vaccines, immunomodulation.

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) has been declared a pandemic, affecting human health worldwide [1]. Coronaviruses (CoVs) are extremely variable positive-sense single-stranded RNA viruses that belong to the Coronaviridae family [2]. The highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to the genus *Betacoronavirus* [3] and may cause respiratory, hepatic, neurological, and gastrointestinal problems in people and animals. Close contact, sneezing, talking, and coughing are ways through which SARS-CoV-2 can be transmitted from person to person [4-6]. The droplets expelled during a cough typically fall onto the surfaces of objects and can spread to long distances through the air. In some cases, they have been reported to remain in the air for as long as 10 minutes [7]. On March 11, 2020, the Director General of the World Health Organization (WHO) declared COVID-19 a pandemic, based on the shocking levels of its spread [7]. Despite the fact that the epidemic has been ravaging the world for more than a year, no medications have been developed that can totally and efficiently eradicate the virus [8]. Worldwide, 126,708,448 people have been infected with COVID-19, 2,779,848 have died, and 102,178,870 recovered from this viral disease (as of March 27, 2021) [9].

The common symptoms associated with this disease include fatigue, fever (88%), loss of smell and taste, cough (68%), and shortness of breath. If pneumonia and acute respiratory distress syndrome (ARDS) occur, the situation worsens. SARS, the disease caused by the related SARS-CoV virus, is 18 times more likely to infect individuals at lower temperatures than at higher temperatures [10, 11]. Various antiviral medicines can activate the immune system, including favipiravir, remdesivir, ribavirin (RVN), hydroxychloroquine, chloroquine, azithromycin, teicoplanin, nitazoxanide, and others. These antiviral therapies have been suggested as potential treatment options for this virus and are currently under study [12]. In addition, proper handwashing, covering one's mouth when coughing, keeping social distance, wearing a mask in public settings, improving ventilation and air filtration inside, and sanitizing surfaces have all been advised as ways to reduce the viral spread [13]. Monitoring and self-isolation are required for individuals who consider themselves as infected [14].

This global pandemic has induced social and economic distress worldwide. In 172 countries, schools, universities, and colleges have closed, affecting approximately 98.5% percent of the world's student population [15]. Nanopharmaceuticals and nanocarriers refer to new pharmaceutical materials that facilitate the delivery of effective drugs to targeted sites without affecting healthy tissues. Zinc nanoparticles (NPs) and copper NPs also have infection neutralizing properties [16-18]. In this article, we critically evaluate the global pandemic caused by SARS-CoV-2, including an overview of the mechanisms, efficacies, and current applications of several drugs that might be beneficial for fighting against COVID-19 infection.

2. STRUCTURE OF SARS-COV-2

Coronaviruses are massive, generally round particles with tubercular surface projections. Their genomes contain 30,000 nucleo-

*Address correspondence to this author at the Department of Pharmacy, Southeast University, Dhaka, Bangladesh and Pharmakon Neuroscience Research Network, Dhaka, Bangladesh; E-mails: msu-neuropharma@hotmail.com; msu_neuropharma@hotmail.com

1873-4286 $65.00+.00

tides, and a viral particle measures approximately 125 nm in diameter. The nucleocapsid (N) protein, the membrane (M) protein, the spike (S) protein, and the envelope (E) protein, as well as a few nonstructural proteins, make up the viral envelope, which is made up of a lipid bilayer (nsps; Fig. **1**). Coronavirus molecules generally feature 74 surface spikes, each measuring 20 nm in length [2, 19].

A subset of coronaviruses, belonging to *Betacoronavirus* subgroup A, also expresses a more limited, spike-like surface protein, known as hemagglutinin esterase (HE; Fig. **1**). The spikes consist of homotrimers of the S protein, consisting of one S1 and one S2 subunit. The S1 subunit, which includes the receptor-binding domain, frames the apex of the spike. The S2 subunit secures the S protein within the viral envelope [20]. The E and M proteins surround the viral envelope to maintain its underlying shape. The N protein forms a protein shell known as a capsid around the positive, single-strand RNA material and allows the virus to enter human cells and infect the host [21]. The N-terminal region of the N protein plays a significant role in viral replication. The lipid bilayer envelope, film proteins, and nucleocapsid help protect the virus before host cell entry [22, 23].

3. FUNDAMENTAL MOLECULAR PATHOGENESIS OF COVID-19

Patients who develop COVID-19 experience numerous symptoms, including fever, dyspnea, shortness of breath, diminished levels of leukocytes, pneumonia, and myalgia [24]. These signs and symptoms are strikingly similar to those seen in Middle East respiratory disease (MERS) and SARS. The pathophysiology of COVID-19 development is not well known, but these commonalities can give important clues [25].

3.1. Replication Cycle

3.1.1. Cell Entry

Infection occurs when the viral S protein comes into contact with a complementary host cell receptor. Host cell proteases cause proteolysis, and the receptor-bound S protein becomes activated. SARS-S CoV-2's glycoprotein interacts with the angiotensin-converting enzyme 2 (ACE2) receptor on human cell surfaces (Fig. **2**). The binding of the S protein with the ACE2 receptor results in membrane fusion, followed by viral infection through an essential proteolytic cleavage process. SARS-CoV and MERS-CoV infection can occur through an unusual two-step furin activation process (resulting in either clathrin-independent or clathrin-dependent endocytosis) or through the direct fusion of the viral envelope with the cell membrane [26-29].

3.1.2. Genome Translation

The viral particle becomes uncoated after entering the host cell and penetrates the cytoplasm directly. The CoV-RNA genome functions as a messenger RNA, which is translated by the ribosomes of the host cell. The replication/transcription complex (RTC) mediates replication and transcription processes in the cytoplasm (Fig. **2**) [30].

3.1.3. Replication/Transcription Complex

The main transcriptase protein identified in the RTC is RNA-dependent RNA polymerase (RdRp), which directly clones RNA strands to replicate the viral genome [31]. The transcription of the viral genome is another significant function of the RTC complex. The RdRp can distinguish between the negative-sense subgenomic RNA and the positive-sense genomic RNA [32], and the RTC causes genetic recombination to occur if two viral genomes are available in the same contaminated cell (Fig. **2**) [33].

3.1.4. Assembly and Release

Viral replicates are generated when the positive-sense genomic RNA is copied. The viral S, E, and M proteins translocate into the Golgi compartment after RNA translation takes place within the endoplasmic reticulum. The M protein controls the protein-protein interactions required to collect viral components and newly generated viruses are subsequently exocytosed from the host cell, allowing the virus to infect neighboring cells [34].

4. CLINICAL PRESENTATION OF COVID-19 PATIENTS

4.1. Pathology and Pathogenesis of COVID-19

Following SARS-CoV-2 infection and COVID-19 development, increased alveolar destruction can be observed in the lungs. Numerous respiratory diseases, including influenza and MERS, can induce lung damage [35]. The COVID-19 disease primarily manifests as a pulmonary infection [36-38] but can also cause endothelial damage, microangiopathy, angiogenesis, and stroke [39, 40].

4.1.1. Symptoms and Signs of COVID-19

Several signs and symptoms are associated with COVID-19, including headache (70.3%), nasal congestion (67.8%), loss of smell (70.2%), cough (63.2%), fatigue (63.3%), rhinorrhea (60.1%), loss of taste (54.2%), myalgia (62.5%), and throat irritation (52.9%), according to observations of 1,420 patients [41]. Fever has been observed in 88% of cases. Recently, a study involving 25,849 hospitalized patients with positive COVID-19 diagnosis

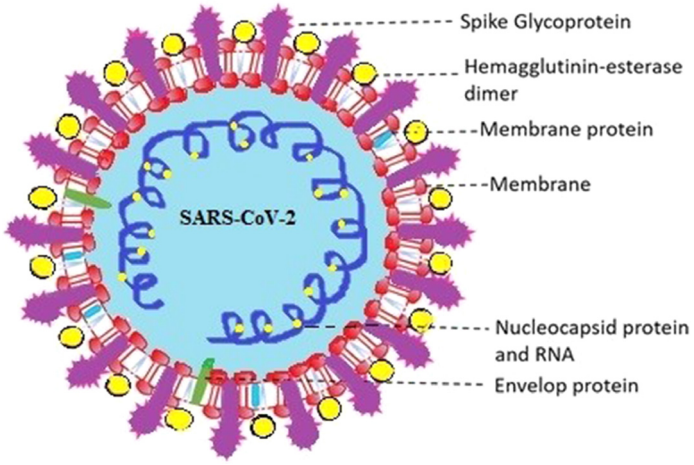

Fig. (1). The structure of SARS-COV-2. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

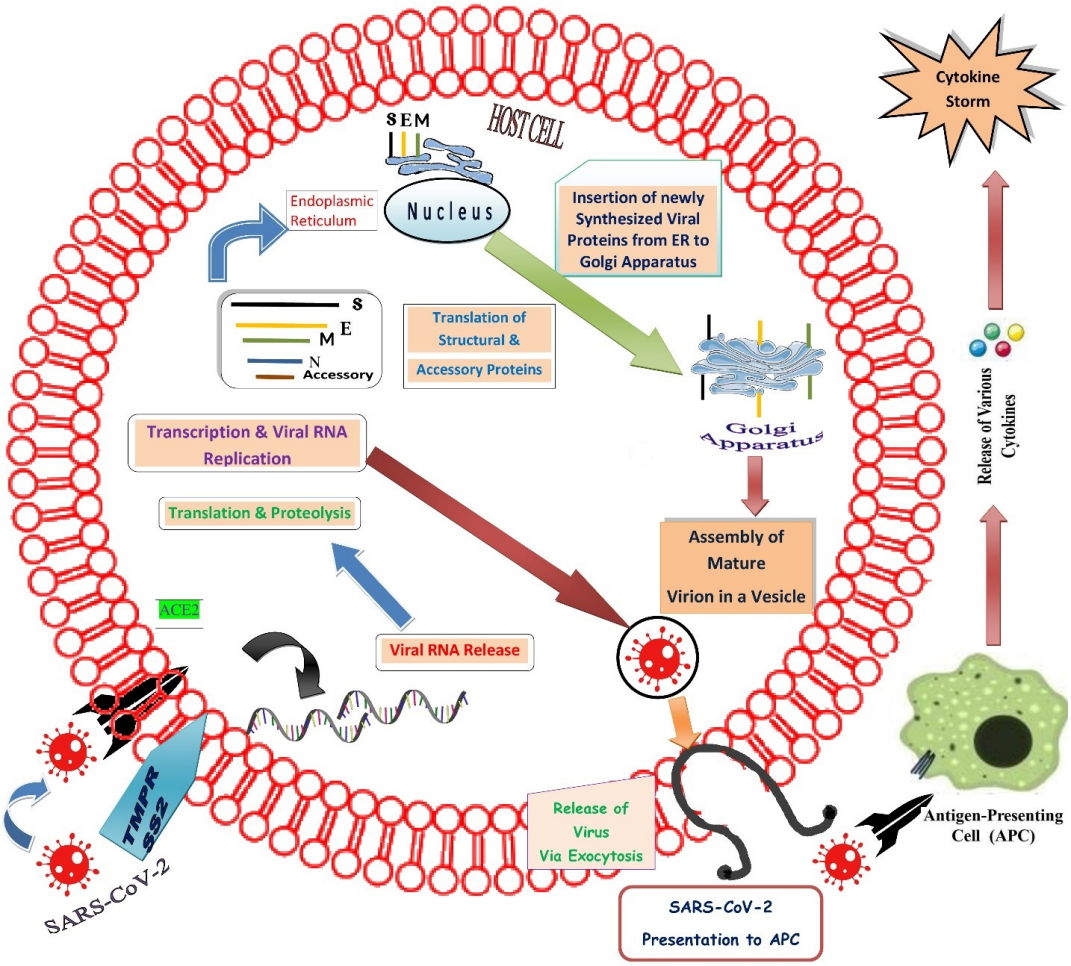

Fig. (2). Replication cycle of COVID-19. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

indicated the disease presentation to be associated with a wide clinical symptoms range (Fig. **3**), as reported by the "International Severe Acute Respiratory and Emerging Infections Consortium." Fever, shortness of breath, cough, fatigue/malaise, and disorientation were the five most commonly reported symptoms (N = 25,849), according to further data [42]. An analysis of 4,203 patients from the top city of China (Wuhan) reported the percentage of fever cases and provided information regarding cough and dyspnea reports individually (80.5%, 58.3%, and 23.8%, respectively). Hypertension (16.4%), cardiovascular disease (12.1%), and diabetes (9.8%) have been reported to be the most common clinical side effects of COVID-19 [43]. Specific COVID-19 manifestations, including the loss of smell and taste, were found to occurr in 52.73% of a pooled sample across 10 studies, including a total of 1,627 patients from Europe, Asia, and North America. Approximately 49.8% of COVID-19 patients reported experiencing a change in taste sensation in an investigation that included 817 patients [44, 45].

4.1.2. Difficulties in COVID-19 Infection

ARDS is a major complication associated with severe COVID-19 infection, which can initially present as dyspnea, leading to acute respiratory failure, and requires treatment with mechanical ventilation [46]. Cardiovascular sequelae have been associated with COVID-19, including arrhythmias, cardiomyopathy, cardiopathy, myocardial injury, and acute stroke, in addition to neural problems, such as encephalopathy [47-49] and encephalitis, which have been reported in rare cases. Coagulopathies, presenting as thrombosis in various areas of the body, have also been associated with severe COVID-19 symptoms and injuries. Endothelial cells are destroyed by SARS-CoV-2, causing blood vessels to bleed and leading to clot formation, which can cause discomfort throughout the body, allowing COVID-19 to infect individuals [50]. COVID-19 infection in children has been reported in several countries to result in hospitalization and the development of a rare pediatric disease known as multisystem inflammatory in children (MIS-C); This disease has been suggested to be linked to severe SARS-CoV-2 infection [51-53]. Children with MIS-C present with abdominal pain, prolonged fever (50%-60%), rash, and sometimes heart issues. Some present with metabolism symptoms and dyspnea associated with simultaneous shock. The WHO established a preliminary case definition to follow up on this newly discovered complication so that onset of MIS-C can be watched for in the children with COVID-19 [54, 55].

5. COMPARISON BETWEEN NORMAL ALVEOLI AND SARS-COV-2-AFFECTED ALVEOLI IN THE LUNGS

SARS-CoV-2 infection begins in the nose, mouth, or eyes, and spreads to alveoli, which are the small sacs in the lungs where gas exchange occurs. Two types of alveolar cells are involved in the gas exchange: Type I and Type II cells. Type II cells secrete a surfactant that surrounds the alveolus to prevent it from collapsing. SARS-CoV-2 attacks Type II cells (Fig. **4**) [56].

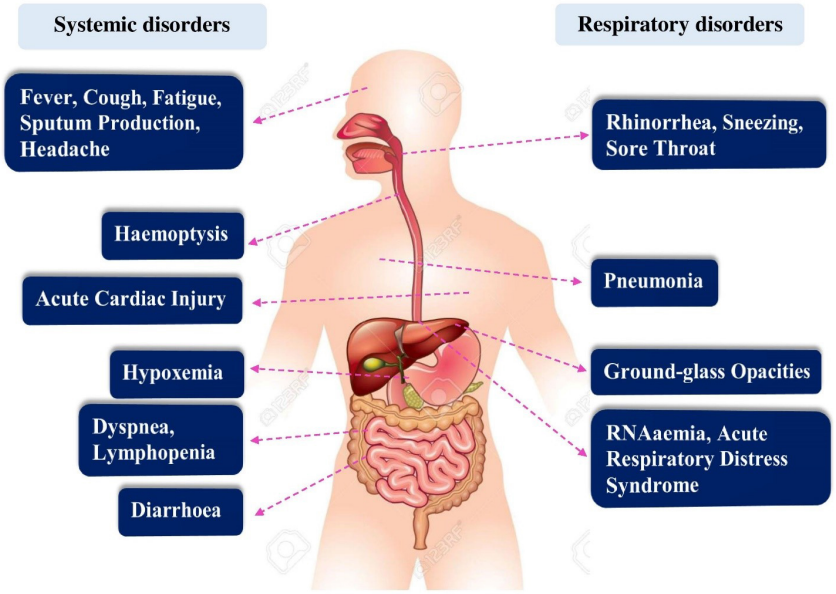

Fig. (3). Symptoms exhibited by COVID-19 patients. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

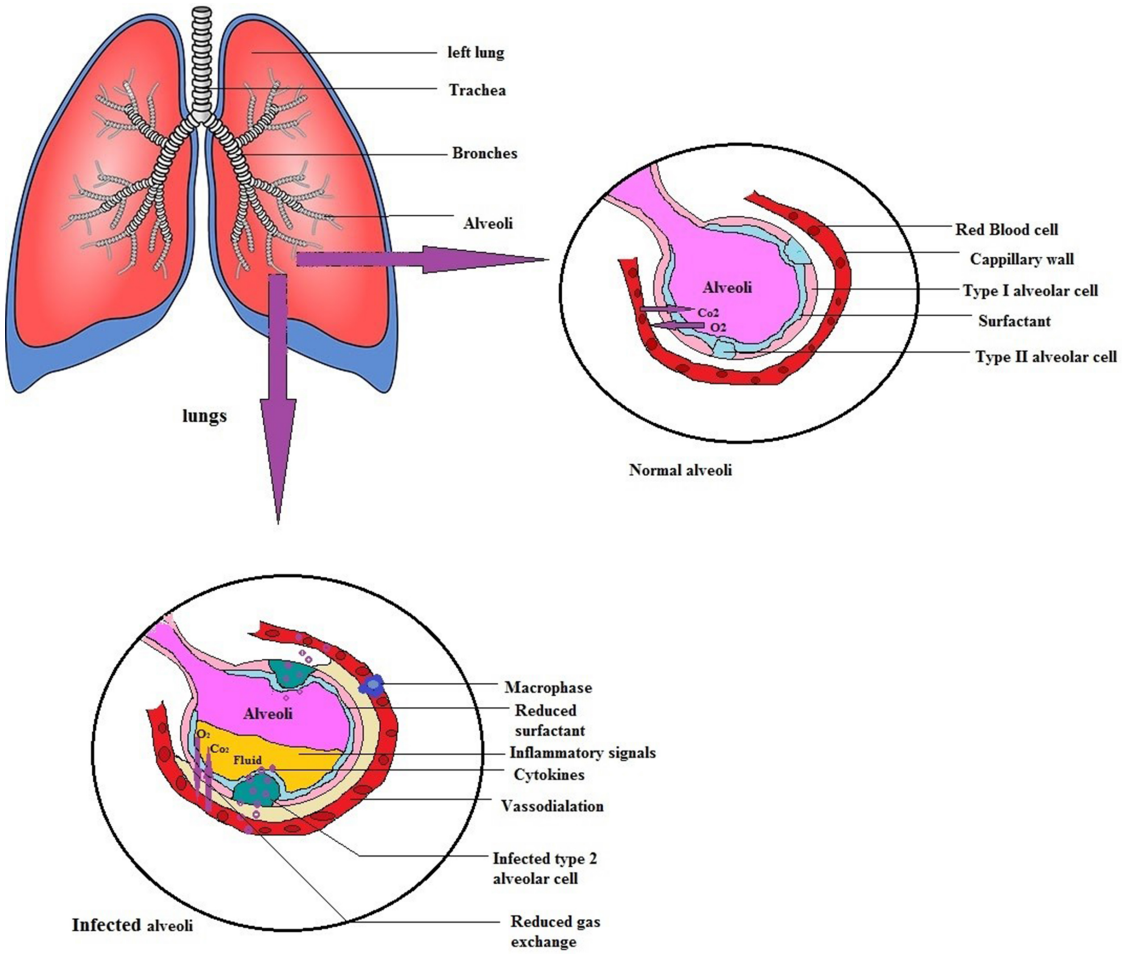

Fig. (4). Normal alveoli and affected alveoli of SARS-CoV-2 on human lungs. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Upon entering cells, SARS-CoV-2 presents its antigen to the antigen-presenting cells, which allow virus-specific cytotoxic T lymphocytes to identify SARS-CoV-2 antigens. Type II cells infected with SARS-CoV-2 release inflammatory signals to recruit immune cells, such as macrophages [57]. Macrophages release cytokines that cause vasodilation and recruit additional immune cells to the affected cells, resulting in fluid accumulation within the alveolus (Fig. **4**).

Fluid dilutes the surfactant, resulting in an increased breathing rate. Neutrophils are recruited to the infection site and release reactive oxygen species (ROS) to destroy infected cells. Both Type I and Type II alveolar cells are attached during this process, leading to the development of ARDS. ARDS is typically accompanied by a cytokine storm, which can lead to multiple organ failure and death [58].

6. LABORATORY DIAGNOSIS OF COVID-19

6.1. Nucleic Acid Test for the Detection of SARS-CoV-2

The suggested methodology for diagnosing SARS-CoV-2 disease is a nucleic acid amplification test that recognizes at least one RNA target specific to the infection. To date, five SARS-CoV-2 tests have received emergency use authorization for testing asymptomatic patients or as a component of local observation. The testing of asymptomatic patients who have potentially been exposed to SARS-CoV-2 is also important, as this can reduce the viral spread and improve the negative predictive value of various tests. For SARS-CoV-2 RNA testing, when symptoms indicate the presence of the virus, the Infectious Diseases Society of America recommends using a combination of nasal mid-turbinate swabs (MT), front nasal swabs (FN), spit, or front nasal/oropharyngeal swabs (OP) [59].

6.2. Serum Antibody Test for COVID-19

Immune tests detect the presence of antibodies, which are disease-related proteins. Individuals with few or no symptoms can benefit significantly from antibody tests because they can discriminate between current and prior illnesses. Researchers at the Centers for Disease Control and Prevention (CDC) have studied as to whether antibodies provide protection against reinfection, as this can manage the pandemic and ensure the general safety of the population [60].

6.3. Lung Imaging Test

A total of 128 patients who were admitted to the Combined Military Hospital Dhaka between April 11 and May 27, 2020, underwent both chest high-resolution computed tomography (HRCT) and reverse transcription-polymerase chain reaction (RT-PCR) in order to be identified as COVID-19 infected. The lungs were examined for evidence of ground-glass opacity (GGO), consolidation, reversed halo sign, crazy pavement pattern, thickened vascular marking, lymphadenopathy, and pleural effusion [61]. The virus was detected in all 128 of the individuals, based on a positive RT-PCR result, including 112 patients (87.5%) presenting with fever and 58 (45.31%) with fatigue. In 123 (96.09%) patients, GGO was the most commonly observed CT phenomenon. GGO combined with consolidation was discovered in 81 cases (63.28%), whereas 42 patients showed GGO alone (32.8%). The crazy pavement pattern was observed in 65 (50.78%) cases. All five lung lobes were impacted in 96 (75.00%) cases. Primarily, peripheral (123.96%) and posterior (103.87%) injuries were reported [61].

6.4. Serum Creatinine and Urea Levels

Although COVID-19 is not thought to attack the kidneys, renal injury has been reported based on the extensive ranges of creatinine and blood urea levels identified in patients with COVID-19, with some patients experiencing severe renal damage. In a study on 99 people infected with COVID-19, 3% of them had serious renal injury [62, 63]. The patients were admitted to the intensive care unit (ICU) when acute kidney damage was detected, which was associated with rapid deterioration and steady increases in blood urea and creatinine levels prior to death [64].

6.5. Antigen Tests for COVID-19 Diagnosis

SARS-CoV-2 comprises various virus-encoded proteins, including the S, N, E, and M proteins. SARS-CoV-2 antibodies are primarily focused on the S and N proteins [65]. The viral S protein is essential for infection transmission, whereas the N protein is more abundant and milder in its interactions with RNA [66]. The S1 subunit of the S protein is specific to SARS-CoV-2 and may represent a superior antigen for COVID-19 serologic recognition than the full-length S or S2 subunit [66]. Various forms of the N and S proteins have been utilized as potential antibody targets, including the full-length S, the S1 region, the S2 region, and the RBD [67-70]. The most broadly used device for distinguishing SARS-CoV-2 antigens is the immunochromatographic test [70, 71].

6.6. Manual Laboratory-based Antibody Tests

6.6.1. Enzyme-linked Immunosorbent Assay

At various phases of the SARS-CoV-2 disease, Niko *et al.* [72] analyzed the presentation of COVID-19 IgG (recombinant N protein, Vircell) and SARS-CoV-2 IgG (recombinant S protein, Euroimmun) using specific enzyme-linked immunosorbent assay (ELISA) kits. The Vircell ELISA detected COVID-19 antibodies in 70.6% of cases, whereas the Euroimmun ELISA detected antibodies in 58.8% of cases during days 5-9 following the PCR confirmation of COVID-19 infection. The Vircell ELISA detected antibodies in 100% of cases after 10-18 days, whereas the Euroimmun ELISA detected antibodies in 93.8% of cases after 10-18 days [72]. Similarly, Liu *et al.* tested two ELISA kits for the recognition of IgG and IgM antibodies against the SARS-CoV-2 S and N proteins. Anti-SARS-CoV-2 IgG antibodies could be detected in fewer than 60% of tests 6-10 days after the onset of illness, which increased to >90% after 20 days [73]. In contrast with the N protein-based ELISA, S protein-based ELISA had a higher detection rate [73].

6.6.2. Immunofluorescence Assay

Immunofluorescence assay (IFA) was utilized to identify SARS-CoV-2 IgM and IgG antibodies in serum from a COVID-19 case in Finland [74]. At various phases of the SARS-CoV-2 infection, Niko *et al.* performed IFA. From days 5-9 to days 10-18 following PCR confirmation, IFA detection increased from 76.5% to 100% [72]. IFA is ambiguous and might lead to unintended consequences, and this technique should be studied further.

6.6.3. Chemiluminescence Immunoassay

Chemiluminescence immunoassay (CLIA) is regularly used to obtain a quantitative measure of the immune response [75-78]. To identify SARS-CoV-2 antibodies against ORF1 a/b, N, and S proteins, Cai *et al.* designed a peptide-based magnetic CLIA [77].

6.7. Virological Tests

The gold standard for virological identification is culture-based infection assays, which are necessary to identify specific pathogens and perform systemic assessments. The serum obtained from COVID-19 patients was tested for its ability to reduce the cytopathic effects (CPE) generated by SARS-CoV-2 infection *in vitro*. It is an infection that keeps alive in serum or plasma until it is contaminated and hatched. The virus neutralization test (VNT) and pseudovirus-based VNT (PVNT) are the most commonly used tests [60].

6.8. Rapid Serological Tests

Most rapid IgM/IgG tests are based on immunoassay discovery and take 10-15 minutes to complete. A colloidal gold-labeled SARS-CoV-2 recombinant protein and murine IgG antibody antagonists are found in the G zone, whereas a counteracting agent is located in the M zone. Before COVID-19 mass screening, rapid tests should be thoroughly evaluated for clinical accuracy [79].

6.9. Reverse-Transcription-Loop-mediated Isothermal Amplification

A combination of loop-mediated isothermal amplification (LAMP) and reverse transcription (RT-LAMP) can be used to identify SARS-CoV-2 RNA. Huang *et al.* [80] utilized 16 clinical examples to test RT-LAMP, including eight positive and eight negative for SARS-CoV-2 according to RT-PCR, which showed that RT-LAMP outcomes were similar to those for conventional RT-PCR [81].

7. THE USEFULNESS OF INDIVIDUAL PREVENTIVE MEASURES

Although no specific drugs have been developed for COVID-19 treatment, personal defensive actions and practical attitudes and practices can prevent transmission, such as avoiding unnecessary travel and one-on-one contact with individuals suspected of COVID-19 infection [82, 83].

7.1. Significance of Hand-washing

The necessity of maintaining regular and proper hand hygiene is undeniable [84]. Adequate hand-washing with soap will disrupt the SARS-CoV-2 lipid envelope, disrupting the ability of the virus to infect cells. Therefore, adequate hand-washing should be performed for everyone's safety [85-87]. The duration of hand-washing with soap is also important. Many health-related organizations have recommended that effective hand-washing should last for a minimum of 20 seconds. Research has found that among 3,749 persons in a college city environment, only 5% followed the recommended hand-washing standards, including washing, rinsing, and rubbing [88-91].

7.2. Face Mask Use

To create a physical barrier, face mask use by all individuals has been recommended by the WHO. A surgical mask that provides unidirectional protection can prevent respiratory droplets from spreading during coughing and sneezing [92-94]. Healthcare professionals who are treating or in direct contact with confirmed COVID-19 patients should wear a specialized breathing apparatus (N95 or similar) to prevent any droplets from entering the respiratory system, reducing the risk of contracting the disease. People must exercise extreme caution when handling bodily fluids, such as blood, urine, or feces, from infected individuals [95-97].

8. NANOTECHNOLOGY AGAINST COVID-19

Nanotechnology and nanoscience refer to techniques developed to enhance, expand, or supplement molecular structures. NPs are nanoscale (1 to 100 nm) in size in at least one dimension, *i.e.*, shape, morphology, and composition [98]. Over recent decades, nanopharmaceuticals and nanocarriers have been exploited in various formulations to deliver effective drugs to targeted sites without affecting healthy tissues. SARS-CoV-2 can easily disseminate through cough, sputum, respiratory droplets, contact with bodily fluids or contaminated surfaces (Fig. **5**) [99].

The most important examples of strategies for virus inactivation include nanotechnology-based viral therapies that help detect viral peptides attached to the host cell surface receptors; more sophisticated methods remain necessary to be addressed in this pandemic, including improved diagnostic approaches, viral isolation methods, and treatment. Current clinical diagnostic methods rely on PCR performed in the laboratory or serological detection tests (SDTs) for viruses based on immunoassays [100-102].

Methods for the direct detection of different viruses continued to be developed following the discovery of electron microscope and tissue culture techniques. To detect SARS-CoV-2, RT-PCR has typically been applied as a routine diagnostic method. The introduction of nanosensors, which can detect germs and viruses at concentrations as low as 0.22 pm, might help alert patients of potential infection before they develop symptoms [103-106].

The LAMP technique can identify target sequences using RNA templates [107]. Many systems and techniques must be applied to prevent the spread of SARS-CoV-2 [108]. Optical biosensor-based nanotechnology is capable of detecting COVID-19 and influenza infection within 30 minutes [109]. Another nanotechnology under development is the nano-pore target sequencing method, which can recognize SARS-CoV-2 and 11 other respiratory viruses within 8-10 hours. Increasing host resistance is another goal for reducing SARS-CoV-2 infection [110-113]. Zinc NPs have strong antiviral effects against rhinoviruses and have been shown to reduce the infection rate associated with the common cold and influenza viruses. Zinc NPs can reduce the severity and virulence of SARS-CoV-2 and H1N1 influenza infections, and zinc NPs disrupt SARS-CoV replication [114, 115]. Copper NPs also antagonize viruses, such as human papillomavirus (HPV), bronchitis virus, human immunodeficiency virus type-1 (HIV-1), and other enveloped and non-enveloped single and double-stranded DNA and RNA viruses. Copper alloys have been shown to rapidly inactivate CoVs. Cu (I) and Cu (II) moieties regulate the inactivation of ROS generation by viral surface proteins. Copper NPs can inhibit the activity of papain-like protease-2, a highly specific protein required for SARS-CoV-2 replication [18, 116].

8.1. Nanoparticle-mediated Treatment Modes

NPs have the potential for use in the development of promising theranostic applications for coronavirus in clinical settings. Drug delivery systems, such as erlotinib-containing liposomes, have been used to treat cellular damage in the lungs, demonstrating that nanoformulations might enhance *in vivo* drug biodistribution. Coronavirus therapy is expected to be successful when AP2 associated kinase (AAK1)-related oncology tests indicate viral entry into target cells. NP interactions with various medicines and the progression of intranasal or intravenous delivery are expected to result in beneficial outcomes [117].

8.2. Definite siRNA Transport

Transporting small interfering RNA (siRNA) to target cells is a potential solution to single-stranded RNA viruses which rely on ORF1a and ORF1b for growth; RNA interference (RNAi) may represent a novel method for reducing viral replication. Gold NPs, which interact with iron oxide, and silica NPs, which pay little attention to quantum dots (QDs) and carbon nanotubes (CNTs), have been proposed as siRNA transporters; QDs and CNTs are attracting research interest for antiviral applications [118]. Biocompatibility, flexible designs, and surface modifications, along with the potential for additional enhancements, have made gold NPs an attractive option for siRNA transporters for the targeted treatment of viral diseases and cancer [119]. Chitosan-based NPs have been applied in the treatment various diseases and have been examined for increasing the response to vaccination, including the increased production of HBV antibodies, Newcastle disease antibodies, and DNA antibodies [120].

8.3. Peptide Inhibitors

Both MERS-CoV and SARS-CoV-2 produce the same type of S protein in the viral coat. The development of appropriate and safe antiviral treatments for specific viruses becomes increasingly difficult due to the emergence of mutant strains. The natural char-

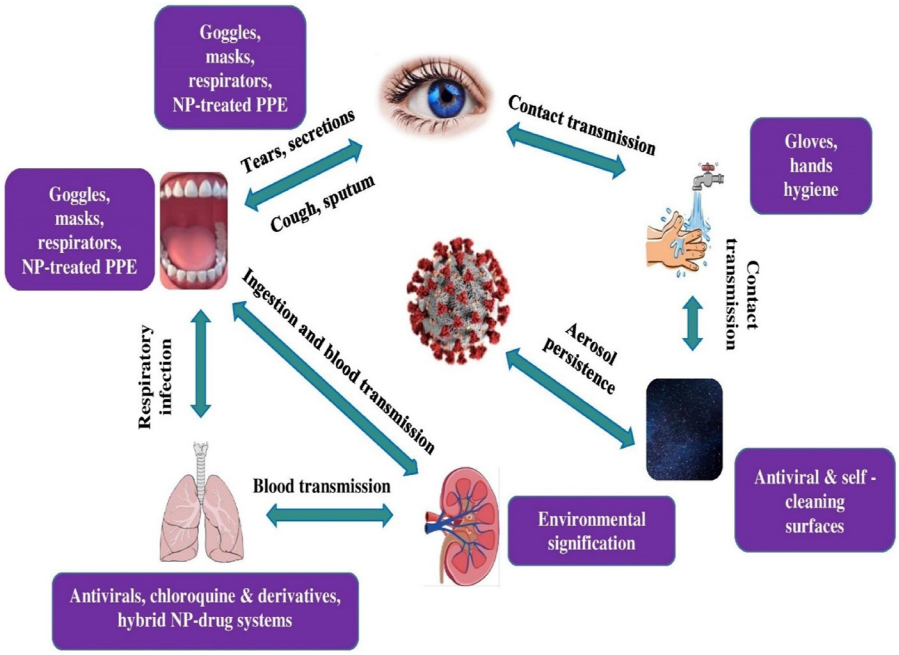

Fig. (5). Transmission pathways of SARS-COV-2 and possible confinement means. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

acteristics of peptide inhibitors allow for their use as sequence-specific antiviral therapies, including the ability to be prepared in an aqueous solution and an average width of 10 nm, making them attractive candidates in the fight against coronavirus [121, 122].

8.4. Use of Virus-like Nanoparticles to Stimulate the Immune System

NPs can carry antigens on their surfaces that can be identified by differentiated and antigen-presenting cells [123]. One study focused on improving the limitations of gold NPs that prevent them from incorporation into free-streaming mixtures, such as the lymphatic system, and strong interactions between NPs and the S protein were found to prolong beneficial outcomes. They revealed that NP attached to the S protein could be used as a promising and effective method for enhancing immunity and protecting individuals from MERS-CoV. A similar approach can be used against SARS-CoV-2 because both viruses rely on a similar spike protein approach [124].

8.5. Nanomaterial-based Vaccine Development and Immunomodulation

Nanomaterials can assist in antibody and vaccine studies, such as upregulating immune activity and directing the immune response against specific antigens. The judicious construction of nanotherapeutics at the nanoscale level can help increase the immune system's antiviral resistance, such as administering inoculations [125].

8.6. Nanomedicine as Combined Drug Therapeutics

Combined drug therapy is another potential option for the treatment of COVID-19, resulting in the use of lower doses of single medicines, fewer side effects, and the achievement of therapeutic objectives, in addition to reducing the potential for the development of drug resistance. Many drugs with different physicochemical characteristics may be transported using nanocarriers, increasing the potential implementation of combination therapies. Therapeutic combinations transported by nanocarriers show better-preserved pharmacokinetics and synergistic effects that minimize unwanted adverse effects. As a result, chemotherapeutics and plasmid DNA/RNA or siRNA and microRNA can be co-encapsulated in a nano-carrier, allowing for the sequential release of two treatments, referred to as ratiometric loading for the precise release of up to three drug candidates [103].

8.7. Personal Protective Equipment

The use of nanomaterial-embedded textiles has been intensely investigated to expand the physicochemical properties of textiles, such as providing self-cleaning, fire-retardant, UV-protection, and antimicrobial attributes [126]. Fibers embedded with metallic NPs, such as silver/copper NPs, show antiviral and antimicrobial properties [127-129]. Mao [130] recently studied the use of nanotechnology in personal protective equipment (PPE) such as laboratory aprons, coats, and facemasks, because nanomaterials can deliver novel characteristics to materials. The use of NPs in textiles has grown rapidly, and approximately 35 tons of silver NPs alone are being utilized for various uses. Wearable intelligent electronics and materials for detecting various health-related statuses have also been developed [103].

9. INVESTIGATED POTENTIAL THERAPIES AGAINST COVID-19

9.1. Development of Antiviral Drugs

Numerous antiviral therapies for COVID-19 are being studied in clinical trials, including repurposed drugs. SARS and MERS were previously treated with a mixture of lopinavir (LNV) and ritonavir (RTV) [109, 131]. Remdesivir combats a variety of RNA-virus-mediated infections that are adenosine-dependent, providing a wide range of antiviral effects. Remdesivir is currently being explored for the treatment of Ebola infections and shows a robust response against SARS-CoV-2. Antiviral therapies are significant tools for the general treatment of COVID-19 patients. However, antiviral treatments can induce further injuries and cause organ damage, often requiring additional, mitigating treatments to counteract these effects [132, 133].

Chloroquine is a small, antimalarial drug with broad-spectrum antiviral activity, including potent efficacy against SARS-CoV-2 [134]. Chloroquine blocks the fusion of the viral and cell membranes by increasing the required endosomal pH for virus infection [135]. The glycosylation of cellular receptors utilized by SARS-CoV-2 is also disrupted by chloroquine [136]. The reports have clarified that the rate of SARS is much lower than COVID-19 contagion rates [100].

9.1.1. Remdesivir

Remdesivir is a nucleotide analog that inhibits the viral RNA polymerase and has shown potency against SARS-CoV-2. Although remdesivir was developed for the treatment of hepatitis C, some clinical trials failed to demonstrate its anti-hepatitis C activity [137-140]. Remdesivir has since been tested against the Ebola virus and CoVs and is currently being tested in the developmental pipeline for therapy against these viral infections. However, the process of producing remdesivir is complex, requiring 70 raw materials, reagents, and catalysts, and approximately 25 steps [141-143].

9.1.2. Favipiravir

Favipiravir is an antiviral drug used to treat the influenza virus; it has also been examined for the treatment of COVID-19. The Bangladesh Society of Medicine confirmed the effectiveness of favipiravir for clinical use in the treatment of COVID-19 patients. After clinical trials from the Wuhan, China, and Russia declared it as promising, the Dhaka trial demonstrated efficacy of favipiravir for the treatment of patients infected with COVID-19 [108-111].

9.1.3. Lopinavir

HIV is commonly treated with a combination of RTV and LNV, which are protease inhibitors [144]. However, the antiviral effects of LNV against MERS-CoV were inconclusive in an *in vitro* model [145]. LNV is usually combined with RTV to increase the half-life of LNV, which is metabolized by cytochrome P450 enzymes [146]. Various studies have recommended that the LNV/RTV ratio must be optimized to prevent the replication of SARS-CoV2, and the concentration necessary in the lungs may be high compared to the level found in serum [146, 147].

9.1.4. Ribavirin

The antiviral therapy RVN is typically used to treat hepatitis C [148]. An *in vitro* study showed that RVN alone does not demonstrate antiviral activity against SARS-CoV-2 [149], but RVN combined with interferon (IFN)-β synergistically inhibited the replication of SARS-CoV in animal models and human cell lines [150]. However, clinical trials examining the combined treatment of RVN with various antiviral medications have shown little ability to prevent viral infection.

9.1.5. Arbidol

Arbidol (ARB) is an indole ring containing an alkaloidal and has been approved in both Russia and China for the prevention and treatment of various respiratory infections, such as the flu [151]. ARB can inhibit the viral fusion pathways of hepatitis C, hepatitis B, and influenza viruses [152]. An *in vitro* study indicated that ARB could inhibit hepatitis C by obstructing viral spread and replication [153]. Additionally, arbidol mesylate, an ARB derivative, has shown preventive effects against the spread of SARS-CoV, and its ability to reduce SARS-CoV propagation *in vitro* appeared to be greatly more effective than the effects due to ARB [154].

9.1.6. Epigallocatechin Gallate

The antiviral effects of the polyphenolic compound, epigallocatechin gallate (EGCG), which is commonly found in green tea, have been demonstrated both in *in vitro* and *in vivo* models [155]. A new report suggested that EGCG could reduce the infectivity of flu in cell culture [156], and the study suggested that EGCG may be effective against other viral infections, such as hepatitis C, mediated by agglutination and the inactivation of proteins in the viral phospholipid layer. The combination of EGCG with dactavira prevents viral infection from entering the cells. Additional clinical trials are recommended to determine the adequacy of EGCG against SARS-CoV-2 infection [157].

9.1.7. Umifenovir

Due to a broad range of antiviral activities, umifenovir is commonly used to treat flu, hepatitis B and hepatitis C infections [152]. Umifenovir acts through two pathways, one of which attacks the virus and one suppresses infection through actions against the host cell membrane. It inhibits the replication of the SARS-CoV-2 virus [152].

9.1.8. Ivermectin

The parasitic medication ivermectin has shown promising antiviral activities in a few *in vitro* studies [158-162]. Ivermectin inactivates the importin (Impα/β1) heterodimer, preventing COVID-19 proteins from reaching the nucleus of infected cells through the nuclear pore complex (NPC), which neutralizes SARS-CoV-2 [163]. Additional investigations remain necessary to determine the efficacy of ivermectin against SARS-CoV-2 prior to utilization in clinical practice (Table **1**) [164].

9.2. Inhibitors of Viral Fusion and Cytokine Storm

9.2.1. Chloroquine

Chloroquine is primarily utilized as an antimalarial drug but is also used to treat various autoimmune conditions, such as lupus erythematosus and rheumatoid joint pain. Amazingly, chloroquine can prevent viral fusion by regulating the endosomal pH of the host's cell membrane. Chloroquine can also alter the glycosylation patterns of cell receptors utilized by SARS-CoV for viral infection [64, 165]. However, the use of chloroquine to treat COVID-19 infection remains an off-label use. Chloroquine use is also associated with some adverse effects, including delayed QT with ventricular dysrhythmia and hepatic and renal damage [166].

9.2.2. Hydroxychloroquine

Hydroxychloroquine (HCQ) is a hydroxy derivative of chloroquine, marketed as Plaquenil [167], and similar to chloroquine, it is primarily used as an antimalarial drug [168]. HCQ has been proposed to be able to prevent or reduce the strength of cytokine storm, which is an adverse effect that can occur in patients with late-stage COVID-19 [169]. HCQ offers a more effective treatment than chloroquine, demonstrating significantly improved outcomes for SARS-CoV-2 infection *in vitro* [169].

9.3. Immunity Enhancing Agents

9.3.1. Interferons

Cytokines are significant components of the immune system, and IFNs represent a primary cytokine category. IFNs can be categorized into two main groups: Type I and Type II. Type I IFN, particularly IFN-β, has been effectively tested *in vitro* against SARS-CoV infection; however, IFN-γ did not show any antiviral action against SARS-CoV replication [150, 170]. According to Kuri *et al.*, the anti-CoV activity of IFNs relies on their ability to present a typical immune reaction against the virus [171]. Additional studies have suggested that the cytopathogenic properties and alterations in the viral structure can be overcome by particular IFN-α and β subtypes, including αn1, α3, β1b, and the human leukocyte IFN-α, *in vitro* [172]. The most frequent adverse effects of interferon alfa include flu-like symptoms, nausea, fatigue, weight loss, hematological toxicities, and others. Precautions should be taken for these targeted therapeutics if administered 3 days before the infection [173].

Table 1. Antiviral drugs approved by the FDA.

Name of Antiviral Drugs	Features	Applications	Present Status
Nitazoxanide	Antiprotozoal actions	Antiprotozoal	Approved by FDA
Rivapirin	Alleviates HP-C virus and other RNA viruses	Alleviates HP-C virus and other RNA viruses	Approved by FDA
Chloroquine diphosphate	Autophagy and Toll-like receptors inhibitor	Aminoquinoline antimalarial	Approved by FDA
Camostat mesilate	Trypsin-like protease inhibitor	Inhibits the epithelial sodium channel function	Preclinical/Approved
Remdesivir	Antiviral action against SARS-CoV and MERS-Cov	Antiviral activity against MERS-Cov and SARS-CoV	Clinical
Baricitinib	Inhibitor of Janus kinases 1&2 (JAK1/2)	Antineoplastic, anti-inflammatory, and immune-modulating action	Approved by FDA
Favipiravir	Effective RdRp inhibitor	Used to treat infection of influenza virus	Clinical/Approved
Darunavir	HIV protease inhibitor	Used against HIV and AIDS infections	Approved by FDA

9.3.2. Tocilizumab

Tocilizumab (TCZ) is a recombinant monoclonal antibody that inhibits the IL-6 receptor [174]. Patients with COVID-19 have demonstrated the upregulation of inflammatory cytokines, such as IL-6 [175]. In studies examining TCZ as a targeted treatment for COVID-19, IL6 levels decreased sharply following TCZ administration. However, inconsistent outcomes were observed in severe COVID-19 infection patients following repeated TCZ treatments, and the efficacy remains inconclusive [176].

9.3.3. Thymosin α-1

Thymosin α-1 (Tα-1) is utilized to treat the downregulated immune system by normalizing T lymphocyte levels and other elements of the immune system [177]. Tα-1 acts through various pathways to promote lymphocyte development in the thymus and prevent cell death by improving glucocorticoid antagonism [178]. During the 2003 SARS pandemic, Tα-1 showed significant effects related to improving the pandemic conditions [179]. During the current COVID-19 pandemic, the administration of methylprednisolone in patients has been associated with a decrease in thymocytes due to the use of glucocorticoids. The simultaneous administration of Tα-1 might prevent this effect of methylprednisolone.

9.3.4. Cyclosporine A

Under transplantation conditions, the immune response must be minimized to improve the acceptance of the unfamiliar tissue. Cyclosporine A (CYCP-A) is an immunosuppressive agent that is often utilized to improve transplant acceptance [180] and minimize the effects of autoimmune disease. Cyclophilin is a specific cytosolic binding protein responsible for the concentration of the immunosuppressant cyclosporin A. Cyclophilin A prevents SARS-CoV-2 replication following bronchial infection [181]. CYCP-A may present similar activity, and treatments that include CYCP-A are considered likely candidates for the treatment of COVID-19.

9.3.5. Levamisole

Levamisole (LVM) is a low sub-atomic weight drug that has been shown to enhance the adaptive immune response and protect cells from infection in animal models [182]. Clinical trials utilizing it were performed cautiously because LVM can either enhance or reduce the patient's resistance in a dose-dependent manner. LVM upregulates lymphocytes to improve the immune response [183], and LVM can repress the papain-like protease, which is necessary for successful infection and may reduce the severity of COVID-19 [184]. LVM can also reduce the expression of tumor necrosis factor-α (TNFα) and IL-6, which are responsible for COVID-19 pathogenesis. Therefore, LVM may be used as a specific therapy for COVID-19.

9.3.6. Nitazoxanide

Nitazoxanide is used as an anti-parasitic and antiviral drug [185], with broad-spectrum antiviral activity against various viruses, including parainfluenza, respiratory syncytial virus, influenza, rotavirus, and CoV [185]. Nitazoxanide affects antiviral outcomes by restricting host-controlled systems required for viral replication rather than affecting virus-specific pathways [185]; it has demonstrated potential benefits against CoV.

9.3.7. Sarilumab

Sarilumab inhibits both the membrane-bound (mIL-6R) and soluble IL-6 receptors (sIL-6R). The clinical adequacy of sarilumab against SARS-CoV-2 is currently being assessed, and its pharmacological capabilities must be optimized when evidence of efficacy is obtained [185].

9.3.8. Leronlimab

Leronlimab is a monoclonal antibody that is being examined for the ability to decrease cytokine storm, and it is considered a primary contributor to the development of severe COVID-19 infection. Leronlimab acts by repressing chemokine receptor-5 (CCR5), reducing the effects of the cytokine storm. The binding of leronlimab to the CCR5 receptor competitively inhibits (Chemokine ligand 5) CCL5 and reduces the downstream release of proinflammatory cytokines. The adequacy of leronlimab is currently being assessed for severe SARS-CoV-2-infected patients under an emergency use application provided by the FDA [186].

9.3.9. Baricitinib

Baricitinib is a Janus kinase (JAK) receptor inhibitor and can prevent the activation of the JAK-signal transducer and activator of transcription (STAT) signaling pathway, which supports the viral advancement in host cells. The possibility that baricitinib may serve as a favorable treatment for COVID-19 patients is being assessed [2, 145, 187, 188].

In the management of rheumatoid arthritis, baricitinib is frequently used as a reversible and selective inhibitor of JAK1 and JAK2, which transduce intracellular signals for developmental factors and cytokines related to inflammation, the immune reaction, and hematopoiesis. Baricitinib might serve as an additional treatment for COVID-19 management [189].

9.4. Adjunctive Medications

9.4.1. Antimicrobial Agents

The occurrence of multiple infections varies significantly among patients who have COVID-19. According to several findings, various microorganisms, diseases, and bacteria can coexist in individuals

with COVID-19, including flu. The majority of infections can co-occur in patients with COVID-19 [190], and long-term (longer than 6 days) hospitalized patients require the administration of carefully selected antibiotic(s) with broad-spectrum activity to prevent infection [191, 192].

9.4.2. Corticosteroids

Using corticosteroids to treat SARS-CoV infections has resulted in several discoveries, and one study [193] recommended that corticosteroids can be used to minimize the death rates of severely ill patients [194, 195].

9.4.3. ACE Inhibitors, Angiotensin II Receptor Blockers, and Statins

One study indicated that COVID-19 has a more severe impact among people taking ACE inhibitors or angiotensin II receptor blockers (ARB IIs) [196]. Improved ACE2 activity has been linked to reduced ARDS severity in individuals with the respiratory syncytial virus-induced lower respiratory tract disease [197].

9.4.4. Nonsteroidal Anti-inflammatory Drugs

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) is controversial because they can increase the ACE2 receptor activity. Compared to other NSAIDs, acetaminophen has been recommended for fever control in individuals with severe COVID-19, because it does not lead to bleeding and is less harmful for kidney and liver [198].

9.4.5. Anticoagulant Therapy

Anticoagulant treatment with heparin, particularly low-molecular-weight heparin, can improve the outcomes among patients with severe COVID-19 infection, and heparin recipients have been observed to die at a slower rate than non-users [199].

9.4.6. Bronchodilators

Bronchodilators are thought to reduce the danger of viral transmission when administered *via* a nebulizer. Although bronchodilators represent a small contribution to adjunctive therapy and the management of COVID-19, patients face the constant risk of developing obstructive pneumonic infection or asthma [200]. However, even in the presence of underlying disorders, only the metered fraction of inhalers is recommended because inhaling the medication allows it to get to the lungs fast, and it is possible to take smaller doses causing fewer side effects.

9.4.7. Inhaled Pulmonary Vasodilators

The use of pneumonic vasodilators is being investigated, and aerosolized vasodilators are avoided when managing COVID-19 patients. To date, the efficacy of inhaled pneumonic vasodilators for preventing or treating severe respiratory failure due to SARS-CoV-2 infection has not been determined [201].

9.5. Vitamins and Omega-3 Fatty Acids

9.5.1. Vitamin A

Nutrients are thought to prevent infectious diseases [202], and other respiratory dysfunctions, such as asthma and chronic obstructive pulmonary disease (COPD), are frequently linked to nutrient deficiency. CoV infections can have severe repercussions for the respiratory system. Patients with balanced nutrient intake demonstrate better outcomes [203]. Clinical studies have shown that food can improve the immune response to illness [204]. In this vein, nutritional delivery offers less potential in the treatment of COVID-19-related lower respiratory diseases (LRD) than previously thought because it is seldom affected by supplementation therapy, such as vitamin A. This fact has been proved in a separate study that involved children.

9.5.2. B Vitamins

B vitamins are water-soluble and act as coenzymes, and every identified B vitamin has been shown to have beneficial effects. Because vitamin B deficiency can contribute to a deficiency in the host immune response, infected patients can be administered vitamin B supplementation to strengthen their immune systems. COVID-19 patients present with normal oxidative pressure, which can be monitored by a protein marker named homocysteine. In a randomized controlled trial (RCT), over a short time (half of a year), multivitamin supplements, particularly those containing vitamin B complexes, were found to reduce elevated levels of plasma homocysteine [205]. Similar findings were reported in a 7-year RCT involving a large sample size. However, more research remains necessary to determine whether supplementation with vitamin B complexes can improve the immune response against COVID-19.

9.5.3. Vitamin D

Vitamin D is a vitamin that can be produced by the body in response to sunlight, promoting the growth of numerous cells, including immune cells, and is necessary for maintaining bone integrity. An investigation found that vitamin D supplementation reduced the risk of COVID-19, similar to flu viruses, and reduced mortality associated with inflammation, with similar efficacy as the antimicrobial peptide cathelicidin [206]. As a result, vitamin D may be a viable therapy option for this novel virus.

9.5.4. Vitamin C

Along with collagen synthesis, immune strengthening, and aging [206], vitamin C plays an essential role as an enzymatic cofactor in various physiological reactions. In mouse models, vitamin C plays a critical role in antiviral protection against infection by flu. Flu infection (H3N2) is associated with increased IFN-α/β expression, which occurs mainly during the vital stages of the disease [207].

9.5.5. Vitamin E

Vitamin E has high antioxidant capabilities and can alter the immunological responses of the host. Vitamin E deficiency can disrupt both humoral and cellular immune responses [208]. In a small pilot RCT, vitamin E showed positive outcomes for the treatment of chronic hepatitis B [209]. In another RCT, Vitamin E supplementation also increased anti-HBe seroconversion and viral response in children [210].

9.5.6. Omega-3 Polyunsaturated Fatty Acids

Omega-3 polyunsaturated fatty acids (ω-3 PUFAs) are large complexes that regulate different inflammatory cytokines, similar to the regulation provided by chemokines [211, 212]. In a recent study, combining protein D1 with peramivir lowered the death rate of mice after exposure to influenza. Various PUFAs have been discovered to have anti-hepatitis C virus properties, and ω-3 supplementation has previously been used in the treatment of ARDS [213]. The impact of regulating ω-3 PUFA levels in ARDS requires additional study; however, ω-3 PUFAs appear to play essential roles in reducing abnormal oxygen levels as well as the steady production of inflammatory cytokines, such as IL-1, IL-8, IL-6, and TNF-α [214]. Therefore, ω-3 PUFAs can be considered an antiviral target for COVID-19.

9.6. Oligo-elements and Immune Response

9.6.1. Selenium

Selenium (Se) is an essential component [215], and Se deficiency can worsen flu infection and activate coxsackievirus genome modifications, allowing an avirulent infection to become harmful after genetic transformations [216, 217]. The synergistic effects of Se combined with ginseng stem-leaf saponins showed an

effective immune response against live infectious bronchitis associated with COVID-19 [218]. Se could represent a useful agent in the treatment of COVID-19.

9.6.2. Zinc

Zinc (Zn) impacts the host immune system and is among the most commonly studied microcomponents [219]. Zn deficiency increases host vulnerability to various infectious diseases [220, 221], and low Zn levels have been linked to reduced T cell function, resulting in a lack of antibody response [222]. Inadequate Zn levels result in deficient humoral and cellular immune responses and increased susceptibility to infectious diseases [223]. Therefore, Zn supplements can be used to reduce symptoms associated with viral infections, including COVID-19.

9.6.3. Iron

Iron is vital for both the host and the microorganism. Iron deficiency affects the host immunity; low iron levels can affect oxidative pressure following harmful viral changes [224]. In addition, iron deficiency is linked to an increase in recurrent respiratory tract distress [225], which has been observed in older adults; iron deficiency is also associated with both disrupted cellular and innate immunity [226]. Recently, a case-control study involving hospitalized children aged 2 to 5 years found that long-term iron supplementation significantly reduced the incidence of gastroenteritis, urinary tract infections, and severe respiratory tract infections [225]. Therefore, iron could prove to be helpful for combating COVID-19.

9.6.4. Copper

Copper plays an essential role in immune cell progression [227]. The influenza virus's life cycle is controlled by intracellular copper [228, 229]. Improved copper delivery significantly reduced serum IL-2R, antibody titers, and circulating neutrophils in response to a Beijing strain of influenza [230].

9.6.5. Magnesium

Magnesium regulates the immune response by altering the macrophage response to lymphokines, antibody-dependent cytolysis, T helper and B cell support, immune cell adhesion, IgM lymphocyte binding, and immunoglobulin synthesis [231]. Various studies have suggested that magnesium may potentially play a role in the immunological response to viral infections [232].

9.7. Convalescent Plasma

Previously, plasma treatment was used as a terminal treatment to increase the survival rate of persons with various viral infections and serious diseases caused by Ebola, SARS, and flu pandemics, including H1N1 and H5N1 avian flu [233, 234]. Viremia can be hampered in patients treated with plasma-derived immunoglobulin antibodies. The clinical conditions of patients typically improve after convalescent plasma treatment, including reduced viral burden, enhanced inhibitory SARS-CoV-2-specific antibody titers as assessed by ELISA, improved ARDS outcomes, reduced fever, improved partial pressure of oxygen and the fraction of inspired oxygen, and reduced need for mechanical ventilation [234].

9.8. Coronavirus Protease Inhibitors

9.8.1. Chymotrypsin-like Inhibitors

The selective serotonin receptor blocker cinanserin (CIN) can be used to inhibit chymotrypsin-like protease (CTLpro), encoded by SARS-CoV-2. In recent investigations, CIN was also found to be active against SARS-CoV [235, 236].

9.8.2. Papain-like Protease Inhibitors

The papain-like protease (PLpro) inhibits the host's IFN immune response. Various factors have been developed to specifically target PLpro. As a result, a combination of CIN/flavonoids and diarylheptanoids (DIH) can be used to block both CTLpro and Plpro, thereby protecting against COVID-19 [237].

9.8.3. ACE2 Inhibitors

As a carboxypeptidase, ACE2 hydrolyzes the peptide bonds of identical polypeptides [238]. The spike (S) protein on the SARS-CoV envelope interacts with the ACE2 receptor to enter human cells [26, 239]. SARS-CoV-2 is only able to enter the body through the ACE2 receptor. Therefore, increased ACE2 expression may increase SARS-CoV-2 infection among hypertensive and diabetic patients, increasing the risk of lethal COVID-19 development [240]. Consequently, patients should be closely monitored when using ACE2-stimulating drugs, including ACE inhibitors or ARBs. Currently, a clinical trial is being conducted to determine whether the use of renin-angiotensin system inhibitors affects the occurrence and severity of COVID-19 [241]. Along these lines, ACE2 antagonists have a bright future for the treatment of COVID-19 [242].

9.8.4. Promazine and Nicotianamine

A phenothiazine supplement, comparable to promazine (PRZ), effectively inhibited SARS-CoV replication [243], with a structure similar to an anthraquinone named emodin (EMD), and is able to bind ACE2 similarly to the S protein, preventing interaction [244]. SARS-CoV-2 antagonists may be more feasible than ACE2 receptor protein inhibitors, and human mAbs, such as EMD and PRZ, can be used during the current pandemic. Nicotianamine (NTA) is a metal chelating agent found in soybean seeds and other plants [245] that was recently discovered to block ACE2 and may represent another COVID-19 treatment option [246]. NTA is currently being explored in stage III clinical trials for individuals with COVID-19 who have been hospitalized for respiratory side effects [247].

9.9. Development of Vaccines

The vaccination procedure is the most cost-effective and sensible method for controlling, preventing, and combating infections, particularly severe pulmonary and respiratory disorders. Vaccines help prevent infections by strengthening the immune system's defenses against the pathogen [248-250]. SARS-CoV-2 requires the ACE2 enzyme to enter the living cells; however, if a vaccine inhibits the ACE2 enzyme, SARS-CoV-2 cannot enter the cell or replicate. Vaccines are being developed with demonstrated efficacy, with many in various phases of development. Phase I represents the earliest stages of validation, whereas Phases II and III confirm the efficacy and potency of a vaccine against viral illnesses, such as SARS-CoV-2 [251-253].

9.9.1. ChAdOx1 Vaccine

The ChAdOx1 vaccination includes a shuttle plasmid that promotes MERS-CoV spike protein expression *in vitro*. ChAdOx1 uses a robust immune response mechanism that encodes a green fluorescent protein (GEP) to entrap the viral protein in Phase I and Phase II vaccine trials; it involves tissue culture infective dose that does not show early safety concerns [254-256]. By inducing a T cell response, this vaccination provided a promising result within 14 days, with antibody generation detected after 28 days. According to the Oxford University researchers [257, 258], Phase III trials in low- and middle-income nations, such as Brazil and South Africa, have exhibited excellent results (Table **2**) [259].

9.10. Herbal Medicines

Chinese traditional medicines have been investigated as potential preventive strategies against SARS-CoV-2, based on their traditional uses [260-262]. Some clinical trials reported unsatisfactory results when typical pharmaceuticals were examined for the prevention of

Table 2. Probable vaccines under clinical trial for COVID-19.

Vaccine Platform	Candidate Vaccine	Manufacturer	Route of Administration	
			Intramuscular	Intradermal
Protein subunit	S-2P protein + CpG 1018	NIAID/Dynavax/Medigen Vaccine Biologics Corporation	Yes	No
	Peptide	FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo	Yes	No
	Trimeric subunit Spike protein (Native) vaccine	GSK/Dynavax/Clover Biopharmaceuticals	Yes	No
	RBD + Adjuvant	Instituto Finlay de Vacunas, Cuba	Yes	No
	Adjuvanted recombinant protein (RBD-Dimer)	Chinese Academy of Sciences (Microbiology Institute) / Anhui ZhifeiLongcom Biopharmaceutical	Yes	No
	Molecular clamp stabilized Spike protein with MF59 adjuvant	CSL/Seqirus/University of Queensland	Yes	No
	RBD-based	Kentucky Bioprocessing, Inc	Yes	No
	Adjuvanted recombinant SARS-CoV-2 glycoprotein nanoparticle vaccine	Novavax	Yes	No
	Advax™ adjuvant + Recombinant spike protein	Vaccine Pty Ltd/Medytox	Yes	No
RNA	mRNA	Duke-NUS/Arcturus	Yes	No
		Walvax Biotech/Academy of Military Sciences (PLA)	Yes	
		Curevac	Yes	
	LNP-encapsulated mRNA	NIAID/Moderna	Yes	
	LNP-nCoVsaRNA	Imperial College, London	Yes	
	3LNP-mRNAs	Pfizer/FosunPharma/BioNTech	Yes	
DNA	Plasmid vaccine	Cadila Healthcare Limited	-	Yes
	Plasmid vaccine + Adjuvant	AnGes/Takara Bio/Osaka University	Yes	-
	Plasmid vaccine with electroporation	International Vaccine Institute/Inovio Pharmaceuticals	-	Yes
Non-replicating viral vector	Replication defective Simian Adenovirus (GRAd) encoding S	Univercells /ReiThera/LEUKOCARE	Yes	No
	Adeno-based	Gamaleya Research Institute	Yes	
	Adenovirus Type 5 Vector	CanSino Biological Inc./ Beijing Institute of Biotechnology	Yes	
	ChAdOx1-S	AstraZeneca/Oxford University	Yes	
	Ad26COVS1	Janssen Pharmaceuticals	Yes	
Inactivated	Inactivated	Sinovac	Yes	No
		Chinese Academy of Medical Sciences	Yes	
		Sinopharm/Wuhan Institute of Biological Products	Yes	
	Whole-Virion Inactivated	Bharat Biotech	Yes	

SARS-CoV-2 infection. However, some clinical study results have suggested that herbal treatments may contribute to COVID-19 prevention and control [40, 263]. Traditional Chinese medicine has historically played critical roles in the prevention of epidemic diseases, including the response to SARS in 2003. Traditional Chinese herbal medications are approved by Chinese herbalists based on the patient's specific symptoms, as identified during diagnosis, including hearing, smelling, injury, and palpation [176]. The Wu Huangqin Decoction, Lianhuaqingwen capsule, and Yinhuapingan granule, prescribed by Chinese herbalists, have demonstrated impacts against several pandemic antiviral diseases, including influenza virus [264].

Chinese herbal medications can be combined with Western medicine to develop therapeutic regimens that reduce the adverse effects and improve the efficacy of glucocorticoids, antibiotics, and antiviral treatments [265]. According to some clinical trials, *Scutellariae radix*, *Artemisiae annuae* Herba, and *Belamcandae rhizome*

have fever-reducing effects, particularly when used together in herbal formulation granules [266].

The China Food and Drug Administration has given *Scutelliariae radix* its highest approval to treat viral disorders, including influenza, upper respiratory infection, and pneumonia. Baicalin, an active pharmaceutical ingredient derived from *Scutelliariae radix*, has also been used to treat SARS-CoV-2. *Artemisiae annuae* Herba has demonstrated efficacy in clinical studies against SARS-CoV-2 [267]. *Belamcandae rhizoma* plants are used to treat inflammation and throat disorders and are applicable against some viral illnesses. Other herbs, such as *Armeniacae semen*, exert antiviral action, but clinical research has been inconclusive regarding their effectiveness; however, some evidence suggests that these herbs can treat lung damage [84, 268].

CONCLUSION

The SARS-CoV-2 pandemic, also known as the COVID-19 pandemic, has led to serious world health problems. We have attempted to provide an overview of the current status of COVID-19 research and treatments, including the potential for nanotechnology, resulting in the development of nanovaccines, antiviral compositions, biosensors, and nanochemistry-based nanomaterials, such as polymeric coatings, proteins, inorganic components, and peptide-based constituents, designed to improve treatment efficacy against SARS-CoV-2. Furthermore, people should wash their hands for at least 20 seconds or longer and avoid crowded situations.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This project was financially supported by the Pharmakon Neuroscience Research Network, Dhaka, Bangladesh.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Hasana S, Hossain MF, Jalouli M, *et al.* Genetic diversity of sars-cov2 and environmental settings: Possible association with neurological disorders. Mol Neurobiol 2021; 58(5): 1917-31. http://dx.doi.org/10.1007/s12035-020-02239-z PMID: 33404977

[2] Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol 2015; 1282: 1-23. http://dx.doi.org/10.1007/978-1-4939-2438-7_1 PMID: 25720466

[3] Kumar R, Srivastava JK, Singh R, *et al.* Available compounds with therapeutic potential against COVID-19: Antimicrobial therapies, supportive care, and probable vaccines. Front Pharmacol 2020; 11: 582025. http://dx.doi.org/10.3389/fphar.2020.582025 PMID: 33123014

[4] Zalinger ZB, Elliott R, Weiss SR. Role of the inflammasome-related cytokines Il-1 and Il-18 during infection with murine coronavirus. J Neurovirol 2017; 23(6): 845-54. http://dx.doi.org/10.1007/s13365-017-0574-4 PMID: 28895072

[5] Qaseem A, Etxeandia-Ikobaltzeta I, Yost J, *et al.* Use of N95, surgical, and cloth masks to prevent COVID-19 in health care and community settings: Living practice points from the American college of physicians (version 1). Ann Intern Med 2020; 173(8): 642-9. http://dx.doi.org/10.7326/M20-3234 PMID: 32551813

[6] Stadnytskyi V, Bax CE, Bax A, Anfinrud P. The airborne lifetime of small speech droplets and their potential importance in SARS-CoV-2 transmission. Proc Natl Acad Sci USA 2020; 117(22): 11875-7. http://dx.doi.org/10.1073/pnas.2006874117 PMID: 32404416

[7] Ting DSW, Carin L, Dzau V, Wong TY. Digital technology and COVID-19. Nat Med 2020; 26(4): 459-61. http://dx.doi.org/10.1038/s41591-020-0824-5 PMID: 32284618

[8] Shahriar S, Rana MS, Hossain MS, *et al.* COVID-19: Epidemiology, pathology, diagnosis, treatment, and impact. Curr Pharm Des 2021; 27(33): 3502-25. http://dx.doi.org/10.2174/1381612827666210224142446 PMID: 33655825

[9] Coronavirus Update (Live). 126,727,456 cases and 2,780,162 deaths from COVID-19 virus pandemic - worldometer. Available from: https://www.worldometers.info/coronavirus/ (accessed on 2021).

[10] Abdelli I, Hassani F, Bekkel Brikci S, Ghalem S. *In silico* study the inhibition of angiotensin converting enzyme 2 receptor of COVID-19 by *Ammoides verticillata* components harvested from Western Algeria. J Biomol Struct Dyn 2021; 39(9): 3263-76. http://dx.doi.org/10.1080/07391102.2020.1763199 PMID: 32362217

[11] Song Z, Hu Y, Zheng S, Yang L, Zhao R. Hospital pharmacists' pharmaceutical care for hospitalized patients with COVID-19: Recommendations and guidance from clinical experience. Res Social Adm Pharm 2021; 17(1): 2027-31. http://dx.doi.org/10.1016/j.sapharm.2020.03.027 PMID: 32273253

[12] Lin K, Yee-Tak Fong D, Zhu B, Karlberg J. Environmental factors on the SARS epidemic: air temperature, passage of time and multiplicative effect of hospital infection. Epidemiol Infect 2006; 134(2): 223-30. http://dx.doi.org/10.1017/S0950268805005054 PMID: 16490124

[13] Shams SA, Haleem A, Javaid M. Analyzing COVID-19 pandemic for unequal distribution of tests, identified cases, deaths, and fatality rates in the top 18 countries. Diabetes Metab Syndr 2020; 14(5): 953-61. http://dx.doi.org/10.1016/j.dsx.2020.06.051 PMID: 32604014

[14] CDC. COVID-19 employer information for office buildings. Develop hazard controls using the hierarchy of controls to reduce transmission among workers Include a combination of controls noted below. 2021. Available from: https://www.cdc.gov/coronavirus/2019-ncov/community/office-buildings.html

[15] Abbas SN, Naushad A. Covid-19 pandemic: A remedial measure through convalescent serum. Int J Innov Sci Technol 2020; 2(2): 46-50.

[16] Lawand NM, Al Tabbah S. Coronavirus disease 2019 (COVID-19). Prevention and disinfection 2020.

[17] UNESCO. COVID-19 Educational Disruption and Response. 2020. Available from: https://en.unesco.org/news/covid-19-educational-disruption-and-response

[18] Valdiglesias V, Laffon B. The impact of nanotechnology in the current universal COVID-19 crisis. Let's not forget nanosafety! Nanotoxicology 2020; 14(8): 1013-6. http://dx.doi.org/10.1080/17435390.2020.1780332 PMID: 32552140

[19] Goldsmith CS, Tatti KM, Ksiazek TG, *et al.* Ultrastructural characterization of SARS coronavirus. Emerg Infect Dis 2004; 10(2): 320-6. http://dx.doi.org/10.3201/eid1002.030913 PMID: 15030705

[20] Neuman BW, Kiss G, Kunding AH, *et al.* A structural analysis of M protein in coronavirus assembly and morphology. J Struct Biol 2011; 174(1): 11-22. http://dx.doi.org/10.1016/j.jsb.2010.11.021 PMID: 21130884

[21] de Groot RJ, Baker SC, Baric RS, *et al.* Middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the Coronavirus Study Group. J Virol 2013; 87(14): 7790-2. http://dx.doi.org/10.1128/JVI.01244-13 PMID: 23678167

[22] Chang CK, Hou M-H, Chang C-F, Hsiao CD, Huang TH. The SARS coronavirus nucleocapsid protein--forms and functions. Antiviral Res 2014; 103: 39-50. http://dx.doi.org/10.1016/j.antiviral.2013.12.009 PMID: 24418573

[23] Timani KA, Ye L, Ye L, Zhu Y, Wu Z, Gong Z. Cloning, sequencing, expression, and purification of SARS-associated coronavirus nucleocapsid protein for serodiagnosis of SARS. J Clin Virol 2004; 30(4): 309-12. http://dx.doi.org/10.1016/j.jcv.2004.01.001 PMID: 15163419

[24] Leng Z, Zhu R, Hou W, *et al.* Transplantation of ACE2- mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging Dis 2020; 11(2): 216-28. http://dx.doi.org/10.14336/AD.2020.0228 PMID: 32257537

[25] Peiris JSM, Guan Y, Yuen KY. Severe acute respiratory syndrome. Nat Med 2004; 10(12)(Suppl.): S88-97. http://dx.doi.org/10.1038/nm1143 PMID: 15577937

[26] Li W, Moore MJ, Vasilieva N, *et al.* Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003; 426(6965): 450-4. http://dx.doi.org/10.1038/nature02145 PMID: 14647384

[27] Zhou P, Yang X-L, Wang X-G, *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579(7798): 270-3. http://dx.doi.org/10.1038/s41586-020-2012-7 PMID: 32015507

[28] Belouzard S, Chu VC, Whittaker GR. Activation of the SARS coronavirus spike protein *via* sequential proteolytic cleavage at two distinct sites. Proc Natl Acad Sci USA 2009; 106(14): 5871-6. http://dx.doi.org/10.1073/pnas.0809524106 PMID: 19321428

[29] Wang H, Yang P, Liu K, *et al.* SARS coronavirus entry into host cells through a novel clathrin- and caveolae-independent endocytic pathway. Cell Res 2008; 18(2): 290-301. http://dx.doi.org/10.1038/cr.2008.15 PMID: 18227861

[30] Novak JE, Kirkegaard K. Coupling between genome translation and replication in an RNA virus. Genes Dev 1994; 8(14): 1726-37. http://dx.doi.org/10.1101/gad.8.14.1726 PMID: 7958852

[31] Taanman J-W. The mitochondrial genome: structure, transcription, translation and replication. Biochim Biophys Acta 1999; 1410(2): 103-23. http://dx.doi.org/10.1016/S0005-2728(98)00161-3 PMID: 10076021

[32] Tijms MA, van Dinten LC, Gorbalenya AE, Snijder EJ. A zinc finger-containing papain-like protease couples subgenomic mRNA synthesis to genome translation in a positive-stranded RNA virus. Proc Natl Acad Sci USA 2001; 98(4): 1889-94. http://dx.doi.org/10.1073/pnas.98.4.1889 PMID: 11172046

[33] Liu T, Hu J, Xiao J, *et al.* Time-varying transmission dynamics of novel coronavirus pneumonia in china. BioRxiv 2020. http://dx.doi.org/10.1101/2020.01.25.919787

[34] Arava Y, Wang Y, Storey JD, Liu CL, Brown PO, Herschlag D. Genome-wide analysis of mRNA translation profiles in *Saccharomyces cerevisiae.* Proc Natl Acad Sci USA 2003; 100(7): 3889-94. http://dx.doi.org/10.1073/pnas.0635171100 PMID: 12660367

[35] Zhang R, Wang X, Ni L, *et al.* COVID-19: Melatonin as a potential adjuvant treatment. Life Sci 2020; 250: 117583. http://dx.doi.org/10.1016/j.lfs.2020.117583 PMID: 32217117

[36] Chan JF-W, Zhang AJ, Yuan S, *et al.* Simulation of the clinical and pathological manifestations of coronavirus disease 2019 (covid-19) in golden Syrian hamster model: Implications for disease pathogenesis and transmissibility. Clin Infect Dis 2020; 71(9): 2428-46. http://dx.doi.org/10.1093/cid/ciaa325 PMID: 32215622

[37] Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020; 20(6): 355-62. http://dx.doi.org/10.1038/s41577-020-0331-4 PMID: 32376901

[38] Chu H, Chan JF-W, Wang Y, *et al.* 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. http://dx.doi.org/10.1093/cid/ciaa410 PMID: 32270184

[39] Ackermann M, Verleden SE, Kuehnel M, *et al.* Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020; 383(2): 120-8. http://dx.doi.org/10.1056/NEJMoa2015432 PMID: 32437596

[40] Shi Y, Wang Y, Shao C, *et al.* COVID-19 infection: the perspectives on immune responses. Cell Death Differ 2020; 27(5): 1451-4. http://dx.doi.org/10.1038/s41418-020-0530-3 PMID: 32205856

[41] Lechien JR, Chiesa-Estomba CM, Place S, *et al.* Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. J Intern Med 2020; 288(3): 335-44. http://dx.doi.org/10.1111/joim.13089 PMID: 32352202

[42] ISARIC. International severe acute respiratory and emerging infections consortium (ISARIC). 2021. Available from: https://isaric.tghn.org/

[43] Zhang JJY, Lee KS, Ang LW, Leo YS, Young BE. Risk factors for severe disease and efficacy of treatment in patients infected with COVID-19: A systematic review, meta-analysis, and meta-regression analysis. Clin Infect Dis 2020; 71(16): 2199-206. http://dx.doi.org/10.1093/cid/ciaa576 PMID: 32407459

[44] Tong JY, Wong A, Zhu D, Fastenberg JH, Tham T. The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: A systematic review and meta-analysis. Otolaryngol Head Neck Surg 2020; 163(1): 3-11. http://dx.doi.org/10.1177/0194599820926473 PMID: 32369429

[45] Aziz M, Perisetti A, Lee-Smith WM, Gajendran M, Bansal P, Goyal H. Taste changes (dysgeusia) in COVID-19: A systematic review and meta-analysis. Gastroenterology 2020; 159(3): 1132-3. http://dx.doi.org/10.1053/j.gastro.2020.05.003 PMID: 32387496

[46] Helms J, Kremer S, Merdji H, *et al.* Neurologic features in severe SARS-CoV-2 infection. N Engl J Med 2020; 382(23): 2268-70. http://dx.doi.org/10.1056/NEJMc2008597 PMID: 32294339

[47] Mao L, Jin H, Wang M, *et al.* Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020; 77(6): 683-90. http://dx.doi.org/10.1001/jamaneurol.2020.1127 PMID: 32275288

[48] Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, *et al.* Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. Neurology 2020; 95(8): e1060-70. http://dx.doi.org/10.1212/WNL.0000000000009937 PMID: 32482845

[49] Liotta EM, Batra A, Clark JR, *et al.* Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann Clin Transl Neurol 2020; 7(11): 2221-30. http://dx.doi.org/10.1002/acn3.51210 PMID: 33016619

[50] Moriguchi T, Harii N, Goto J, *et al.* A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis 2020; 94: 55-8. http://dx.doi.org/10.1016/j.ijid.2020.03.062 PMID: 32251791

[51] Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost 2020; 18(6): 1421-4. http://dx.doi.org/10.1111/jth.14830 PMID: 32271988

[52] Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020; 395(10237): 1607-8. http://dx.doi.org/10.1016/S0140-6736(20)31094-1 PMID: 32386565

[53] Verdoni L, Mazza A, Gervasoni A, *et al.* An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020; 395(10239): 1771-8. http://dx.doi.org/10.1016/S0140-6736(20)31103-X PMID: 32410760

[54] Denise A, Anne-Sophie B, Fanny C, *et al.* COVID-19 chez l'enfant: état des connaissances en amont de la réouverture des écoles. Paris: Santé publique France 2020.

[55] Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. Available from: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19 [Cited 2020].

[56] Steinberg J, Schiller HJ, Halter JM, *et al.* Tidal volume increases do not affect alveolar mechanics in normal lung but cause alveolar overdistension and exacerbate alveolar instability after surfactant deactivation. Crit Care Med 2002; 30(12): 2675-83. http://dx.doi.org/10.1097/00003246-200212000-00011 PMID: 12483058

[57] Ramirez J, Harlan WR Jr. Pulmonary alveolar proteinosis. Nature and origin of alveolar lipid. Am J Med 1968; 45(4): 502-12. http://dx.doi.org/10.1016/0002-9343(68)90166-6 PMID: 5678094

[58] Xu Z, Shi L, Wang Y, *et al.* Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020; 8(4): 420-2. http://dx.doi.org/10.1016/S2213-2600(20)30076-X PMID: 32085846

[59] Hanson KE, Caliendo AM, Arias CA, *et al.* Infectious diseases society of America guidelines on the diagnosis of covid-19. Clin Infect Dis 2020; ciaa1343. Online ahead of print. http://dx.doi.org/10.1093/cid/ciaa1343 PMID: 32918466

[60] CDC. Serology Testing for COVID-19 at CDC. 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/lab/serology-testing.html [Cited 2021]

[61] Alam SZ, Muid SA, Akhter A, *et al.* HRCT chest evaluation of covid-19 patients: Experience in combined military hospital Dhaka, Bangladesh. J Bangladesh Coll Phys Surg 2020; 38: 21-8. http://dx.doi.org/10.3329/jbcps.v38i0.47441

[62] Chen H, Guo J, Wang C, *et al.* Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 2020; 395(10226): 809-15. http://dx.doi.org/10.1016/S0140-6736(20)30360-3 PMID: 32151335

[63] Chen N, Zhou M, Dong X, *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395(10223): 507-13. http://dx.doi.org/10.1016/S0140-6736(20)30211-7 PMID: 32007143

[64] Wang D, Hu B, Hu C, *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323(11): 1061-9. http://dx.doi.org/10.1001/jama.2020.1585 PMID: 32031570

[65] Meyer B, Drosten C, Müller MA. Serological assays for emerging coronaviruses: challenges and pitfalls. Virus Res 2014; 194: 175-83. http://dx.doi.org/10.1016/j.virusres.2014.03.018 PMID: 24670324

[66] Ward S, Lindsley A, Courter J, Assa'ad A. Clinical testing for COVID-19. J Allergy Clin Immunol 2020; 146(1): 23-34. http://dx.doi.org/10.1016/j.jaci.2020.05.012 PMID: 32445839

[67] Okba NMA, Müller MA, Li W, *et al.* Severe acute respiratory syndrome coronavirus 2-specific antibody responses in coronavirus disease patients. Emerg Infect Dis 2020; 26(7): 1478-88. http://dx.doi.org/10.3201/eid2607.200841 PMID: 32267220

[68] Lv H, Wu NC, Tsang OTY, *et al.* Cross-reactive antibody response between SARS-CoV-2 and SARS-CoV infections. bioRxiv 2020. http://dx.doi.org/10.1016/j.celrep.2020.107725

[69] Mahari S, Roberts A, Shahdeo D, Gandhi S. eCovsens-ultrasensitive novel in-house built printed circuit board based electrochemical device for rapid detection of ncovid-19 antigen, a spike protein domain 1 of sars-cov-2. bioRxiv 2020. http://dx.doi.org/10.1101/2020.04.24.059204

[70] Diao B, Wen K, Chen J, *et al.* Diagnosis of acute respiratory syndrome coronavirus 2 infection by detection of nucleocapsid protein medRxiv 2020. http://dx.doi.org/10.1101/2020.03.07.20032524

[71] Weitzel T, Legarraga P, Iruretagoyena M, *et al.* Head-to-head comparison of four antigen-based rapid detection tests for the diagnosis of SARS-CoV-2 in respiratory samples bioRxiv 2020. http://dx.doi.org/10.1101/2020.05.27.119255

[72] Kohmer N, Westhaus S, Rühl C, Ciesek S, Rabenau HF. Clinical performance of different SARS-CoV-2 IgG antibody tests. J Med Virol 2020; 92(10): 2243-7. http://dx.doi.org/10.1002/jmv.26145 PMID: 32510168

[73] Liu W, Liu L, Kou G, *et al.* Evaluation of nucleocapsid and spike protein-based enzyme-linked immunosorbent assays for detecting antibodies against SARS-CoV-2. J Clin Microbiol 2020; 58(6): e00461-20. http://dx.doi.org/10.1128/JCM.00461-20 PMID: 32229605

[74] Li C, Zhao C, Bao J, Tang B, Wang Y, Gu B. Laboratory diagnosis of coronavirus disease-2019 (COVID-19). Clin Chim Acta 2020; 510: 35-46. http://dx.doi.org/10.1016/j.cca.2020.06.045 PMID: 32621814

[75] Long Q, Deng H, Chen J, *et al.* Antibody responses to SARS-CoV-2 in COVID-19 patients: The perspective application of serological tests in clinical practice. medRxiv 2020. http://dx.doi.org/10.1101/2020.03.18.20038018

[76] Zhang J, Zhang X, Liu J, *et al.* Serological detection of 2019-nCoV respond to the epidemic: A useful complement to nucleic acid testing. Int Immunopharmacol 2020; 88: 106861. http://dx.doi.org/10.1016/j.intimp.2020.106861 PMID: 32771946

[77] Cai XF, Chen J, Li Hu J, *et al.* A Peptide-based magnetic chemiluminescence enzyme immunoassay for serological diagnosis of coronavirus disease 2019. J Infect Dis 2020; 222(2): 189-93. http://dx.doi.org/10.1093/infdis/jiaa243 PMID: 32382737

[78] Montesinos I, Gruson D, Kabamba B, *et al.* Evaluation of two automated and three rapid lateral flow immunoassays for the detection of anti-SARS-CoV-2 antibodies. J Clin Virol 2020; 128: 104413. http://dx.doi.org/10.1016/j.jcv.2020.104413 PMID: 32403010

[79] Li Z, Yi Y, Luo X, *et al.* Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. J Med Virol 2020; 92(9): 1518-24. http://dx.doi.org/10.1002/jmv.25727 PMID: 32104917

[80] Huang WE, Lim B, Hsu C-C, *et al.* RT-LAMP for rapid diagnosis of coronavirus SARS-CoV-2. Microb Biotechnol 2020; 13(4): 950-61. http://dx.doi.org/10.1111/1751-7915.13586 PMID: 32333644

[81] Russo A, Minichini C, Starace M, Astorri R, Calò F, Coppola N. Current status of laboratory diagnosis for covid-19: A narrative review. Infect Drug Resist 2020; 13: 2657-65. http://dx.doi.org/10.2147/IDR.S264020 PMID: 32801804

[82] Martin TR, Mathison JC, Tobias PS, *et al.* Lipopolysaccharide binding protein enhances the responsiveness of alveolar macrophages to bacterial lipopolysaccharide. Implications for cytokine production in normal and injured lungs. J Clin Invest 1992; 90(6): 2209-19. http://dx.doi.org/10.1172/JCI116106 PMID: 1281827

[83] Ramirez MI, Millien G, Hinds A, Cao Y, Seldin DC, Williams MC. T1α, a lung type I cell differentiation gene, is required for normal lung cell proliferation and alveolus formation at birth. Dev Biol 2003; 256(1): 61-72. http://dx.doi.org/10.1016/S0012-1606(02)00098-2 PMID: 12654292

[84] Kabir MT, Uddin MS, Hossain MF, *et al.* nCOVID-19 pandemic: From molecular pathogenesis to potential investigational therapeutics. Front Cell Dev Biol 2020; 8: 616. http://dx.doi.org/10.3389/fcell.2020.00616 PMID: 32754599

[85] Cavanaugh KJ Jr, Oswari J, Margulies SS. Role of stretch on tight junction structure in alveolar epithelial cells. Am J Respir Cell Mol Biol 2001; 25(5): 584-91. http://dx.doi.org/10.1165/ajrcmb.25.5.4486 PMID: 11713100

[86] Massaro GD, Massaro D, Chambon P. Retinoic acid receptor-α regulates pulmonary alveolus formation in mice after, but not during, perinatal period. Am J Physiol Lung Cell Mol Physiol 2003; 284(2): L431-3. http://dx.doi.org/10.1152/ajplung.00245.2002 PMID: 12533315

[87] Hislop A, Reid L. Persistent hypoplasia of the lung after repair of congenital diaphragmatic hernia. Thorax 1976; 31(4): 450-5. http://dx.doi.org/10.1136/thx.31.4.450 PMID: 968803

[88] Tang Y-W, Schmitz JE, Persing DH, Stratton CW. Laboratory diagnosis of COVID-19: Current issues and challenges. J Clin Microbiol 2020; 58(6): e00512-20. http://dx.doi.org/10.1128/JCM.00512-20 PMID: 32245835

[89] Lippi G, Simundic A-M, Plebani M. Potential preanalytical and analytical vulnerabilities in the laboratory diagnosis of coronavirus disease 2019 (COVID-19). Clin Chem Lab Med 2020; 58(7): 1070-6. http://dx.doi.org/10.1515/cclm-2020-0285 PMID: 32172228

[90] Chan JF-W, Yip CC-Y, To KK-W, *et al.* Improved molecular diagnosis of COVID-19 by the novel, highly sensitive and specific COVID-19-RdRp/Hel real-time reverse transcription-PCR assay validated *in vitro* and with clinical specimens. J Clin Microbiol 2020; 58(5): e00310-20. http://dx.doi.org/10.1128/JCM.00310-20 PMID: 32132196

[91] Hong KH, Lee SW, Kim TS, *et al.* Guidelines for laboratory diagnosis of coronavirus disease 2019 (COVID-19) in Korea. Ann Lab Med 2020; 40(5): 351-60. http://dx.doi.org/10.3343/alm.2020.40.5.351 PMID: 32237288

[92] Sabino-Silva R, Jardim ACG, Siqueira WL. Coronavirus COVID-19 impacts to dentistry and potential salivary diagnosis. Clin Oral Investig 2020; 24(4): 1619-21. http://dx.doi.org/10.1007/s00784-020-03248-x PMID: 32078048

[93] Gandhi RT, Lynch JB, Del Rio C. Mild or moderate COVID-19. N Engl J Med 2020; 383(18): 1757-66. http://dx.doi.org/10.1056/NEJMcp2009249 PMID: 32329974

[94] Cascella M, Rajnik M, Aleem A, Cuomo A, Dulebohn SC, Di Napoli R. Features, evaluation and treatment coronavirus (COVID-19). In: StatPerals Publishing Treasure Island (FL) 2020. PMID: 32150360

[95] Kannan S, Shaik Syed Ali P, Sheeza A, Hemalatha K. COVID-19 (novel coronavirus 2019) - recent trends. Eur Rev Med Pharmacol Sci 2020; 24(4): 2006-11. http://dx.doi.org/10.26355/eurrev_202002_20378 PMID: 32141569

[96] Liang T, Ed. Handbook of COVID-19 prevention and treatment. Zhejiang Province 2020.

[97] Pradhan D, Biswasroy P, Kumar Naik P, Ghosh G, Rath G. A review of current interventions for COVID-19 prevention. Arch Med Res 2020; 51(5): 363-74. http://dx.doi.org/10.1016/j.arcmed.2020.04.020 PMID: 32409144

[98] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese center for disease control and prevention. JAMA 2020; 323(13): 1239-42. http://dx.doi.org/10.1001/jama.2020.2648 PMID: 32091533

[99] Sivasankarapillai VS, Pillai AM, Rahdar A, *et al.* On facing the sars-cov-2 (covid-19) with combination of nanomaterials and medicine: Possible strategies and first challenges. Nanomaterials (Basel) 2020; 10(5): 852. http://dx.doi.org/10.3390/nano10050852 PMID: 32354113

[100] Ding S, Liang TJ. Is SARS-CoV-2 also an enteric pathogen with potential Fecal-Oral transmission: A covid-19 virological and clinical review. Gastroenterology 2020; 159(1): 53-61. http://dx.doi.org/10.1053/j.gastro.2020.04.052 PMID: 32353371

[101] Hu TY, Frieman M, Wolfram J. Insights from nanomedicine into chloroquine efficacy against COVID-19. Nat Nanotechnol 2020; 15(4): 247-9. http://dx.doi.org/10.1038/s41565-020-0674-9 PMID: 32203437

[102] Weiss C, Carriere M, Fusco L, *et al.* Toward nanotechnology-enabled approaches against the covid-19 pandemic. ACS Nano ACS Publications 2020. http://dx.doi.org/10.1021/acsnano.0c03697

[103] Vazquez-Munoz R, Lopez-Ribot JL. Nanotechnology as an alternative to reduce the spread of COVID-19. Challenges 2020; 11(2): 15. http://dx.doi.org/10.3390/challe11020015

[104] Nasrollahzadeh M, Sajjadi M, Soufi GJ, Iravani S, Varma RS. Nanomaterials and nanotechnology-associated innovations against viral infections with a focus on coronaviruses. Nanomaterials (Basel) 2020; 10(6): 1072. http://dx.doi.org/10.3390/nano10061072 PMID: 32486364

[105] Qiu G, Gai Z, Tao Y, Schmitt J, Kullak-Ublick GA, Wang J. Dual-functional plasmonic photothermal biosensors for highly accurate severe acute respiratory syndrome coronavirus 2 detection. ACS Nano 2020; 14(5): 5268-77. http://dx.doi.org/10.1021/acsnano.0c02439 PMID: 32281785

[106] Seo G, Lee G, Kim MJ, *et al.* Rapid detection of COVID-19 causative virus (SARS-CoV-2) in human nasopharyngeal swab specimens using field-effect transistor-based biosensor. ACS Nano 2020; 14(4): 5135-42. http://dx.doi.org/10.1021/acsnano.0c02823 PMID: 32293168

[107] Rabiee N, Bagherzadeh M, Ghasemi A, *et al.* Point-of-use rapid detection of sars-cov-2: Nanotechnology-enabled solutions for the covid-19 pandemic. Int J Mol Sci 2020; 21(14): 5126. http://dx.doi.org/10.3390/ijms21145126 PMID: 32698479

[108] Shin MD, Shukla S, Chung YH, *et al.* COVID-19 vaccine development and a potential nanomaterial path forward. Nat Nanotechnol 2020; 15(8): 646-55. http://dx.doi.org/10.1038/s41565-020-0737-y PMID: 32669664

[109] Gupta R, Misra A. Contentious issues and evolving concepts in the clinical presentation and management of patients with COVID-19 infectionwith reference to use of therapeutic and other drugs used in Co-morbid diseases (Hypertension, diabetes *etc*). Diabetes Metab Syndr 2020; 14(3): 251-4. http://dx.doi.org/10.1016/j.dsx.2020.03.012 PMID: 32247213

[110] Chan WCW. Nano Research for COVID-19. ACS Nano 2020; 14(4): 3719-20. http://dx.doi.org/10.1021/acsnano.0c02540 PMID: 32227916

[111] Barar J. COVID-19 clinical implications: the significance of nanomedicine. Bioimpacts 2020; 10(3): 137-8. http://dx.doi.org/10.34172/bi.2020.16 PMID: 32793434

[112] Waris A, Ali M, Khan AU, Ali A, Bangash AK, Baset A. COVID-19 incidence in Pakistan: Gender disparity. Iran J Psychiatry Behav Sci Kowsar 2020; 14(3): e105990. http://dx.doi.org/10.5812/ijpbs.105990

[113] Couper K, Taylor-Phillips S, Grove A, *et al.* COVID-19 in cardiac arrest and infection risk to rescuers: A systematic review. Resuscitation 2020; 151: 59-66. http://dx.doi.org/10.1016/j.resuscitation.2020.04.022 PMID: 32325096

[114] Vafea MT, Atalla E, Georgakas J, *et al.* Emerging technologies for use in the study, diagnosis, and treatment of patients with COVID-19. Cell Mol Bioeng 2020; 13: 249-57. http://dx.doi.org/10.1007/s12195-020-00629-w

[115] Xiao K, Hou F, Huang X, Li B, Qian ZR, Xie L. Mesenchymal stem cells: current clinical progress in ARDS and COVID-19. Stem Cell Res Ther 2020; 11(1): 305. http://dx.doi.org/10.1186/s13287-020-01804-6 PMID: 32698898

[116] Pillarsetty N, Carter LM, Lewis JS, Reiner T. Oncology-inspired treatment options for COVID-19. J Nucl Med 2020; 61(12): 1720-3. http://dx.doi.org/10.2967/jnumed.120.249748 PMID: 32680924

[117] Itani R, Tobaiqy M, Al Faraj A. Optimizing use of theranostic nanoparticles as a life-saving strategy for treating COVID-19 patients. Theranostics 2020; 10(13): 5932-42. http://dx.doi.org/10.7150/thno.46691 PMID: 32483428

[118] Jiang Y, Huo S, Hardie J, Liang XJ, Rotello VM. Progress and perspective of inorganic nanoparticle-based siRNA delivery systems. Expert Opin Drug Deliv 2016; 13(4): 547-59. http://dx.doi.org/10.1517/17425247.2016.1134486 PMID: 26735861

[119] Lytton-Jean AKR, Langer R, Anderson DG. Five years of siRNA delivery: spotlight on gold nanoparticles. Small 2011; 7(14): 1932-7. http://dx.doi.org/10.1002/smll.201100761 PMID: 21681985

[120] Feng G, Jiang Q, Xia M, *et al.* Enhanced immune response and protective effects of nano-chitosan-based DNA vaccine encoding T cell epitopes of Esat-6 and FL against Mycobacterium tuberculosis infection. PLoS One 2013; 8(4): e61135. http://dx.doi.org/10.1371/journal.pone.0061135 PMID: 23637790

[121] Raj VS, Mou H, Smits SL, *et al.* Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 2013; 495(7440): 251-4. http://dx.doi.org/10.1038/nature12005 PMID: 23486063

[122] Szunerits S, Barras A, Khanal M, Pagneux Q, Boukherroub R. Nanostructures for the Inhibition of Viral Infections. Molecules 2015; 20(8): 14051-81. http://dx.doi.org/10.3390/molecules200814051 PMID: 26247927

[123] Moon JJ, Suh H, Li AV, Ockenhouse CF, Yadava A, Irvine DJ. Enhancing humoral responses to a malaria antigen with nanoparticle vaccines that expand Tfh cells and promote germinal center induction. Proc Natl Acad Sci USA 2012; 109(4): 1080-5. http://dx.doi.org/10.1073/pnas.1112648109 PMID: 22247289

[124] Coleman CM, Venkataraman T, Liu YV, *et al.* MERS-CoV spike nanoparticles protect mice from MERS-CoV infection. Vaccine 2017; 35(12): 1586-9. http://dx.doi.org/10.1016/j.vaccine.2017.02.012 PMID: 28237499

[125] Palestino G, García-Silva I, González-Ortega O, Rosales-Mendoza S. Can nanotechnology help in the fight against COVID-19? Expert Rev Anti Infect Ther 2020; 18(9): 849-64. http://dx.doi.org/10.1080/14787210.2020.1776115 PMID: 32574081

[126] Yetisen AK, Qu H, Manbachi A, *et al.* Nanotechnology in Textiles. ACS Nano 2016; 10(3): 3042-68. http://dx.doi.org/10.1021/acsnano.5b08176 PMID: 26918485

[127] Springer. Commercialization of nanotechnologies-a case study approach Available from: https://www.springerprofessional.de/en/commercialization-of-nanotechnologies-a-case-study-approach/15032310

[128] Sim W, Barnard RT, Blaskovich MAT, Ziora ZM. Antimicrobial silver in medicinal and consumer applications: A patent review of the past decade. Antibiotics (Basel) 2018; 7(4): 93. http://dx.doi.org/10.3390/antibiotics7040093 PMID: 30373130

[129] Suryaprabha T, Sethuraman MG. Fabrication of copper-based superhydrophobic self-cleaning antibacterial coating over cotton fabric. Cellulose 2017; 24(1): 395-407. http://dx.doi.org/10.1007/s10570-016-1110-z

[130] Mao N. Textile Materials for Protective Textiles. High Performance Technical Textiles. In: Paul R, Ed. NewYork: John Wiley & Sons, Ltd 2019; pp. 107-57. http://dx.doi.org/10.1002/9781119325062.ch5

[131] Duintjer Tebbens RJ, Pallansch MA, Thompson KM. Modeling the prevalence of immunodeficiency-associated long-term vaccine-derived poliovirus excretors and the potential benefits of antiviral drugs. BMC Infect Dis 2015; 15(1): 379. http://dx.doi.org/10.1186/s12879-015-1115-5 PMID: 26382043

[132] Heimfarth L, Serafini MR, Martins-Filho PRS, Quintans JSS, Quintans-Júnior LJ. Drug repurposing and cytokine management in response to COVID-19: A review. Int Immunopharmacol 2020; 88: 106947. http://dx.doi.org/10.1016/j.intimp.2020.106947 PMID: 32919216

[133] Marashi SM, Raeiszadeh M, Workman S, *et al.* Inflammation in common variable immunodeficiency is associated with a distinct CD8(+) response to cytomegalovirus. J Allergy Clin Immunol 2011; 127(6): 1385-93.e4. http://dx.doi.org/10.1016/j.jaci.2011.04.001 PMID: 21536322

[134] Ali N. Relationship between COVID-19 infection and liver injury: A review of recent data. Front Med (Lausanne) 2020; 7: 458. http://dx.doi.org/10.3389/fmed.2020.00458 PMID: 32793619

[135] Tarr PE, Sneller MC, Mechanic LJ, *et al.* Infections in patients with immunodeficiency with thymoma (Good syndrome). Report of 5 cases and review of the literature. Medicine (Baltimore) 2001; 80(2): 123-33. http://dx.doi.org/10.1097/00005792-200103000-00005 PMID: 11307588

[136] Hussain A, do Vale Moreira NC. Clinical considerations for patients with diabetes in times of COVID-19 pandemic. Diabetes Metab Syndr 2020; 14(4): 451-3. http://dx.doi.org/10.1016/j.dsx.2020.03.005 PMID: 32388324

[137] Hui DSC, Zumla A. Severe acute respiratory syndrome: Historical, epidemiologic, and clinical features. Infect Dis Clin North Am 2019; 33(4): 869-89. http://dx.doi.org/10.1016/j.idc.2019.07.001 PMID: 31668196

[138] Beigel JH, Tomashek KM, Dodd LE. Remdesivir for the treatment of Covid-19—preliminary report. N Engl J Med 2020; 383(10): 994. http://dx.doi.org/10.1056/NEJMc2022236 PMID: 32649078

[139] Wang Y, Zhang D, Du G, *et al.* Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020; 395(10236): 1569-78. http://dx.doi.org/10.1016/S0140-6736(20)31022-9 PMID: 32423584

[140] Cao YC, Deng QX, Dai SX. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: An evaluation of the evidence. Travel Med Infect Dis 2020; 35: 101647. http://dx.doi.org/10.1016/j.tmaid.2020.101647 PMID: 32247927

[141] Hendaus MA. Remdesivir in the treatment of coronavirus disease 2019 (COVID-19): a simplified summary. J Biomol Struct Dyn 2021; 39(10): 3787-92. http://dx.doi.org/10.1080/07391102.2020.1767691 PMID: 32396771

[142] Eastman RT, Roth JS, Brimacombe KR, *et al.* Remdesivir: A review of its discovery and development leading to emergency use authorization for treatment of covid-19. ACS Cent Sci 2020; 6(5): 672-83. http://dx.doi.org/10.1021/acscentsci.0c00489 PMID: 32483554

[143] Al-Tawfiq JA, Al-Homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID-19. Travel Med Infect Dis 2020; 34: 101615. http://dx.doi.org/10.1016/j.tmaid.2020.101615 PMID: 32145386

[144] Tsang K, Zhong NS. SARS: pharmacotherapy. Respirology 2003; 8(Suppl.): S25-30. http://dx.doi.org/10.1046/j.1440-1843.2003.00525.x PMID: 15018130

[145] Arabi YM, Alothman A, Balkhy HH, *et al.* Treatment of Middle East Respiratory Syndrome with a combination of lopinavir-ritonavir and interferon-β1b (MIRACLE trial): study protocol for a randomized controlled trial. Trials 2018; 19(1): 81. http://dx.doi.org/10.1186/s13063-017-2427-0 PMID: 29382391

[146] Sheahan TP, Sims AC, Leist SR, *et al.* Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 2020; 11(1): 222. http://dx.doi.org/10.1038/s41467-019-13940-6 PMID: 31924756

[147] Cao B, Wang Y, Wen D, *et al.* A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020; 382(19): 1787-99. http://dx.doi.org/10.1056/NEJMoa2001282 PMID: 32187464

[148] Hossain MF, Hasana S, Mamun AA, *et al.* COVID-19 outbreak: pathogenesis, current therapies, and potentials for future management. Front Pharmacol 2020; 11: 563478. http://dx.doi.org/10.3389/fphar.2020.563478 PMID: 33178016

[149] Booth CM, Matukas LM, Tomlinson GA, *et al.* Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. JAMA 2003; 289(21): 2801-9. http://dx.doi.org/10.1001/jama.289.21.JOC30885 PMID: 12734147

[150] Morgenstern B, Michaelis M, Baer PC, Doerr HW, Cinatl J Jr. Ribavirin and interferon-β synergistically inhibit SARS-associated coronavirus replication in animal and human cell lines. Biochem Biophys Res Commun 2005; 326(4): 905-8. http://dx.doi.org/10.1016/j.bbrc.2004.11.128 PMID: 15607755

[151] Blaising J, Polyak SJ, Pécheur E-I. Arbidol as a broad-spectrum antiviral: an update. Antiviral Res 2014; 107: 84-94. http://dx.doi.org/10.1016/j.antiviral.2014.04.006 PMID: 24769245

[152] Boriskin YS, Leneva IA, Pécheur E-I, Polyak SJ. Arbidol: a broad-spectrum antiviral compound that blocks viral fusion. Curr Med Chem 2008; 15(10): 997-1005. http://dx.doi.org/10.2174/092986708784049658 PMID: 18393857

[153] Pécheur E-I, Borisevich V, Halfmann P, *et al.* The synthetic antiviral drug arbidol inhibits globally prevalent pathogenic viruses. J Virol 2016; 90(6): 3086-92. http://dx.doi.org/10.1128/JVI.02077-15 PMID: 26739045

[154] Khamitov RA, Loginova SIa, Shchukina VN, Borisevich SV, Maksimov VA, Shuster AM. Antiviral activity of arbidol and its derivatives against the pathogen of severe acute respiratory syndrome in the cell cultures. Vopr Virusol 2008; 53(4): 9-13. PMID: 18756809

[155] Ling JX, Wei F, Li N, *et al.* Amelioration of influenza virus-induced reactive oxygen species formation by epigallocatechin gallate derived from green tea. Acta Pharmacol Sin 2012; 33(12): 1533-41. http://dx.doi.org/10.1038/aps.2012.80 PMID: 22941291

[156] Weber JM, Ruzindana-Umunyana A, Imbeault L, Sircar S. Inhibition of adenovirus infection and adenain by green tea catechins. Antiviral Res 2003; 58(2): 167-73. http://dx.doi.org/10.1016/S0166-3542(02)00212-7 PMID: 12742577

[157] Shiha G, Soliman R, Elbasiony M, Darwish NHE, Mousa SA. Addition of epigallocatechin gallate 400 mg to sofosbuvir 400 mg + daclatisvir 60 mg with or without ribavirin in treatment of patients with chronic hepatitis c improves the safety profile: A pilot study. Sci Rep 2019; 9(1): 13593. http://dx.doi.org/10.1038/s41598-019-49973-6 PMID: 31537880

[158] González Canga A, Sahagún Prieto AM, Diez Liébana MJ, Fernández Martínez N, Sierra Vega M, García Vieitez JJ. The pharmacokinetics and interactions of ivermectin in humans--a mini-review. AAPS J 2008; 10(1): 42-6. http://dx.doi.org/10.1208/s12248-007-9000-9 PMID: 18446504

[159] Götz V, Magar L, Dornfeld D, *et al.* Corrigendum: Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import. Sci Rep 2016; 6: 25428. http://dx.doi.org/10.1038/srep25428 PMID: 27156930

[160] Lundberg L, Pinkham C, Baer A, *et al.* Nuclear import and export inhibitors alter capsid protein distribution in mammalian cells and reduce *Venezuelan Equine Encephalitis* Virus replication. Antiviral Res 2013; 100(3): 662-72. http://dx.doi.org/10.1016/j.antiviral.2013.10.004 PMID: 24161512

[161] Tay MYF, Fraser JE, Chan WKK, *et al.* Nuclear localization of dengue virus (DENV) 1-4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. Antiviral Res 2013; 99(3): 301-6. http://dx.doi.org/10.1016/j.antiviral.2013.06.002 PMID: 23769930

[162] Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochem J 2012; 443(3): 851-6. http://dx.doi.org/10.1042/BJ20120150 PMID: 22417684

[163] Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*. Antiviral Res 2020; 178: 104787. http://dx.doi.org/10.1016/j.antiviral.2020.104787 PMID: 32251768

[164] Heidary F, Gharebaghi R. Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. J Antibiot (Tokyo) 2020; 73(9): 593-602. http://dx.doi.org/10.1038/s41429-020-0336-z PMID: 32533071

[165] Vincent MJ, Bergeron E, Benjannet S, *et al.* Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2005; 2(1): 69. http://dx.doi.org/10.1186/1743-422X-2-69 PMID: 16115318

[166] Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care 2020; 57: 279-83. http://dx.doi.org/10.1016/j.jcrc.2020.03.005 PMID: 32173110

[167] Kumar R, Sharma A, Srivastava JK, Siddiqui MH, Uddin MS, Aleya L. Hydroxychloroquine in COVID-19: therapeutic promises, current status, and environmental implications. Environ Sci Pollut Res Int 2021; 28(30): 40431-44. http://dx.doi.org/10.1007/s11356-020-12200-1 PMID: 33447984

[168] Sinha N, Balayla G. Hydroxychloroquine and COVID-19. Postgrad Med J 2020; 96(1139): 550-5. http://dx.doi.org/10.1136/postgradmedj-2020-137785 PMID: 32295814

[169] Yao T-T, Qian J-D, Zhu W-Y, Wang Y, Wang GQ. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treatment option. J Med Virol 2020; 92(6): 556-63. http://dx.doi.org/10.1002/jmv.25729 PMID: 32104907

[170] Chen F, Chan KH, Jiang Y, *et al. In vitro* susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol 2004; 31(1): 69-75. http://dx.doi.org/10.1016/j.jcv.2004.03.003 PMID: 15288617

[171] Kuri T, Zhang X, Habjan M, *et al.* Interferon priming enables cells to partially overturn the SARS coronavirus-induced block in innate immune activation. J Gen Virol 2009; 90(Pt 11): 2686-94. http://dx.doi.org/10.1099/vir.0.013599-0 PMID: 19625461

[172] Tan EL, Ooi EE, Lin C-Y, *et al.* Inhibition of SARS coronavirus infection *in vitro* with clinically approved antiviral drugs. Emerg Infect Dis 2004; 10(4): 581-6. http://dx.doi.org/10.3201/eid1004.030458 PMID: 15200845

[173] Bijlenga G. Proposal for vaccination against SARS coronavirus using avian infectious bronchitis virus strain H from The Netherlands. J Infect 2005; 51(3): 263-5. http://dx.doi.org/10.1016/j.jinf.2005.04.010 PMID: 16045996

[174] Giamarellos-Bourboulis EJ, Netea MG, Rovina N, *et al.* Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe 2020; 27(6): 992-1000.e3. http://dx.doi.org/10.1016/j.chom.2020.04.009 PMID: 32320677

[175] Messina G, Polito R, Monda V, *et al.* Functional role of dietary intervention to improve the outcome of COVID-19: A hypothesis of work. Int J Mol Sci 2020; 21(9): 3104. http://dx.doi.org/10.3390/ijms21093104 PMID: 32354030

[176] Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. J Med Virol 2020; 92(7): 814-8. http://dx.doi.org/10.1002/jmv.25801 PMID: 32253759

[177] Matteucci C, Grelli S, Balestrieri E, *et al.* Thymosin alpha 1 and HIV-1: recent advances and future perspectives. Future Microbiol 2017; 12(2): 141-55. http://dx.doi.org/10.2217/fmb-2016-0125 PMID: 28106477

[178] Baumann CA, Badamchian M, Goldstein AL. Thymosin α 1 antagonizes dexamethasone and CD3-induced apoptosis of CD4+ CD8+ thymocytes through the activation of cAMP and protein kinase C dependent second messenger pathways. Mech Ageing Dev 1997; 94(1-3): 85-101. http://dx.doi.org/10.1016/S0047-6374(96)01860-X PMID: 9147362

[179] Kumar V, Jung Y-S, Liang P-H. Anti-SARS coronavirus agents: a patent review (2008 - present). Expert Opin Ther Pat 2013; 23(10): 1337-48. http://dx.doi.org/10.1517/13543776.2013.823159 PMID: 23905913

[180] Ziaei M, Ziaei F, Manzouri B. Systemic cyclosporine and corneal transplantation. Int Ophthalmol 2016; 36(1): 139-46. http://dx.doi.org/10.1007/s10792-015-0137-8 PMID: 26463642

[181] Pfefferle S, Schöpf J, Kögl M, *et al.* The SARS-coronavirus-host interactome: identification of cyclophilins as target for pan-coronavirus inhibitors. PLoS Pathog 2011; 7(10): e1002331. http://dx.doi.org/10.1371/journal.ppat.1002331 PMID: 22046132

[182] Renoux G. The general immunopharmacology of levamisole. Drugs 1980; 20(2): 89-99. http://dx.doi.org/10.2165/00003495-198020020-00001 PMID: 6995097

[183] Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr 2020; 109(6): 1088-95. http://dx.doi.org/10.1111/apa.15270 PMID: 32202343

[184] Oladele OA, Emikpe BO, Adeyefa CAO, *et al.* Effects of levamisole hydrochloride on cellular immune response and flock performance of commercial broilers. Braz J Poult Sci SciELO Brasil 2012; 14(4): 259-65. http://dx.doi.org/10.1590/S1516-635X2012000400005

[185] Rossignol J-F. Nitazoxanide, a new drug candidate for the treatment of Middle East respiratory syndrome coronavirus. J Infect Public Health 2016; 9(3): 227-30. http://dx.doi.org/10.1016/j.jiph.2016.04.001 PMID: 27095301

[186] CytoDyn. Treatment with Cytodyn's Leronlimab Indicates Significant Trend Toward Immunological Restoration in Severely Ill Covid-19 patients. Available from: https://www.cytodyn.com/newsroom/press-releases/detail/405/treatment-with-cytodyns-leronlimab-indicates-significant [Cited 2020]

[187] Zhang L, Pang R, Xue X, *et al.* Anti-SARS-CoV-2 virus antibody levels in convalescent plasma of six donors who have recovered from COVID-19. Aging (Albany NY) 2020; 12(8): 6536-42. http://dx.doi.org/10.18632/aging.103102 PMID: 32320384

[188] Lu C-L, Murakowski DK, Bournazos S, *et al.* Enhanced clearance of HIV-1-infected cells by broadly neutralizing antibodies against HIV-1 *in vivo*. Science 2016; 352(6288): 1001-4. http://dx.doi.org/10.1126/science.aaf1279 PMID: 27199430

[189] Richardson P, Griffin I, Tucker C, *et al.* Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet 2020; 395(10223): e30-1. http://dx.doi.org/10.1016/S0140-6736(20)30304-4 PMID: 32032529

[190] Jean S-S, Lee P-I, Hsueh P-R. Treatment options for COVID-19: The reality and challenges. J Microbiol Immunol Infect 2020; 53(3): 436-43. http://dx.doi.org/10.1016/j.jmii.2020.03.034 PMID: 32307245

[191] Chou C-C, Shen C-F, Chen S-J, *et al.* Recommendations and guidelines for the treatment of pneumonia in Taiwan. J Microbiol Immunol Infect 2019; 52(1): 172-99. http://dx.doi.org/10.1016/j.jmii.2018.11.004 PMID: 30612923

[192] Jean S-S, Chang Y-C, Lin W-C, Lee WS, Hsueh PR, Hsu CW. Epidemiology, treatment, and prevention of nosocomial bacterial pneumonia. J Clin Med 2020; 9(1): 275. http://dx.doi.org/10.3390/jcm9010275 PMID: 31963877

[193] Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med 2006; 3(9): e343. http://dx.doi.org/10.1371/journal.pmed.0030343 PMID: 16968120

[194] Chen RC, Tang XP, Tan SY, *et al.* Treatment of severe acute respiratory syndrome with glucosteroids: the Guangzhou experience. Chest 2006; 129(6): 1441-52. http://dx.doi.org/10.1378/chest.129.6.1441 PMID: 16778260

[195] Wu C, Chen X, Cai Y, *et al.* Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020; 180(7): 934-43. http://dx.doi.org/10.1001/jamainternmed.2020.0994 PMID: 32167524

[196] Yang X, Yu Y, Xu J, *et al.* Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8(5): 475-81. http://dx.doi.org/10.1016/S2213-2600(20)30079-5 PMID: 32105632

[197] Wösten-van Asperen RM, Bos AP, Bem RA, *et al.* Imbalance between pulmonary angiotensin-converting enzyme and angiotensin-converting enzyme 2 activity in acute respiratory distress syndrome. Pediatr Crit Care Med 2013; 14(9): e438-41. http://dx.doi.org/10.1097/PCC.0b013e3182a55735 PMID: 24226567

[198] UBC. Acetaminophen *vs* NSAIDs during COVID-19 pandemic Available from: https://www.ti.ubc.ca/2020/03/18/acetaminophen-vs-nsaids-during-covid-19-pandemic/ [Cited 2020]

[199] Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020; 18(5): 1094-9. http://dx.doi.org/10.1111/jth.14817 PMID: 32220112

[200] Acute Care. Available from: https://www.ismp.org/newsletters/acute-care [Cited 2020]

[201] Feng W-X, Yang Y, Wen J, Liu YX, Liu L, Feng C. Implication of inhaled nitric oxide for the treatment of critically ill COVID-19 patients with pulmonary hypertension. ESC Heart Fail 2021; 8(1): 714-8. http://dx.doi.org/10.1002/ehf2.13023 PMID: 33205620

[202] Kańtoch M, Litwińska B, Szkoda M, Siennicka J. [Importance of vitamin A deficiency in pathology and immunology of viral infections]. Rocz Panstw Zakl Hig 2002; 53(4): 385-92. PMID: 12664666

[203] Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. J Heart Lung Transplant 2020; 39(5): 405-7. http://dx.doi.org/10.1016/j.healun.2020.03.012 PMID: 32362390

[204] Villamor E, Mbise R, Spiegelman D, *et al.* Vitamin A supplements ameliorate the adverse effect of HIV-1, malaria, and diarrheal infections on child growth. Pediatrics 2002; 109(1): E6. http://dx.doi.org/10.1542/peds.109.1.e6 PMID: 11773574

[205] Ford TC, Downey LA, Simpson T, McPhee G, Oliver C, Stough C. The effect of a high-dose vitamin b multivitamin supplement on the relationship between brain metabolism and blood biomarkers of oxidative stress: A randomized control trial. Nutrients 2018; 10(12): 1860. http://dx.doi.org/10.3390/nu10121860 PMID: 30513795

[206] Grant WB, Lahore H, McDonnell SL, *et al.* Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 2020; 12(4): 988. http://dx.doi.org/10.3390/nu12040988 PMID: 32252338

[207] Kim Y, Kim H, Bae S, *et al.* Vitamin C is an essential factor on the anti-viral immune responses through the production of interferon-α/β at the initial stage of influenza A virus (H3N2) infection. Immune Netw 2013; 13(2): 70-4. http://dx.doi.org/10.4110/in.2013.13.2.70 PMID: 23700397

[208] Moriguchi S, Muraga M. Vitamin E and immunity. Elsevier 2000. http://dx.doi.org/10.1016/S0083-6729(00)59011-6

[209] Andreone P, Fiorino S, Cursaro C, *et al.* Vitamin E as treatment for chronic hepatitis B: results of a randomized controlled pilot trial. Antiviral Res 2001; 49(2): 75-81. http://dx.doi.org/10.1016/S0166-3542(00)00141-8 PMID: 11248360

[210] Fiorino S, Bacchi-Reggiani ML, Leandri P, Loggi E, Andreone P. Vitamin E for the treatment of children with hepatitis B e antigen-positive chronic hepatitis: A systematic review and meta-analysis. World J Hepatol 2017; 9(6): 333-42. http://dx.doi.org/10.4254/wjh.v9.i6.333 PMID: 28293383

[211] Parolini C. Effects of fish n-3 PUFAs on intestinal microbiota and immune system. Mar Drugs 2019; 17(6): 374. http://dx.doi.org/10.3390/md17060374 PMID: 31234533

[212] Radzikowska U, Rinaldi AO, Çelebi Sözener Z, *et al.* The influence of dietary fatty acids on immune responses. Nutrients 2019; 11(12): 2990. http://dx.doi.org/10.3390/nu11122990 PMID: 31817726

[213] Luo C, Luo H, Zheng S, *et al.* Nucleocapsid protein of SARS coronavirus tightly binds to human cyclophilin A. Biochem Biophys Res Commun 2004; 321(3): 557-65. http://dx.doi.org/10.1016/j.bbrc.2004.07.003 PMID: 15358143

[214] Langlois PL, D'Aragon F, Hardy G, Manzanares W. Omega-3 polyunsaturated fatty acids in critically ill patients with acute respiratory distress syndrome: A systematic review and meta-analysis. Nutrition 2019; 61: 84-92. http://dx.doi.org/10.1016/j.nut.2018.10.026 PMID: 30703574

[215] Rayman MP. Selenium and human health. Lancet 2012; 379(9822): 1256-68. http://dx.doi.org/10.1016/S0140-6736(11)61452-9 PMID: 22381456

[216] Beck MA, Nelson HK, Shi Q, *et al.* Selenium deficiency increases the pathology of an influenza virus infection. FASEB J 2001; 15(8): 1481-3. http://dx.doi.org/10.1096/fj.00-0721fje PMID: 11387264

[217] Beck MA, Shi Q, Morris VC, Levander OA. Rapid genomic evolution of a non-virulent coxsackievirus B3 in selenium-deficient mice results in selection of identical virulent isolates. Nat Med 1995; 1(5): 433-6. http://dx.doi.org/10.1038/nm0595-433 PMID: 7585090

[218] Ma X, Bi S, Wang Y, Chi X, Hu S. Combined adjuvant effect of ginseng stem-leaf saponins and selenium on immune responses to a live bivalent vaccine of Newcastle disease virus and infectious bronchitis virus in chickens. Poult Sci 2019; 98(9): 3548-56. http://dx.doi.org/10.3382/ps/pez207 PMID: 31220864

[219] Kabir MT, Uddin MS, Zaman S, *et al.* Molecular mechanisms of metal toxicity in the pathogenesis of Alzheimer's disease. Mol Neurobiol 2021; 58(1): 1-20. http://dx.doi.org/10.1007/s12035-020-02096-w PMID: 32889653

[220] Fraker PJ, Gershwin ME, Good RA, Prasad A. Interrelationships between zinc and immune function. Fed Proc 1986; 45(5): 1474-9. PMID: 3485544

[221] Haase H, Rink L. The immune system and the impact of zinc during aging. Immun Ageing 2009; 6(1): 9. http://dx.doi.org/10.1186/1742-4933-6-9 PMID: 19523191

[222] Kruse-Jarres JD. The significance of zinc for humoral and cellular immunity. J Trace Elem Electrolytes Health Dis 1989; 3(1): 1-8. PMID: 2535314

[223] Tuerk MJ, Fazel N. Zinc deficiency. Curr Opin Gastroenterol 2009; 25(2): 136-43. http://dx.doi.org/10.1097/MOG.0b013e328321b395 PMID: 19528881

[224] Wessling-Resnick M. Crossing the iron gate: Why and how transferrin receptors mediate viral entry. Annu Rev Nutr 2018; 38: 431-58. http://dx.doi.org/10.1146/annurev-nutr-082117-051749 PMID: 29852086

[225] Jayaweera JAAS, Reyes M, Joseph A. Childhood iron deficiency anemia leads to recurrent respiratory tract infections and gastroenteritis. Sci Rep 2019; 9(1): 12637. http://dx.doi.org/10.1038/s41598-019-49122-z PMID: 31477792

[226] Kemahli AS, Babacan E, Çavdar AO. Cell mediated immune responses in children with iron deficiency and combined iron and zinc deficiency. Nutr Res Elsevier 1988; 8(2): 129-36. http://dx.doi.org/10.1016/S0271-5317(88)80016-2

[227] Li C, Li Y, Ding C. The role of copper homeostasis at the host-pathogen axis: From bacteria to fungi. Int J Mol Sci 2019; 20(1): 175. http://dx.doi.org/10.3390/ijms20010175 PMID: 30621285

[228] Rupp JC, Locatelli M, Grieser A, *et al.* Host Cell Copper Transporters CTR1 and ATP7A are important for Influenza A virus replication. Virol J 2017; 14(1): 11.

http://dx.doi.org/10.1186/s12985-016-0671-7 PMID: 28115001

[229] Miyamoto D, Kusagaya Y, Endo N, *et al.* Thujaplicin-copper chelates inhibit replication of human influenza viruses. Antiviral Res 1998; 39(2): 89-100. http://dx.doi.org/10.1016/S0166-3542(98)00034-5 PMID: 9806486

[230] Turnlund JR, Jacob RA, Keen CL, *et al.* Long-term high copper intake: effects on indexes of copper status, antioxidant status, and immune function in young men. Am J Clin Nutr 2004; 79(6): 1037-44. http://dx.doi.org/10.1093/ajcn/79.6.1037 PMID: 15159234

[231] Liang RY, Wu W, Huang J, Jiang SP, Lin Y. Magnesium affects the cytokine secretion of $CD4^+$ T lymphocytes in acute asthma. J Asthma 2012; 49(10): 1012-5. http://dx.doi.org/10.3109/02770903.2012.739240 PMID: 23134345

[232] Chaigne-Delalande B, Li F-Y, O'Connor GM, *et al.* Mg2+ regulates cytotoxic functions of NK and CD8 T cells in chronic EBV infection through NKG2D. Science 2013; 341(6142): 186-91. http://dx.doi.org/10.1126/science.1240094 PMID: 23846901

[233] Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis 2020; 20(4): 398-400. http://dx.doi.org/10.1016/S1473-3099(20)30141-9 PMID: 32113510

[234] Shen C, Wang Z, Zhao F, *et al.* Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020; 323(16): 1582-9. http://dx.doi.org/10.1001/jama.2020.4783 PMID: 32219428

[235] Chen L, Gui C, Luo X, *et al.* Cinanserin is an inhibitor of the 3C-like proteinase of severe acute respiratory syndrome coronavirus and strongly reduces virus replication *in vitro.* J Virol 2005; 79(11): 7095-103. http://dx.doi.org/10.1128/JVI.79.11.7095-7103.2005 PMID: 15890949

[236] Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. J Med Virol 2020; 92(4): 418-23. http://dx.doi.org/10.1002/jmv.25681 PMID: 31967327

[237] Park J-Y, Jeong HJ, Kim JH, *et al.* Diarylheptanoids from Alnus japonica inhibit papain-like protease of severe acute respiratory syndrome coronavirus. Biol Pharm Bull 2012; 35(11): 2036-42. http://dx.doi.org/10.1248/bpb.b12-00623 PMID: 22971649

[238] Warner FJ, Smith AI, Hooper NM, Turner AJ. Angiotensin-converting enzyme-2: a molecular and cellular perspective. Cell Mol Life Sci 2004; 61(21): 2704-13. http://dx.doi.org/10.1007/s00018-004-4240-7 PMID: 15549171

[239] Dimitrov DS. The secret life of ACE2 as a receptor for the SARS virus. Cell 2003; 115(6): 652-3. http://dx.doi.org/10.1016/S0092-8674(03)00976-0 PMID: 14675530

[240] Li XC, Zhang J, Zhuo JL. The vasoprotective axes of the renin-angiotensin system: Physiological relevance and therapeutic implications in cardiovascular, hypertensive and kidney diseases. Pharmacol Res 2017; 125(Pt A): 21-38. http://dx.doi.org/10.1016/j.phrs.2017.06.005

[241] Italiana S, dell'Ipertensione A. Phase IV Observational Study to Associate Hypertension and Hypertensinon Treatment to COVID19. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04331574

[242] Yeung K-S, Yamanaka GA, Meanwell NA. Severe acute respiratory syndrome coronavirus entry into host cells: Opportunities for therapeutic intervention. Med Res Rev 2006; 26(4): 414-33. http://dx.doi.org/10.1002/med.20055 PMID: 16521129

[243] Zhang L, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. J Med Virol 2020; 92(5): 479-90. http://dx.doi.org/10.1002/jmv.25707 PMID: 32052466

[244] Ho T-Y, Wu S-L, Chen J-C, Li CC, Hsiang CY. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. Antiviral Res 2007; 74(2): 92-101. http://dx.doi.org/10.1016/j.antiviral.2006.04.014 PMID: 16730806

[245] Trampczynska A, Böttcher C, Clemens S. The transition metal chelator nicotianamine is synthesized by filamentous fungi. FEBS Lett 2006; 580(13): 3173-8. http://dx.doi.org/10.1016/j.febslet.2006.04.073 PMID: 16684531

[246] Takahashi S, Yoshiya T, Yoshizawa-Kumagaye K, Sugiyama T. Nicotianamine is a novel angiotensin-converting enzyme 2 inhibitor in soybean. Biomed Res 2015; 36(3): 219-24. http://dx.doi.org/10.2220/biomedres.36.219 PMID: 26106051

[247] Repurposing of chlorpromazine in covid-19 treatment - full text view. Available from: https://clinicaltrials.gov/ct2/show/NCT04366739 [Cited 2020]

[248] Kim D, Lee J-Y, Yang J-S, Kim JW, Kim VN, Chang H. The architecture of SARS-CoV-2 transcriptome. Cell 2020; 181(4): 914-921.e10. http://dx.doi.org/10.1016/j.cell.2020.04.011 PMID: 32330414

[249] Jódar L, Feavers IM, Salisbury D, Granoff DM. Development of vaccines against meningococcal disease. Lancet 2002; 359(9316): 1499-508. http://dx.doi.org/10.1016/S0140-6736(02)08416-7 PMID: 11988262

[250] Byrne MP, Smith LA. Development of vaccines for prevention of botulism. Biochimie 2000; 82(9-10): 955-66. http://dx.doi.org/10.1016/S0300-9084(00)01173-1 PMID: 11086225

[251] Poland GA, Kennedy RB, Ovsyannikova IG, Palacios R, Ho PL, Kalil J. Development of vaccines against Zika virus. Lancet Infect Dis 2018; 18(7): e211-9. http://dx.doi.org/10.1016/S1473-3099(18)30063-X PMID: 29396004

[252] de la Fuente J, Kocan KM. Strategies for development of vaccines for control of ixodid tick species. Parasite Immunol 2006; 28(7): 275-83. http://dx.doi.org/10.1111/j.1365-3024.2006.00828.x PMID: 16842264

[253] Chan JF-W, Yao Y, Yeung M-L, *et al.* Treatment with lopinavir/ritonavir or interferon-β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. J Infect Dis 2015; 212(12): 1904-13. http://dx.doi.org/10.1093/infdis/jiv392 PMID: 26198719

[254] Folegatti PM, Ewer KJ, Aley PK, *et al.* 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. http://dx.doi.org/10.1016/S0140-6736(20)31604-4 PMID: 32702298

[255] Antrobus RD, Coughlan L, Berthoud TK, *et al.* Clinical assessment of a novel recombinant simian adenovirus ChAdOx1 as a vectored vaccine expressing conserved Influenza A antigens. Mol Ther 2014; 22(3): 668-74. http://dx.doi.org/10.1038/mt.2013.284 PMID: 24374965

[256] Alharbi NK, Padron-Regalado E, Thompson CP, *et al.* ChAdOx1 and MVA based vaccine candidates against MERS-CoV elicit neutralising antibodies and cellular immune responses in mice. Vaccine 2017; 35(30): 3780-8. http://dx.doi.org/10.1016/j.vaccine.2017.05.032 PMID: 28579232

[257] Jadhav S, Gautam M, Gairola S. Role of vaccine manufacturers in developing countries towards global healthcare by providing quality vaccines at affordable prices. Clin Microbiol Infect 2014; 20(Suppl. 5): 37-44. http://dx.doi.org/10.1111/1469-0691.12568 PMID: 24476201

[258] Sohag AAM, Hannan MA, Rahman S, *et al.* Revisiting potential druggable targets against SARS-CoV-2 and repurposing therapeutics under preclinical study and clinical trials: A comprehensive review. Drug Dev Res 2020; 21709 http://dx.doi.org/10.1002/ddr.21709 PMID: 32632960

[259] Li Y, Liu X, Guo L, *et al.* Traditional Chinese herbal medicine for treating novel coronavirus (COVID-19) pneumonia: protocol for a systematic review and meta-analysis. Syst Rev 2020; 9(1): 75. http://dx.doi.org/10.1186/s13643-020-01343-4 PMID: 32268923

[260] Ang L, Lee HW, Choi JY, Zhang J, Soo Lee M. Herbal medicine and pattern identification for treating COVID-19: a rapid review of guidelines. Integr Med Res 2020; 9(2): 100407. http://dx.doi.org/10.1016/j.imr.2020.100407 PMID: 32289016

[261] Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther 2020; 14(1): 58-60. http://dx.doi.org/10.5582/ddt.2020.01012 PMID: 32147628

[262] Luo H, Tang QL, Shang YX, *et al.* Can Chinese medicine be used for prevention of corona virus disease 2019 (COVID-19)? A review of historical classics, research evidence and current prevention programs. Chin J Integr Med 2020; 26(4): 243-50. http://dx.doi.org/10.1007/s11655-020-3192-6 PMID: 32065348

[263] Wan S, Xiang Y, Fang W, *et al.* Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol. Wiley Online Library 2020. http://dx.doi.org/10.1002/jmv.25783

[264] Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020; 8(4): e21. http://dx.doi.org/10.1016/S2213-2600(20)30116-8 PMID: 32171062

[265] Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: Early experience and forecast during an emergency response. JAMA 2020; 323(16): 1545-6. http://dx.doi.org/10.1001/jama.2020.4031 PMID: 32167538

[266] Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): A review. JAMA 2020; 323(18): 1824-36. http://dx.doi.org/10.1001/jama.2020.6019 PMID: 32282022

[267] Xie J, Tong Z, Guan X, Du B, Qiu H, Slutsky AS. Critical care crisis and some recommendations during the COVID-19 epidemic in China. Intensive Care Med 2020; 46(5): 837-40. http://dx.doi.org/10.1007/s00134-020-05979-7 PMID: 32123994

[268] Guo Y-R, Cao Q-D, Hong Z-S, *et al.* The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res 2020; 7(1): 11. http://dx.doi.org/10.1186/s40779-020-00240-0 PMID: 32169119