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Life Sciences 261 (2020) 118336

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

COVID-19: Pathophysiology, treatment options, nanotechnology approaches, and research agenda to combating the SARS-CoV2 pandemic

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ARTICLE INFO

Keywords:
COVID-19
Nanotechnology
Research agenda
Therapeutics treatment
Post COVID-19

ABSTRACT

The recent corona virus disease (COVID-19) outbreak has claimed the lives of many around the world and highlighted an urgent need for experimental strategies to prevent, treat and eradicate the virus. COVID-19, an infectious disease caused by a novel corona virus and no approved specific treatment is available yet. A vast number of promising antiviral treatments involving nanotechnology are currently under investigation to aid in the development of COVID-19 drug delivery. The prospective treatment options integrating the ever-expanding field of nanotechnology have been compiled, with the objective to show that these can be potentially developed for COVID-19 treatment. This review summarized the current state of knowledge, research priorities regarding the pandemic and post COVID-19. We also focus on the possible nanotechnology approaches that have proven to be successful against other viruses and the research agenda to combat COVID-19.

1. Introduction

In December 2019, the World Health Organization (WHO) was informed about the pneumonia case of unknown cause, detected in the seafood market of Wuhan city in Hubei province, China. The cause was identified as novel coronavirus (n-CoV) based on the laboratory findings in reference to Severe Acute Respiratory Syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS). In a short span of time, it has become a global phenomenon since the case of single pneumonia in Wuhan. Later, on 30 January 2020, WHO declared the 2019-nCoV outbreak a Public Health Emergency of global health Concern, stressing the need for worldwide action, international co-operation and solidarity and collaboration to control the outbreak? On 11 February 2020, WHO announced a name for the new coronavirus disease: COVID-19, later 11 March 2020, assessed that COVID-19can be characterized as a pandemic. The current areas known to be pandemic for COVID-19 outbreak globally have been summarized in Fig. 1, as on 10 August 2020. The journey status of rapidly progressing COVID-19 outbreak can be categorized into four stages globally. The first stage, is when cases of an infection are imported into a country from the other infectious country. The second stage of an outbreak is when there are cases of local transmission from infected patients. Community transmission is the third stage of an outbreak and fourth stage is when an infection becomes endemic with no clear endpoint. The world has seen three coronaviruses in last two decades, SARS, MERS, and now COVID-19.SARS-CoV was recognized at the end of February 2003 in Guangdong, China, and spread to many countries including European Union (EU), Southeast Asia, South Africa and North America [1].

Transmission was primarily person to person through infectious droplets that occurred during coughing or sneezing, through personal contact (shaking hands), or by touching contaminated surfaces. SARS-CoV-2, SARS and MERS coronaviruses are thought to have originated from bats and transmitted to humans from an intermediate host, civets and dromedary camels, respectively. For SARS-CoV-2, the zoonotic source and intermediate host is not confirmed yet and research is going on [2].The mean incubation period is about 5 days, ranging from 1 to 14 days and 95% of patients are likely to experience symptoms within 12.5 days of contact. However, asymptomatic carriers have been reported and the incubation period is 19 days, making it even more challenging to screen the infection [3].

The care advised is to give fluid management, oxygen supportive as patients condition [4,5] and antibiotic in secondary infection if any reported [6]. Based on evidence from laboratory, animal, and clinical studies, the following treatment options were selected according to

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https://doi.org/10.1016/j.lfs.2020.118336
Received 19 July 2020; Received in revised form 11 August 2020; Accepted 20 August 2020
Available online 23 August 2020

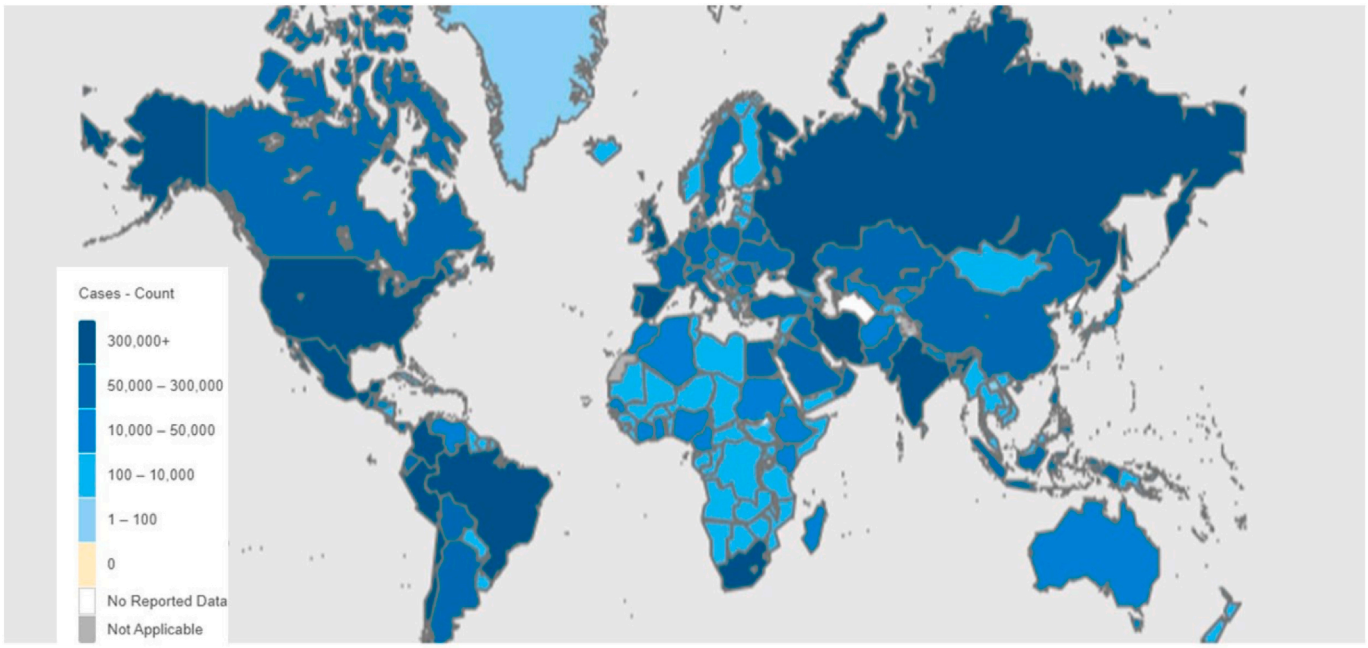

Fig. 1. Globally, as of 3:06 pm CEST, 10 August 2020, there have been 19,718,030 confirmed cases of COVID-19, including 728,013 deaths, reported to WHO.

WHO: Remdesivir; Lopinavir/ritonavir; Lopinavir/ritonavir with interferon β-1a [7]. There is only one way the world can exit this pandemic-and that is through science. We need diagnostic detection kit to detect and prevent the spread of the virus, vaccines for long-term protection, treatments to save lives in the shorter-term and social science to understand the behavioral and societal implications. It's critical that the global research effort is rapid, robust and is conducted at scale and coordinated across multiple countries. The WHO solidarity trial will provide this by testing existing and new drug molecules to treat COVID-19 and ensure equitable access to any drugs that prove effective. Global powers must now step-up to ensure the WHO has all the support needed [7].

A vast number of promising anti-viral treatments are currently under investigation to aid in the development of COVID-19 drug delivery. The current review focuses on the possible particulate delivery approaches and the research agenda to combat COVID-19. The current state of knowledge, research priorities regarding the pandemic and post COVID-19has been discussed. We also summarized the prospective treatments integrating the ever-expanding field of particulate delivery systems that have proven to be successful against other viruses, with the objective of showing that these can potentially be developed for COVID-19 treatment.

2. Virology of COVID-19

The virus causing the COVID-19 pandemic is corona virus, named as SARS-CoV-2, which belongs to genus β coronavirus along with SARS-CoV and MERS-CoV [8]. This genus belongs to sub-family Coronavirinae, family Coronaviridae and order Nidovirales [9]. Morphologically, CoVs are a group of highly diverse, enveloped, positive-sense and single-stranded RNA (ss-RNA) virus. They cause several diseases involving respiratory, enteric, hepatic, and neurological systems with vary severity among humans and animals [10].

In brief, n-CoV consists of four proteins three associated with envelope and one nucleocapsid protein (N) to pack the genome as shown in Fig. 2. The three structural proteins include membrane protein (M), envelope protein (E) and spike protein (S). In which, M determines the shape of the viral envelope and forms the central organizer of n-CoV assembly. Protein E interacts with M protein to form the viral envelope. The crown like appearance of the n-CoV is due to the large protrusions of S protein from the virus envelope. The S protein is a critical determinant of viral host range, tissue tropism and a major inducer of host immune responses [10].

3. Clinical presentations

The clinical presentations of COVID-19are varying from asymptomatic forms to clinical conditions characterized by respiratory failure to multi-organ and systemic manifestations [11].The most common symptoms include fever, cough, and fatigue, while other symptoms include sputum production, headache, haemoptysis, diarrhea, dyspnoea, and lymphopenia [12]. The clinical manifestations of the disease were divided into three categories by authors of Chinese CDC report. First, mild pneumonia and non-pneumonia are in mild category (81% of cases). Second, dyspnea, blood oxygen saturation (SpO_2) ≤ 93%, PaO_2/FiO_2 ratio or P/F [the ratio between the blood pressure of the oxygen (partial pressure of oxygen, PaO_2), respiratory frequency ≥ 30/min, and the percentage of oxygen supplied (fraction of inspired oxygen, FiO_2)] < 300, and/or lung infiltrates > 50% within 24 to 48 h in severe disease category in approximately 14% of cases, and third respiratory failure, septic shock, and/or multiple organ dysfunction or failure in critical condition, as seen in 5% of cases [13].

4. Diagnosis

Computer tomography (CT) imaging and pathology laboratory tests can be considered as two important diagnostic tools to diagnose COVID-19.Clinical features revealed by a chest CT scan presented as pneumonia, however, there were abnormal features such as RNAaemia, acute respiratory distress syndrome, acute cardiac injury, and incidence of grand-glass opacities that led to death [14].

The most common laboratory method for the clinical diagnosis of COVID-19 is nucleic acid detection by real time- PCR, which is further confirmed by next generation sequencing [15]. WHO approved the first two diagnostic tests for emergency use during the COVID-19 pandemic [16]. Both are in vitro diagnostics, the tests are *genesig Real-Time PCR Coronavirus* and *cobas*SARS-CoV-2 Qualitative assay for use on the *cobas® 6800/8800* Systems [17,18].

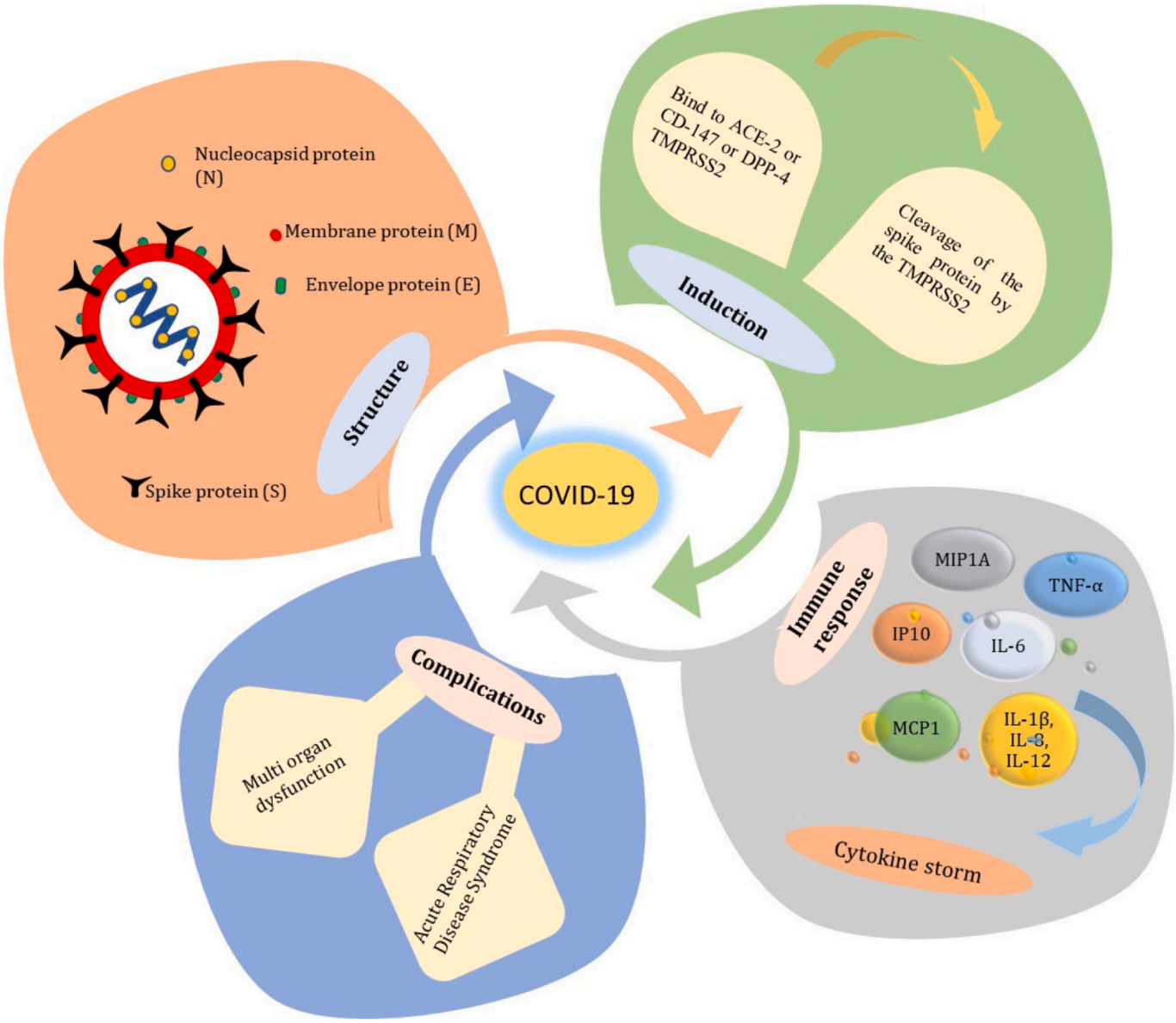

Fig. 2. Overview of COVID-19 with special emphasis on structure, induction, immune response and complications.

5. Transmission

WHO reported the initial cases of COVID-19 were from the Huanan Seafood market, and observed that SARS-CoV-2 was transmitted from animal to human [19]. However, a genomic study has proven that the virus was introduced from another source, yet unknown location into the market where it spread more rapidly, although human-to-human transmission is also reported previously. Person-to-person transmission is thought to occur through near contacts mainly through respiratory droplets produced during coughing or sneezing by an infected person. Fomites may be a large source of transmission, as SARS-CoV has been found to persist on surfaces up to 96 h [20] and other coronaviruses for up to 9 days [21].

The basic reproductive number (R0) measures the transmissibility of a virus, representing the average number of new infections generated by an infectious person in a fully susceptible population. Therefore, R0 can be used to understand the transmissibility of SARS-CoV for predicting the transmission. The number infected is likely to increase with stronger transmission potential, if R0 $>$ 1 and transmission is likely to die out eventually, if R0 $<$ 1 [22]. Study by Ying Liu et al. estimated that R0 was 3.28 with 2.79 median value for COVID-19, which exceed WHO estimates from 1.4 to 2.5 [23]. Studies from previous outbreak found R0 to be 2.7 for SARS [24] and 2.4 for 2009 pandemic H1N1influenza [25]. Because R0represents an average value it is also important to consider the role of super spreaders, who may be hugely responsible for outbreaks within large clusters but who would not largely influence the value of R0 [26]. R0 remains unstable during the initial stages of pandemic due to short onset time and insufficient data availability.

6. Prevention of COVID-19

Prevention is always better than cure to combat of any infectious disease. To fight the unprecedented and rapidly progressing COVID-19, the only solution is to follow preventive measures. Washing hands frequently with water and soap, or clean them with alcohol-based sanitizers, maintaining at least 1 m distance, covering mouth-nose during coughing or sneezing. Practice physical distancing devoid unnecessary travel and staying away from large groups of peoples [27]. For early detection of the virus, public awareness should be created regarding the

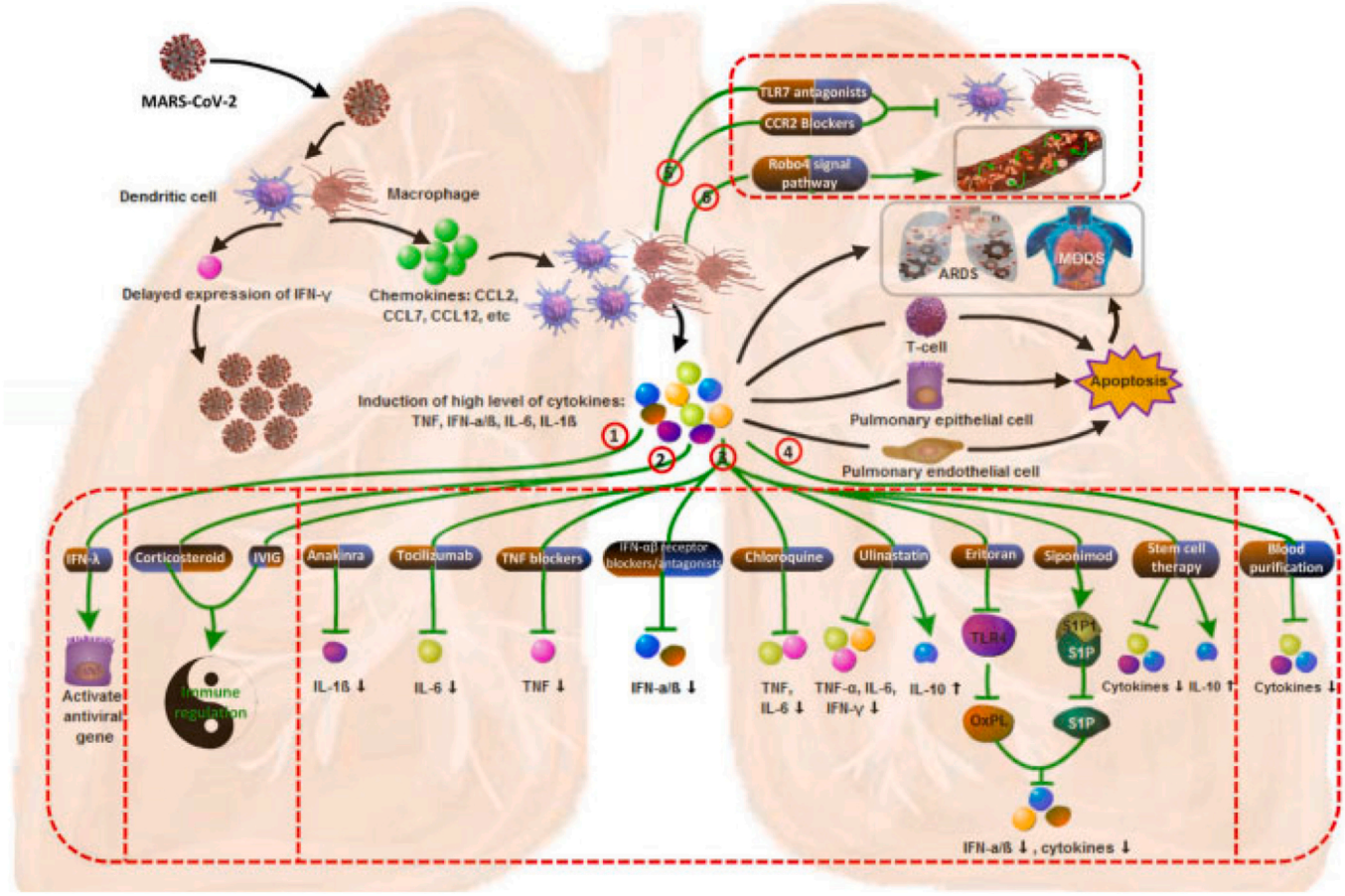

Fig. 3. Mechanism of cytokine storm in COVID-19 and its potential therapy. Adapted with permission, copyright 2017 Elsevier B.V.

unusual symptoms like chronic cough or shortness of breath. Quarantine of suspected people, isolation of the infected people and their close contacts can be the crucial step in eradication of the virus.

Mitigating social gatherings, temporary school closure, home isolation, close monitoring of symptomatic individual, provision of life supports (e.g. oxygen supply, mechanical ventilator), personal hand hygiene, and wearing personal protective equipment such as facemask should also been forced by the government to prevent the further transmission of virus [28].

7. Pathophysiology of SARS-CoV-2

Specific replication mechanism is still unclear for SARS-CoV-2. It had been reported that replication of coronavirus, SARS-CoV-2 is similar to that of other viruses of the coronavirus family, such as SARS-CoV and MERS-CoV. It may be two step reaction of SARS-CoV-2 virus to enter in the body to spread the infection. Firstly, binding to angiotensin-converting enzyme-2 (ACE-2) or CD-147or dipeptidyl peptidase 4 (DPP-4) [29]or transmembrane protease serine 2(TMPRSS2) and the second is cleavage of the spike protein by the TMPRSS2 [30], which exposes the fusion peptide, allowing it to survive in low-pH endosomes [31].

ACE-2 receptors have been found as the main cellular receptor for binding with the receptor-binding domain of virus spikes and responsible receptors for human-to-human transmissions of SARS-CoV. ACE-2 protein is abundantly found in alveolar epithelial cells of lungs and enterocytes of small intestine. It was found that the virus primary binds to the target site on lung epithelial cells. Wang et al also found that ACE-2 was abundantly expressed in gallbladder, liver, kidney, testes, gastrointestinal tract, and bladder suggesting that these organs may be vulnerable to SARS-CoV-2 infection, which may help to understand the routes of infection and disease manifestations [32]. However, patients with SARS-CoV-2 infection primarily exhibit lesions in the lungs, despite the ACE-2 receptor being widely distributed in various organs of the human body, so this connection needs to be investigated further.

In addition, ACE-2 is highly expressed in vascular endothelial cells, which raises the question of whether the virus can cause damage to vascular endothelial cells or impact glomerular function. Xu et al. recently found that it has been seen rare kidney damage in COVID-19 patients in Zhejiang [33]. It is not clear yet that the SARS-CoV-2binds with ACE-receptors only or other receptors also. The organs withACE-2positive cells match the organs involved with the disease, as reported in clinical studies, which raises the question of whether novel coronavirus infection causes more deaths by multiple organ dysfunction syndrome (MODS) or respiratory failure [31].

SARS-CoV-2 spike (S) glycoprotein binds with ACE-2 receptor and it is a crucial step for the virus entry in to host cells. Homotrimers (S1 and S2) of S proteins assists the attachment to the host receptors. The S2 subunit of SARS-Cov-2 is highly conserved and serves as a target for antiviral therapeutics. Several therapeutics approaches of virus-receptor binding affinity are under investigation. Systematic detection of β-CoV receptors showed that human cells expressing ACE-2 was enhanced the detection of entry of SARS-CoV-2 but human Dipeptidyl peptidase-4 (DPP4) or APN (Aminopeptidase N) had not enhanced entry of SARS-CoV-2. While, another study showed that S protein of SARS-CoV2 and ACE-2 binding efficiency is 10- to 20- fold higher than that of SARS-CoV. It is evidenced by Cryo-TEM Structure of the SARS-CoV-2 Spike in the prefusion conformation [34].

After entry of virus in to the cell, IL-6 is produced by activated leukocytes and acts on a large number of cells and tissues. Levels of

tumor necrosis factor α (TNF-α), IL-1β, IL-8, IL-12, monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1A (MIP1A)and interferon-gamma inducible protein (IP10) are also increased in SARS CoV-2 infected patients as shown in Fig. 2 [30]. The incidence of ARDS, shock, secondary infection, acute kidney injury and heart was significantly higher in patients with intensive care unit (ICU) than in non-ICU patients. The main proportion of IL-6 above normal was significantly higher than that in the patients. Infection with MERS coronavirus can induce increased concentration of pro-inflammatory cytokines (tumor 616 necrosis factor α, IL15, and IL17, and interferon-γ,). The severe COVID-19 cases may benefit from IL-6 pathway inhibition given the associated Cytokine Release Syndrome (CRS) and sHLH (Secondary hemophagocytic lymphohistiocytosis) like serum cytokine elevations, which may be a target of the treatment of COVID-19 infected patients [35]. Excessive tissue damage is occurred owing to the excessive release of cytokines. In some cases, a reaction takes place which is labeled as 'cytokine storm'. This is given in Fig. 3 with its possible treatments [36]. It is able to promote the differentiation of B lymphocytes, promotes the growth of some categories of cells, and inhibits the growth of others [30].$CD4^+T/CD8^+T$ counts continued to decline until death. Wan et al. found that $CD4^+T$ and $CD8^+T$ were lower in severe patients, which suggested that lymphocytes were more inhibited in severe patients. Lymphocytopenia may be related to a cytokine storm caused by viral invasion. In mild patient, reduction rate of $CD4^+T$, $CD8^+T$, B cell is less as compared to severe patients [37].

8. Treatment

Avoidance is the principal method of deterrence. Searching of accurate treatment for COVID-19 patients has been in progress and wide range of possible treatments is being tested by researchers. Numerous collaborative efforts to discover and evaluate the effectiveness of antiviral, immune-therapies, monoclonal antibodies, and vaccines have rapidly emerged. These all treatment is symptomatic but oxygen therapy using ventilator plays major role in the treatment of COVID-19. All the recommended treatments for COVID-19 as shown in Fig. 4.

9. Mechanical ventilation

When respiratory failure is occurred in COVID-19 patients, mechanical ventilation becomes the necessary treatment. In addition, hemodynamic support is also required for managing septic shock. Mechanical ventilation should be with lower tidal volumes (4 to 6 ml/kg predicted body weight; PBW) and lower inspiratory pressures, reaching a plateau pressure (Pplat) < 28 to 30 cm H_2O [38]. Positive end-expiratory pressure (PEEP) must be as high as possible to maintain the driving pressure (Pplat-PEEP) and as low as possible (< 14 cmH2O). Moreover, one must always remember that avoiding disconnections from the ventilator for preventing loss of PEEP and atelectasis. Finally, the use of paralytics is not recommended unless PaO2/FiO2 (partial oxygen pressure/fraction of inspired oxygen) < 150 mmHg. The prone ventilation for > 12 h per day, and the use of a conservative fluid management strategy for ARDS patients without tissue hypo perfusion (strong recommendation) are emphasized [30].

10. Drug treatment option strategies to combat COVID-19

As previously discussed, no effective drug treatment is available for fighting this COVID-19. But several drugs including anti-viral, anti-malarial, anti-microbial and several anti-bacterial drugs have been available and using in the treatment against COVID-19. Mostly combination of drugs serves as an effective treatment against COVID-19. Systemic corticosteroids (Hydrocortisone, methyl prednisolone, dexamethasone, and prednisolone) are not recommended in the treatment of viral pneumonia or ARDS due to the increased mortality and secondary infection rates in influenza, impaired clearance of SARS-CoV and MERS-CoV, and complications of corticosteroid therapy in survivors [39].

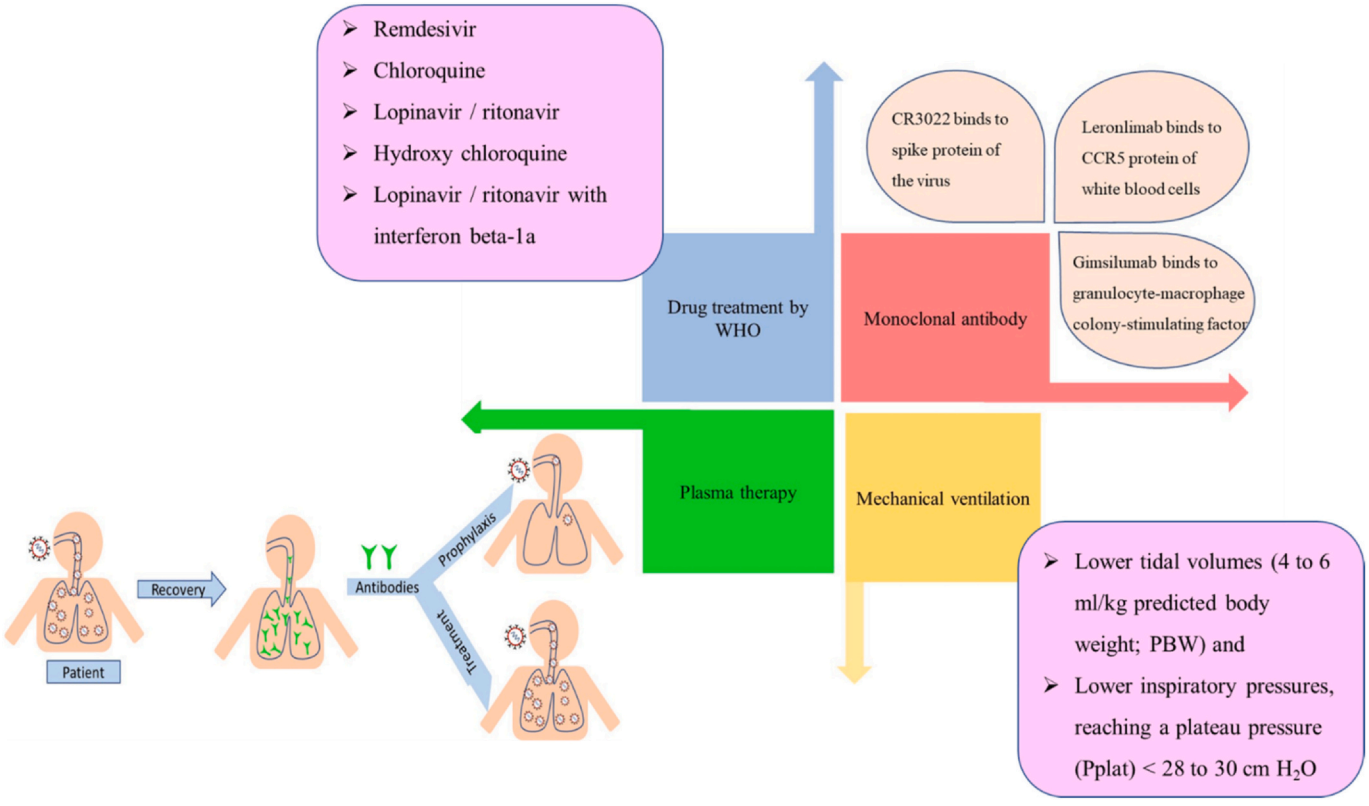

Fig. 4. Treatment options for covid-19 illustrating mechanical ventilation, monoclonal antibodies, drug treatment by WHO, plasma therapy.

Moreover, COVID-19 is a viral disease not bacterial infection. Therefore, one should avoid in-appropriate administration of antibiotics, although some treatment centre recommended it. Several approaches have been proposed such as lopinavir/ritonavir (400/100 mg every 12 h), chloroquine (500 mg every 12 h), and hydroxyl-chloroquine (200 mg every 12 h). Alpha-interferon (e.g., 5 million units by aerosol inhalation twice per day) is also used [30].

Mostly remdesivir, an inhibitor of RNA polymerase with in vitro activity against multiple RNA viruses, including Ebola- could be effective for both prophylaxis and therapy of HCoVs infections. In vitro, Remdesivir inhibits all human and animal coronaviruses tested to date, including SARS-CoV-2 and have shown antiviral and clinical effects in animal models of SARS-CoV-1 and MERS-CoV infections. Remdesivir was found superior to a therapeutic regimen as compared to combination therapy of interferon β and lopinavir-ritonavir in a lethal murine model of MERS. In SARS-CoV-2 replication, Remdesivir is identified as potent inhibitor in bronchial airway epithelial and human nasal cells. Administration of early remdesivir was shown to exert significant antiviral and clinical effects in a non-lethal rhesus macaque model of SARS-CoV-2 infection, (reduced pulmonary infiltrates and virus titres in broncho-alveolar lavages vs. vehicle only. Authors reported that patients received remdesivir had a 31% times faster recovery in comparison to placebo ($p < 0.001$). Specifically, the median time to recovery was 11 days for patients treated with remdesivir compared to 15 days for those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group ($p = 0.059$) [30].

Although several studies have been available suggesting remdesivir give no proper results against COVID-19. Wang et al carried out randomised, double-blind, placebo-controlled, multicentre trial of remdesivir on 237 COVID-19 patients. The 158 patients were given Remdesivir out of 237 patients, and 79 patients were given placebo formulation. It was found that clinical improvement in the remdesivir group was not significantly different to that of the control group. Remdesivir had a numerically faster time to clinical improvement in comparison to placebo. Mortality rate of both the groups was similar [40].

Favipiravir (FPV) is the first approved drug by the national medical products administration of China for the treatment of COVID-19 [41]. Cai et al. performed an open-Label Control Study of FPV on COVID-19 patients. In these experiments, 35 patients were given treatment of FPV and 45 patients were treated with lopinavir and ritonavir (LPV/RTV) combination. It was found that those treated with FPV appeared to have faster viral clearance and better chest imaging change than patients treated with LPV/RTV [42].

Chang et al. carried out studies on COVID-19 patients by giving favipiravir versus Arbidol. Total 240 patients were taken. Among them, 120 patients were given treatments of favipiravir and 120 patients were given the treatments of Arbidol. It was found that no difference was seen in both treatments after 7 days. Favipiravir showed significant relief in cough and pyrexia after 7 days treatments [43].

Clinical trials in the initial stages failed and no difference was observed in COVID-19patients. In addition to remdesivir, we tend to evaluate all of the evidence related to the other antiviral drugs, which called the attention, such as ribavirin, favipiravir, oseltamivir and umifenovir [44]. Ribavirin (Tribavirin) is a broad-spectrum guanosine analogue against RNA and DNA viruses such as hepatitis C and E [45]. Ribavirin in conjunction with interferon showed synergistic activity in in vitro antiviral study. This result suggested that ribavirin elicits antiviral activity at lower concentration with interferon. Therefore, a combination therapy of interferon and ribavirin were widely used due to synergistic effect. Simultaneous use of three or more antiviral drugs is not recommended and patient symptoms will recover after drug withdrawal. Antiviral drugs should be stopped if nucleic acid test results from sputum specimens remain negative for more than three times [46].

Chloroquine and hydroxychloroquine (HC) had received intense attention because of viral enzymes or processes inhibition especially in Iran, U.K, France. However, FDA revoked the emergency use authorization due to severe cardiac adverse events and other potential side effects. The potential benefits of chloroquine and HC no longer outweigh the potential risks for the authorized use [47]. HC is superior to chloroquine and reported positive results in some pre-clinical data in vitro and protocols. Both of these anti-malaria drugs might actually do more harm than good due to many side effects and should be prescribed not more than 7 days. The main concerns in rare cases are cardiac arrest, retinal damage and ocular toxicity, particularly due to the fact that, people with heart conditions are at higher risk of severity [48].

Philippe Gautret et al. conducted study on hydroxychloroquine and azithromycin as a treatment toCOVID-19. It was found that patients treated with hydroxychloroquine showed significant reduction in viral infection as compared to the control. Hydroxychloroquine in combination with azithromycin were more effective in the elimination of virus [49].

Magagnoli et al. conducted study to study the outcomes of hydroxychloroquine in COVID-19 patients. This study was carried out on total 368 patients and it was divided in three groups namely HC treatments, without HC treatments and combination treatments of HC and azithromycin. Primary outcome of this study was analysis of mortality rate and required ventilation facility on these groups. It was found that 27.8, 22.1 and 11.4 mortality rate was found in HC group, combination group and without HC group, respectively. It was also found that mechanical ventilation occurred in 13.3% of the HC group, 6.9% of the combination group, and 14.1% of the without HC group. Therefore, it was investigated that no effect was found in mortality rate after HC treatment and combination treatments but, significant reduction of mechanical ventilation was observed after combinational treatments when compared to other two groups [50].

Atypical gastrointestinal, cardiovascular manifestations may be present in conjunction with constitutional and respiratory symptoms in COVID −19 patients. Akshay Avula *et al.* identified four patients with radiographic confirmation of acute stroke and PCR (polymerase chain reaction) confirmed SARS-CoV-2 infection and elucidated the imaging findings, clinical characteristics, and the clinical course. Average time of onset of stroke after COVID-19 diagnosis was 12 days. Elevated levels of D-dimer, C-reactive protein, ferritin, and interleukin-6 indicating a high inflammatory state and abnormalities with the coagulation cascade, respectively, might play a role in the pathophysiology of stroke in the setting of COVID-19 infection. Despite these reports, all four cases here presented with a cerebrovascular accident in early stages of their illness [51].

The management of venous thromboembolism (VTE) and antithrombotic therapy for acute coronary syndromes (ACS) is very crucial in covid-19 pandemic. Anticoagulants like Vitamin K antagonists, dabigatran, apixaban, betrixaban, edoxaban, rivaroxaban and antiplatelets like clopidogrel, prasugrel ticagrelor, cilostazol may have interactions with COVID −19 investigational drug. Therefore, drug interactions should be kept in mind to mitigate the thrombotic and hemorrhagic events in high-risk patients [52].

11. Monoclonal antibody

Various monoclonal antibody has been explored in the treatment of COVID-19. Mainly, gimsilumab and leronlimab have been used in the treatment of COVID-19. Gimsilumab targets a pro-inflammatory cytokine known as a granulocyte-macrophage colony-stimulating factor (GM-CSF). The expression of pro-inflammatory cytokines was inhibited by gimsilumab, which increases inflammation. By this mechanism, it reduces the cytokine storm in the airway pathways and provides symptomatic relief to patients from COVID-19 [53]. In a recent study, it was identified that monoclonal antibody namelyCR3022 binds and cover the spike RBD of virus. Therefore, ACE-2 receptor cannot bind

with the epitopes of monoclonal antibody, which cover the RBD of virus. Although entry of virus into body, it cannot be replicated due to unavailability of binding site of host virus [41]. CR3022 has the potential to be developed as a therapeutic candidate, alone or in combination with other neutralizing antibodies for the prevention and treatment of COVID-19 infection. Leronlimab CCR5 is a protein on the surface of white blood cells that plays an important role in the way HIV develops in the human body. Leronlimab is a monoclonal antibody being studied as a potential treatment for HIV. It binds to the CCR5 receptor, which inhibits the release of inflammatory cytokine [54].

12. Plasma therapy and its advancement

Convalescent plasma (CP) is a promising plasma antibody treatment that could help patients whose bodies cannot produce enough antibodies fighting against COVID-19 to cure the disease. With support from UK National Institute for Health Research (NIHR), the trial is led with NHS Blood and Transplant and University of Cambridge experts [55]. The UK Government approved a national clinical trial to assess plasma therapy for the treatment of COVID-19 patients. This trial will decide that these treatments should be used or not in the COVID-19 patients in future. If the treatment will become effective, total 10,000 units of convalescent plasma will be supplied to the patients in a scaled-up national programme that enabling the treatment of 5000 patients per week [55]. Duan et al. checked the effectiveness of convalescent plasma therapy for COVID-19 patients. It was observed that anti-bodies levels were sudden increased and reduced the concentration of reactive proteins in COVID-19 patients. The clinical symptoms were significantly improved along with increase of oxy-hemoglobin saturation within 3 days without any adverse effects [56].

Researchers will use plasma from patients recovering for at least 28 days to increase antibody levels. The main findings from available data are as follows: (a)mortality may be reduced by plasma therapy in critically ill patients, (b) neutralizing antibody titers are increased and disappearance of SARS-CoV-2 RNA after CP therapy, and (c) beneficial effect on clinical symptoms after administration of convalescent plasma [57].

Plasma therapy in COVID-19 patients shown safe, clinically effective, and reduces mortality based on the limited scientific data. In this simple method, doctors isolate antibodies from the plasma of recovered patients' blood and administer them to currently exposed and infected patients. Antibodies aid in the recognition of the pathogens and reject the pathogen in the patients [55]. However, large multicenter clinical trials are urgently needed to conclude the optimal doses and treatment time point for the CP therapy to tackle COVID-19 pandemic.

13. Nanotechnology and microparticles based applications for COVID-19

Currently, COVID-19 has non-specific treatment. In humans, COVID-19 kicks off the respiratory system through droplets from coughs and sneezes of infected persons. Generally, respiratory system can be divided into two regions namely upper (nasal cavity, sinuses, nasopharynx, oropharynx, larynx, and trachea) and lower tract (bronchioles, alveolar ducts and alveolar sacs).Their journey to the lower respiratory tract after infecting the upper respiratory tract is the cause of respiratory illness [58].

Major obstacles in drug delivery to upper respiratory tract are smaller surface area, lower blood flow, mucus layer (traps inhaled substances) and filtration of foreign objects [59]. The large surface area, ciliated cells of lower respiratory tract may be ideal area for delivery as it is connected directly to systemic circulation via pulmonary circulation with few challenges like branched nature alveolar macrophages and pulmonary surfactant (phospholipids, proteins and mucins) decrease delivery efficiencies [60]. However, the delivery to lower tract should overcome muco-ciliary and cough clearance mechanisms. To address these barriers nanotechnology-based approaches can be implemented due to their characteristic features.

Studies reported that the microparticles (MPs) with aerodynamic size between 1 and 5 μm could escape the mucociliary clearance and deposit in the lower airways. This aerodynamic size range is mainly using in several commercial inhalation products [61]. Ribavirin, Zanamivir, Laninamivir, Interferon-α2 are currently available inhaled anti-viral agents against the human respiratory viruses RSV, rhinovirus, influenza A and B, parainfluenza, adenovirus and coronavirus [62].

Nanotechnology is defined as the application of particles with dimension(s) of roughly 1 to 100 nm scale by the National Nanotechnology Initiative [63]. The principal mechanisms of particle deposition in the respiratory tract depend on particle size; for larger particles, impaction and sedimentation are important, but for nanoparticles less than 160 nm in diameter, diffusion represents the principal mechanism. Hence, nanoparticles and micro-particles approaches provide a broad range of opportunities for COVID-19 with new solutions for clinical problems [64].

Nanotechnology has immense potential to aid in the development of COVID-19 drug delivery due to wide range of advantages such as (i) the small size and morphology of the nanoparticles (NP) enables the drug delivery to physiologically in-accessible sites and eliminate immune response by reticular endothelial cells [64], (ii) large surface-to-volume ratio of NP increases drug loading [65], (iii) the ability to cross negatively charges membranes due to surface charge modification of NP [66], and (iv) NP possess intrinsic virucidal activity, such as gold and silver NP [67].

The performance of the COVID-19 therapeutics can be ameliorated by various approaches of particulate drug delivery systems such as (i) encapsulation of therapeutics in the core to increase stability (ii) specific targeting through targeting moieties (iii) functionalization with polymer like PEG to decrease the amount of drug required to produce action. Metallic, organic, and hybrid NP as well numerous nanocarriers are different approaches of nanotechnology in conjunction with large porous micro-particles (LPMP), solid lipid micro-particles (SLMs) can be used for anti-viral therapy [64].

LPMP represent an outstanding approach to improve deep lung deposition and to bypass macrophage uptake. LPMP are light particles, with an appropriate aerodynamic diameter of 1–3 μm, large geometric diameter of 5–30 μm and density of < 0.4 g/cm3. The high porosity of LPMP allows them to penetrate deeply into lungs by inhalation. However, particles of 1–5 μm tend to aggregate via van der Waals attraction and 1–3 μm particles are captured by lung macrophages thus reducing their effect. Therefore, longer residence time was observed with MP of geometric diameter $\geq$ 20 μm being too large to be phagocytosed by alveolar macrophages. Therefore, particles should be light with large geometric diameter and low aerodynamic diameter to achieve deep delivery into lungs [68]. Garcia-Contreras et al. formulated large porous particles for treatments of tuberculosis in guinea-pig model [69]. Like COVID-19, in tuberculosis disease also requires to reach the drug at lung site. It was observed that treatments of lung infection using large porous particle significantly reduced bacterial burden as compared to other drug delivery.

Ben-jebria et al. formulated pulmonary aerosol drug delivery for porous microparticles. It was found that particles deposit inside the lower lungs was increased as compared to conventional dosage form. The systemic bioavailability by pulmonary route was increased using porous microparticles [70]. It was also observed that drug release from the formulation was sustained, which is required in COVID-19 patients.

To produce inhalable SLMs with stealth effect and deep lung deposition, cisplatin microcrystals were prepared by high pressure homogenization (HPH) in isopropanol (IPA) then embedded into solubilized lipid (Tristearin, TS) and/or PEGylated components (DSPE-methyl-PEG conjugate-2000, DSPE-mPEG-2000) or D-α-Tocopherol polyethylene glycol 1000 succinate (TPGS) via spray-drying technique. SLMs was explained by the increased solubilization of un-entrapped

cisplatin microcrystals on SLM surface by PEGylated fractions leading to initial burst effect followed by retarded dissolution from the encapsulated microcrystals. Use of biocompatible phospholipids that imitate lung surfactants including dipalmitoyl phosphatidylcholine (DPPC) and dipalmitoyl phosphatidyl ethanolamine methoxy (polyethylene glycol) (DPPE-PEG). These surfactants could possibly minimize the surface tension of particles thus facilitating particle migration deeply to peripheral regions of lungs. Moreover, PEGylation using muco-penetrating DPPE-PEG provided stealth effect, which enabled escape from opsonization by alveolar macrophages and ensured longer residence time in the lungs [71]. In COVID-19 infection, drug has to reach lower respiratory tract. Santo et al. formulated dry powder of quercetin loaded SLM and diffusion of quercetin was enhanced by lipid excipient in lungs [72]. Mezzena et al. prepared budesonide loaded microparticles using spray drying method. It was found that suitable size and controlled release formulation was prepared and it was evaluated using in vitro method [73]. Hence, SLM would become effective delivery in COVID-19 infection.

14. Inorganic NPs (INPs)

Inorganic nanoparticles (INPs) are utilized for a wide variety of purposes such as targeted imaging for diagnostics, photothermal therapy, medication and many promising applications in the biomedical field [74]. Metallic NP (MNP) and nanocarriers (NC) can be categorized under inorganic NP. Smaller particle size, controlled tunability, improved stability, enhanced permeability, large surface-to volume ratio are the characteristic features of inorganic NP [75]. Metallic NP such as silver, gold, iron oxide and nanocarriers of silica, titanium, carbon are the most common inorganic -NP. Silver nanoparticles (AgNP) are widely researched nanotechnology approach to treat viral infections. Many assumptions of NP have already been made to develop a novel strategy to eliminate or improve the severity of the infection.

Anti-viral activity of AgNP is well established in treating viruses such as HIV, HBV, HSV, RSV [74]. The virucidal activity of AgNP may not be similar in all viruses. For example, the viral inhibition in HSV-2 is achieved due to binding of AgNP to sulfhydryl group of surface glycoproteins of virus which prevent viral internalization. In virus like Peste des petits ruminants, AgNP interacts with virion surface and core protein to impair viral entry into target cells [76]. The virucidal activity of AgNP by these modes can be explored to improve the activity of therapeutics. In recent literature survey, Oron Zachar concluded that colloidal silver of particle sizes between 3 nm- 7 nm can be highly effective to prevent and treat viral infection at initial stage of respiratory infections [77]. Sarkar has hypothesized that the application of water dispersed AgNP (10 nm) in conjunction with bronchodilators in lungs through simple nebulizer machine or bi-level ventilation may result in better virucidal activity [78]. Therefore, the anti-viral efficiencies of MNP for the treatment of COVID-19can be explored with particular emphasis on formulation composition, delivery method and safety for clinical evaluation.

Literature on anti-viral activity of gold nanoparticles (AuNP) is inadequate to apply it for COVID-19. However, AuNP stabilized with certain biocompatible polymer work as an effective anti-viral agent against HIV-1, H1N1, H3N2, H5N1, dengue virus, bovine viral diarrhea virus and Foot-and-mouth disease virus [74]. Other metallic NP like Magnetic, Titanium, and Silica need to be perfectly conceptualized to explore the antiviral activity for COVID-19 treatment. Carbon based nanocarriers such as fullerenes, carbon nano-tubes have gained much attention due to optical, electronic, mechanical and thermal properties in past decade. They possess many advantages but their applications in the field of virology are limited to some viruses. Antiviral or virucidal activities of these carbon-based nanomaterials have been evaluated against some viruses such as herpes simplex virus type 1(HIV-1) [79], H3N2 [80], Grass carp reovirus (GCRV) [81]and Respiratory syncytial virus (RSV) [82].

Fullerenes are formed by 60 carbon atoms and have the shape of a truncated icosahedron that form a hollow sphere one nanometer in diameter. Fullerenes are water insoluble, but derivatization makes them water soluble.C60 spontaneously forms a stable aggregate in contact with water with nanoscale dimensions (25–500 nm), termed nano -C60 that are both soluble and toxic to microorganisms. Glyco-fullerenes are the carbohydrate derivatives possess combination of interesting biological properties due to the amphiphilic nature with fullerene lipophilic part. Fullerenes are advantageous compared to other carbon nanostructures due to the 3D structure and the possibility of operating the different locations of the C60 cage in a controlled manner. Fullerenes are advantageous compared to other carbon nanostructures due to the 3D structure and the possibility of operating the different locations of the C60 cage in a controlled manner [83]. Munoz et al. synthesized amphiphilic glycodendro fullerene monoadducts and tested for antiviral activity in an experimental infection assay using Ebola virus glycoprotein pseudotyped viral particles on Jurkat cells over expressing DC-SIGN and an improvement in the IC50 [84]. Siddiquie et al. discussed that fullerene-coated surfaces with size less than 60 nm can be used to decrease the adhesion of virus on the surface, as they will be hydrophobic as well as toxic to the envelope and prevent transmission [85]. In this regard, fullerenes can be considered as attractive spherical frameworks for a multivalent presentation of ligands.

Carbon nanotubes (CNT) are unique, 3D carbon-based nanoparticles, composed of thin graphite tubular sheets rolled up into hollow and tiny nano-needle tubular structure used in the field of biological sciences in last few decades [86]. CNTs belong to the fullerene family. They have small size dimensions (10–100 nm), high dimensionality (2D, and 3D),excellent electrical, thermal and mechanical properties and physicochemical features like surface load capacity and great storage space in the inner tube (inner void space) will result in biological properties, such as good biocompatibility, bio-absorption rate, permeability of biological barriers, multi-energy surface/tube chemical functional group capability, and targeted bio-molecules modification potency, etc. [87]. Currently, the applications of CNTs in the biomedical field are explored by surface functionalization, grafting targeted molecules on the surface for site specific delivery, exploiting it superior near-infrared light absorption characteristics and good photothermal conversion [88,89]. Yang proposed project to illuminate new way to fight COVID-19 with acidizing and RNA lyase-modified CNTs in conjunction with photodynamic thermal effect. Authors explored the nature of CoV, as they are labile to acidic environment and high temperature [90]. These characteristics provide new ideas for the development of new anti-CoV drugs.

Quantum dots (QDs) are the nano (2 to 10 nm) semiconductor crystals with unique electronic and optical properties used in biomedical sector as they cross the BBB in conjugation with a therapeutic molecule [91]. Specifically high quantum yield, size-tunable light emission, intensive fluorescence, appreciable chemical and photo-stability have revolutionized the concept of nano-based sensing or diagnostics [92]. Giaxia et al. showed that QDs in conjugation with transferrin (targeting molecule) and Sequinavir could freely cross an in vitro model of BBB with promising anti-viral activity against HIV [93]. In addition, QDs have been utilized either as therapeutics or for in vitro diagnosis of viral pathogens. Much progress has been made in the evaluation of carbon-based nano-systems against viral infection, but their commercialization depends on the safety and superiority over the competing methods [94].

15. Organic NPs

The use of organic NPs (ONP) over INPs is well studied in biomedical field due to various safety issues [95]. ONP possess many advantages over other nanoparticles platforms, such as self-assembly in physiologically mild conditions, and chemical diversity for

accommodating a variety of modalities, sizes, surface functionalization, shapes, and compositions [75]. Multiple forms of ONP are being exploited in nanomedicine but only few are presently being evaluated for their virucidal activity. These include lipid based NP, polymeric NP, and dendrimers.

NP made from lipids is unique class for biomedical applications comprised of outer biodegradable phospholipid bilayer and an inner hydrophilic core designed to hold aqueous therapeutic agents. The flexibility of liposome is to hold both hydrophobic and hydrophilic molecules. A major advantage of liposomal NP is the versatility of the lipid bilayer, which can be functionalized with targeting moieties. Chemical diversity, high loading capacity, and intrinsic bio-degradability are the characteristics beneficial to drug delivery [96].

The pH-sensitive or thermo sensitive linkers can be used to release the drug payload in response to environmental conditions for prolonged stimulation of immune response. Modifying surface charge of liposomes can also be used to enhance the bioavailability to explore the negative charge of mucosal membrane and escape form the clearance mechanism of mucosal cilia [97]. Das et al. reported that the bioactive lipids such as Arachidonic acid and other unsaturated fatty acids can inactivate enveloped viruses including SARS-CoV-2, SARS and MERS to combat COVID-19 [98]. Furthermore, liposomes with bioactive lipids have the great potential for anti-viral therapy.

Polymeric MP and NP (PNP) has shown the exciting features such as flexible properties, viable synthetic protocols, and biocompatibility, making it an interesting candidate for biomedical applications. PNP can be synthesized with the help of polymers such as linear, branched, and 3D networks (i.e. highly branched) of natural or synthetic origin [99]. Various polymers have immensely contributed to accurate understanding of properties such as biocompatibility, bioavailability, immune-compatibility etc. for biomedical sciences. Poly (lactic-*co*-glycolic acid) (PLGA) is the well explored polymer approved by FDA due to biocompatibility and biodegradability in the human body [58]. Synthetic hydrophobic polymers are commonly used in the fabrication of MPs with the aim of sustained drug release. Inhalable PLGA, PCL or PLA MPs were successfully fabricated by spray-drying of mixed organic solution. But their uses either for development or for improvement of an anti-viral have been investigated only for some pathogenic viruses like influenza, HIV and rabies virus [74].

As an alternative to synthetic polymers, some natural polymers e.g. sodium alginate and chitosan are characterized by unique muco-adhesive properties and therefore used in design of controlled release MPs. Chitosan, and N-(2-hydroxypropyl) methacrylamide/N-isopropyl acrylamide are other examples, which showed promising results as intranasal vaccines against viral infections. Chitosan is attracted particular interest for intranasal administration due to their non-toxic nature, biocompatibility, biodegradability, capability to open up tight junctions between epithelial cells [100] and ability to be easily modified into desired shape and sizes [101]. Chitosan can enhance endurance of PNP in mucosal environment and penetration to mucosal tissue, when conjugate with therapeutics [102]. Some other polymers e.g. sodium hyaluronate (HYA) are utilized for pulmonary drug delivery based on their targeting potential in lungs [103]. HYA played a vital role in controlling tumor proliferation and metastasis via targeting CD-44 receptors [104].

Dendrimers NP are three-dimensional hyperbranched organic compounds, well-organized nanoscopic molecules, possess low polydispersity index, biocompatibility and biodegradability in the field of nanomedicine [105]. This allows the potential utilization of dendrimers NP in various therapies against tumors, bacterial and viral infections. Dendrimers act as extraordinary vehicle for the targeted delivery of drug/ gene/ peptides in biological system with limited utility and application in antiviral therapy [106]. The globular structure of dendrimers enables NP to accommodate drug molecules in the interior cavity i.e. by physical encapsulation and on surface by covalent conjugation [107]. To date, dendrimers with anti-viral activity in conjugation with therapeutic agents have already been documented against some viruses including influenza virus, Ebola-virus, zika virus, HSV-1, 2 and HIV. Research on the efficacy of dendrimers as a nanoparticulate system for designing an anti-viral therapy have been introduced by some of the pioneering researches, but their efficiency against is yet to be evaluated [74].

Hybrid nanosystems are combination of inorganic-organic, inorganic-inorganic, and organic-organic nanoparticulate systems engineered based on specific requirement or use at targeted site. Joshy et al. reported the zidovudine loaded polyvinylpyrrolidone (PVP)/ stearic acid (SA)-polyethylene glycol (PEG) nanoparticles led to significant improvement in cellular internalization murine neuro-2a and HeLa cells. Authors concluded that hybrid nanoparticles may be a promising approach for anti-viral drug delivery for use in HIV/AIDS therapy [108].

Nanoviricides are polymeric micelles designed by NanoViricides Incorporation Company (Shelton, Connecticut, United States)to destroy viruses. As defined by Nanoviricides Inc., nanoviricide is a polymeric single chemical chain with covalently attached ligands that specify the virus target. The attached ligands determine the anti-viral activity of the drug [109]. Nanoviricide binds to specific virus type at several points, coat the virus particles and dismantle the virus particle and attack the viral genome optionally to destroy virus completely. Nanoviricides complete the task of destroying the virus particles without immune system assistance. Currently nanoviricides drug candidates are in preclinical studies with planned clinical trials [54]. The Company has worked on developing an animal model to test anti-coronavirus effectiveness in vivo using a model coronavirus that binds to the same ACE-2 receptor as SARS-CoV-2, namely human coronavirus NL-63 (hCoV-NL63). The researcher anticipates using this animal model to obtain indications of effectiveness of the nano-viricide test drug candidates against the model coronavirus in vivo. Nanoviricides represent the next great advance in anti-viral strategies in “Immunotherapeutic” (antibodies and vaccines) [32].

NPs possess the ability to deliver a wide range of antigenic moieties to the antigen-presenting cells by safeguarding the native structure of the antigen in order to enhance the safety and the efficacy of the vaccine. NPs can target both adaptive and innate immune systems. Nanosize and flexibility are the key advantages of nanocarriers in vaccine development. NPs can be administered by oral, intranasal routes, subcutaneous and intramuscular injections by overcoming tissue barriers and targeting key locations like epithelial, mucosal barriers and lymph nodes [110]. In the roles of various beneficiaries, biocompatibility, in vivo biodistribution, biodegradation, and bio-corona formation are some of the important features that continue to shape the current scientific community to this day.

16. Research agenda for panacea of COVID-19

The objectives of the research agenda are to combat COVID-19 through rapid diagnosis, in facilitating ideal care to all the affected persons, to learn from the current outbreak response and be prepared for unpredictable epidemics in future. The research agenda can be divided into five broad areas of research action as summarized in Fig. 5.

17. Ground work

A myriad of things plays an important role in research and development during outbreaks. To combat any disease the first step in the path of research lies in the success of the ground work. The ground work in the case of COVID-19 begins with understanding the virus origin, transmission and diagnosis then therapeutic treatment strategies.

The research regarding the natural history of virus includes its origin, genomic sequence to support the clinical management and development of interventions. The compartments of replication, prognosis

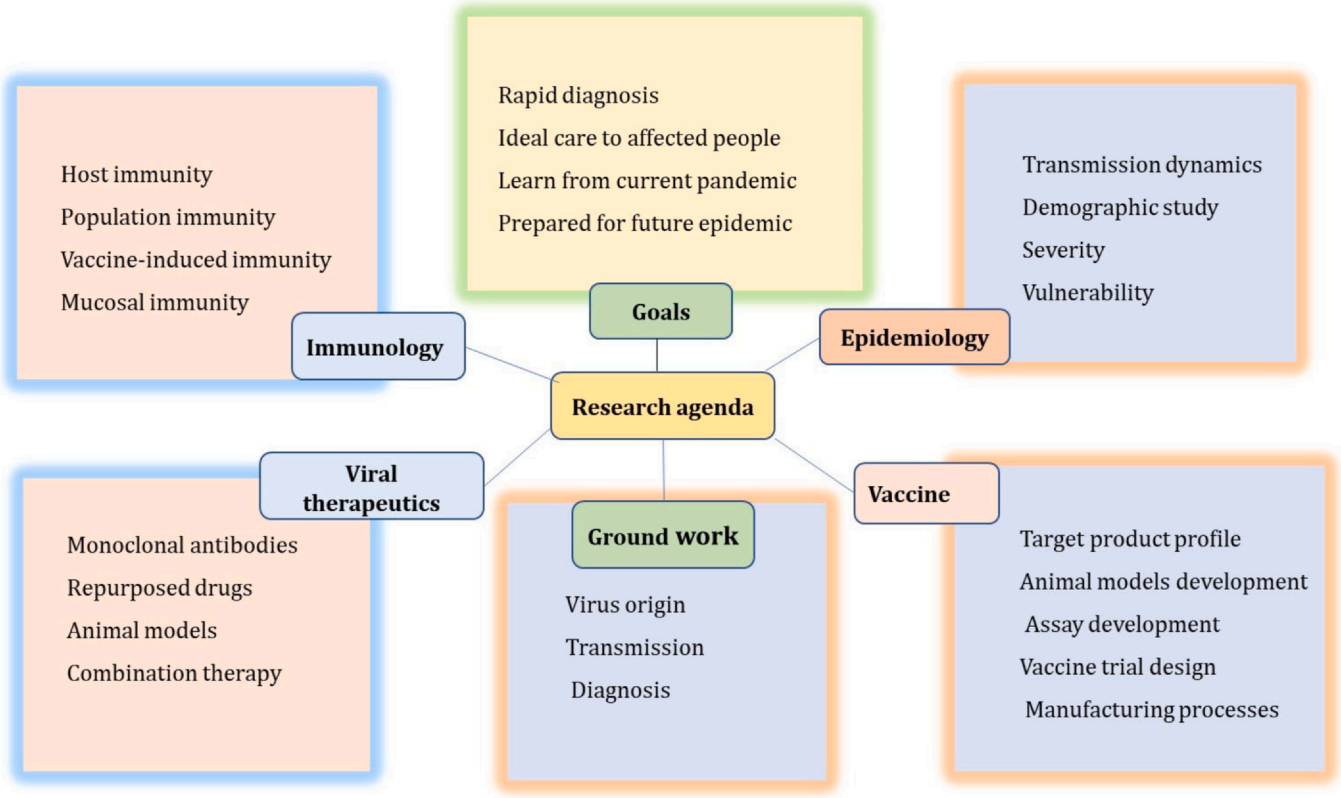

Fig. 5. Research agenda regarding the COVID-19 pandemic and it illustrates the five broad areas of research and goals to combat COVID-19.

information, surrogate markers for infectivity, phenotypic changes are all concerns that need to be addressed in the ground work of research agenda. A rapid task to be undertaken at this moment is the modification of clinical skill for the rapid diagnosis of the infection and tracks the changes in virulence. Newly emerged virus may change its phenotype making it difficult for the research and development of the therapeutics in future. The demanding research activities included termination, development of diagnostic kits with high quality and performance to detect the virus.

18. Epidemiology

The extensive research in the field of epidemiology may help in the prevention of transmission and future spillover of the disease. The research in the epidemiology involves the source, route of transmission, transmission dynamics, demographic study, severity, vulnerability and control the transmission of the disease.

Research in the early stages provided us the information regarding ecological reservoirs for SARS-CoV-2 are bats [111]. Further, the route of transmission from animals to humans remains unclear; it may involve other/ intermediate hosts as seen with SARS-CoV or MERS-CoV. Finally, the original transmission to humans may not have happened at the market itself but elsewhere, with the market serving as a location for viral contamination and further exposure of humans. The reproductive number for the corona virus is yet to be determined accurately to understand the dynamics of transmission. The importance, impact and existence of symptomatic and asymptomatic transmission need to be understood clearly along with the role of environmental factors (temperature, humidity and so on). The severity profile, the range of clinical presentations, classification of symptoms is the essential knowledge gaps in the area of epidemiology. The need to determine asymptomatic or symptomatic transmission of COVID −19, across the range of severity with aid of detailed observational studies [112]. Early studies identified patients with other medical conditions such as diabetes, hypertension and cardiovascular disease had more severe infections, and the disease was more common in men. Very few cases have been reported in children [11]. There is currently limited understanding of severity in different populations and risk groups.

Family cluster studies [113], case studies, mathematical modeling to determine transmission parameters are being investigated carefully to understand COVID-19 in better way [114–116]. The further research in the field of epidemiology should be directed to understand the transmission potential, transmission dynamics, identify effective control and mitigation measures.

19. Immunology

The knowledge of immunology directly or indirectly aids in the development of interventions and clinical management of COVID −19. The basic information of immunology is to know about the role of innate and adaptive immune response in clearance of pathogen. As a part of innate immunity body produces inflammatory proteins like interferons (including IL-1β, IL-6, TNF-α, etc.) as first line defense. Adaptive immune response involves B cell activation resulting in antibody production. In addition, T lymphocytes including CD4+ T cell derived cytokines, CD8+ T cell mediated cytotoxicity play important role in clearance of virus. However, adaptive and innate immune responses work together in sequence to combat any viral infection in healthy immune cells. In case of defective immune response or dysfunctional immune, cytokine storm will be triggered and circulates to other organs, leading to lung and multi-organ damage [117].

Some studies have suggested that SARS-CoV-2 has the capacity to escape innate immune responses but the mechanism remains unclear [117–119]. Further studies to characterize the host immunity, population immunity, vaccine-induced immunity and mucosal immunity are necessary. To support the research and development, studies regarding

Table 1
Updated lists of vaccine candidates being developed to combat COVID-19 with special emphasis on the vaccine status and development.

S.noS.no	Name	Description	Manufacturer (Clinical trial)	Mechanism of action	Clinical phase status	Inference	References
1	AZD1222	Attenuated adenovirus modified with genetic code capable of producing the spike (S) protein of SARS-CoV-2	University of Oxford/ AstraZeneca (ISRCTN89951424)	Vaccination results in the formation of endogenous antibodies to the spike protein.	Phase 3	Previously known as ChAdOx1 nCoV-19 was originally developed to target MERS	[121] [122] [123] [124]
2	Ad5- nCoV	Genetically engineered vaccine with the replication-defective adenovirus type 5 as the vector to express SARS-CoV-2 spike protein	CanSino Biological Inc./Beijing Institute of Biotechnology	After vaccination the cells produce the spike protein and travel to the lymph nodes where the immune system creates antibodies that will recognize that spike protein and fight off the coronavirus.	Phase 2	Vaccine candidate is built upon CanSinoBIO's adenovirus-based viral vector vaccine technology platform, applied to develop the globally innovative vaccine against Ebola virus	[125] [126–128]
3	mRNA-1273	Lipid nanoparticle dispersion containing messenger RNA	Moderna/NIAID (NCT04470427)	Vaccine carries the mRNA strand of the spike protein of the coronavirus to produce antigens by the human cells to fight the virus and gears up the body's immune system	Phase 3	Vaccine consists of lipid nanoparticle (LNP; proprietary ionizable lipid, SM-102, and 3 commercially available lipids, cholesterol, DSPC, and PEG2000 DMG) dispersion and mRNA for spike protein of SARS-CoV-2	[129,130] [131]
4	Inactivated SARS CoV 2 Vaccine	Inactivated virus	Wuhan Institute of Biological Products/Sinopharm (ChiCTR2000034780)	The body generates a diverse immune response against numerous viral antigens after vaccination without any threat of actually being infected as the virus is inactivated	Phase 3	Inactive viral vaccines are created by propagating viruses in cell culture (such as in Vero cells) followed by inactivation using a chemical reagent (such as beta-propiolactone)	[132]
5	New Inactivated SARS CoV 2 Vaccine		Beijing Institute of Biological Products/Sinopharm (ChiCTR2000034780)		Phase 3		[133]
6	Inactivated vaccine		Institute of Medical Biology, Chinese Academy of Medical Sciences		Phase 1		[134]
7	CoronaVac	Inactivated virus + alum	Sinovac (NCT04456595)		Phase 3		[135] [132]
8	NVX-CoV2373	Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M.	Novavax (NCT04368988)	After vaccination, high levels of spike protein-specific antibodies that block the activity of ACE-2 human receptor binding domain, and SARS-CoV-2 wild-type virus neutralizing antibodies are produced to combat the virus	Phase 1	Novavax utilizes proprietary recombinant protein nanoparticle technology platform to generate antigens derived from the coronavirus spike (S) protein.	[136,137]
9	BNT162	BNT162 vaccine trial is comprised of four (a1, b1, b2 and c2) prophylactic SARS-CoV-2 RNA Vaccines Against COVID-19	BioNTech/Fosun Pharma/Pfizer (NCT04368728)	Four individual lipid nanoparticle encapsulated mRNA vaccines encoding spike protein or receptor binding domain (RBD)	Phase 3	Two candidates are nucleoside modified mRNA (modRNA), one is uridine containing mRNA (uRNA) and the last is self-amplifying mRNA (saRNA). Two of the vaccines are also the larger spike sequence from SARS-CoV-2 and the other two are the receptor-binding domain (RBD) sequence only	[138] [139]
10	INO-4800	DNA plasmid delivered by electroporation	Inovio Pharmaceuticals (NCT04336410 NCT04447781)	Electroporation results in small pores on the cells to aid the uptake of the nucleic acid vaccine. The cells then start to create the proteins encoded on the DNA plasmid and produce antibodies.	Phase 2	Vaccine consists of double-stranded DNA plasmid that encodes antigens found in SARS-CoV-2. It is intradermally delivered into the arm of patients using proprietary CELLECTRA technology	[131]
11	LNP-nCoVsaRNA	Messenger RNA	Imperial College London (ISRCTN17072692)	After vaccination into muscle, host cells produce the viral spike protein and host's immune system produces antibodies in response	Phase 1/2	Same platform as vaccine candidates for EBOV, LASV, MARV, Inf (H7N9), RABV	[121]
12	LV-SMENP-DC	Modified dendritic cells (DC) with lentivirus vectors expressing Covid-19 minigene (SMENP) and immune-modulatory genes.	Shenzhen Geno-Immune Medical Institute (NCT04276896)	Upon injection subcutaneously, DCs will prime specific cytotoxic T lymphocytes that are specific to SARS-CoV-2. Alternatively, T cells will be primed ex vivo and intravenously infused into the patient	Phase 1/2	DCs modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins; administered with antigen-specific CTLs	[131,140]
13	COVID-19/Aapc	Artificial antigen presenting cells (aAPCs) modified with lentiviral vector		The functionality is thought to work by priming T lymphocytes against the SARS-CoV-2 virus.	Phase 1		[131] [140]

(*continued on next page*)

Table 1 (*continued*)

S.noS.no	Name	Description	Manufacturer (Clinical trial)	Mechanism of action	Clinical phase status	Inference	References
		expressing synthetic minigene based on domains of selected viral proteins	Shenzhen Geno-Immune Medical Institute (NCT04299724)			Inactivation of proliferation by altering aAPCs with immune-modulatory genes and the viral minigenes to represent SARS-CoV-2 antigens	

the strength, kinetics and the duration of immunity need to be clarified. In addition, detailed investigation of the determinants of healthy versus dysfunctional outcomes is required to combat COVID-19.

20. Viral therapeutics in combating COVID-19

Viral therapeutics to fight COVID-19 includes monoclonal antibodies, repurposed drugs or anti-viral drugs in development stage. To deal with the outbreak immediately, the only option is to repurpose the antiviral drugs due to lack of time by evaluating its safety and efficacy. Among the landscape of therapeutics, based on the broad antiviral spectrum, Remdesivir was considered as first priority. Among the repurposed drugs, the investigation of the anti-retroviral medicine (HIV protease inhibitors), lopinavir/ritonavir, either alone or in combination with Interferon β was considered a suitable second option for rapid implementation in clinical trials [120]. However, immunotherapies like convalescent sera or other agents are also considered for the treatment option.

The research in the field of viral therapeutics should involve identification of more therapeutics candidates for clinical evaluation along with the development of in vitro and in vivo studies. To maximize the efficacy of the treatment, combination therapy needs to be explored to gain additive or synergistic effects, or reduces the risk of drug resistance. The lack of information regarding the clinical evolution, epidemiological studies, and therapeutics as none of them were developed for COVID-19 stands as a major milestone.

To succeed rapidly in the research and development (R&D) of COVID-19, animal models that can mimic the human disease characteristics need to identify urgently to perform in-vivo preclinical studies. Therapeutics (anti-viral agents) and clinical trials of drugs for prophylactic use need to be developed to protect the risk population. To reduce the mortality and improve clinical disease outcome; the research agenda should cover the investigation of prophylaxis, combination therapies, evaluation and safety studies of repurposed agents to progress in the battle against COVID-19outbreak.

21. Vaccination in combating COVID-19

Vaccines serve as therapeutic and prophylactic agent to combat any infection. One of the major challenges is to handle the enhanced diseased condition occurring in immunized animals upon exposure to virus, studied in case of SARS and MERS-CoV vaccine candidates in mice. First step in the vaccine research includes the design of the target product profile (TPP) to provide guidance for the formulators. Animal model development, assay development, vaccine trial design, manufacturing processes can be regarded as the key areas of research in the “safe and effective” vaccine development. A list of vaccine candidates developed to combat COVID-19 with a particular focus on vaccine status and development is described in Table 1 [121]. (See Table 2.)

Animal models, mimic aspects of a diseased condition found in humans are used to evaluate the disease. To evaluate the potential of vaccine, standardize animal models are to be developed to understand the enhanced disease after vaccination. Therefore, a validated animal model should be developed to extrapolate the human conditions prior to large scale efficacy studies. Development and standardization of assay in support the immune responses and clinical case to support the research in the field of vaccine research. Developing of master protocols in determining the safety and efficacy before widespread distribution of vaccine for COVID-19 pandemic [141]. Finally, develop manufacturing processes to rapidly enable the production of high-quality large quantities of clinical grade and GMP materials to aid the research activities.

22. Post COVID-19 era

The devastating COVID −19 led to the social crisis and an economic system failure globally. Post COVID-19 involves complications, lessons

Table 2
List of different types of nanoparticles used for the treatment of other viral infections.

S.noS.no	Nanoparticle	Virus	Mechanism of action	Inference	References
1	Silver nanoparticles (AgNPs)	Poliovirus type-1	–	AgNPs based products were ideal for biomedical applications and to fight against viral infections	[146]
2	siRNA-modified Polyethylenimine (PEI) encapsulated AgNPs	Enterovirus 71 (EV71)	Prevent DNA fragmentation, chromatin condensation and activation of caspase-3 and block entry of EV71 TO host cell	Surface decorated AgNPs with PEI and siRNA might be a prospective silver species with antiviral properties for treatment of viral diseases.	[147]
3	Glutathione-capped Ag_2S nanoclusters (NCs)	Porcine epidemic diarrhea virus (PEDV) as a model of coronavirus	Inhibits the synthesis of viral negative-strand RNA and viral budding	The results suggest the possibility to develop efficient anti-SARS or anti-MARS reagents based on Ag_2S NCs	[148]
4	Amantadine (Ada), on the outermost layer of PVP–PEG-coated silver nanorods (Ada–PVP–PEG silver nanorods)	Human immunodeficiency virus (HIV)	Ada surface-modified silver nanorods promote HIV vaccine-triggered cytotoxic lymphocytes to produce around eightfold stronger tumor necrosis factor alpha in vivo	Surface modifications of nanomaterials in fundamentally improving the immunotherapy of HIV vaccine against HIV-infected cells.	[149]
5	AgNP	Respiratory syncytial virus (RSV)	NPs attach to viral glycoproteins, and block entry into the host cell.	AgNP-mediated reduction in RSV replication, both in epithelial cell lines and in experimentally infected BALB/c mice	[150]
6	Nonlinear globular G2 dendrimer	Rabies virus	–	Adjuvanticity efficacy	[151]
7	Ammonium-terminated amphiphilic Janus dendrimers	Hepatitis C virus (HCV)	Inhibit HCV replication by interacting with viral protein	Nontoxic drug-loaded nanoaggregates inhibit HCV replication at low camptothecin concentration.	[152]
8	Modified dendrimer NPs	Venezuelan equine encephalitis virus (VEEV) replicon RNAs Zika virus	Activation of both CD8 + T-cell and viral E protein-specific IgG responses	This approach can be used to evaluate new candidate antigens and identify immune correlates without the use of live virus.	[153]
9	Glycodendrofullerenes Carbohydrate moieties (Mannose, Galactose)	Pseudotyped viral particles (Ebola virus glycoprotein)	Blocking the dendritic cell–specific intercellular adhesion molecule-3–grabbing non-integrin receptor	Inhibition of viral attachment leading to inhibited viral entry	[154]
10	Gold (Au)/iron-oxide magnetic NP-decorated Carbon nanotubes (CNTs)	H1N1, norovirus	DNA hybridization	High sensitivity and selectivity detection of viral DNA	[155]
11	Monodispersed gold nanoparticles	Herpes simplex virus	Prevented viral attachment and penetration into the Vero cells.	Gold nanoparticles were proposed as a safer alternative in virus chemotherapy	[156]
12	Polyvinylpyrrolidone (PVP)/stearic acid (SA)-polyethylene glycol (PEG) NP	HIV	Appreciable cellular internalization	Favorable loading, sustained release, hemocompatibility and nontoxicity	[108]
13	Lactoferrin NPs	HIV	–	The triple-drug loaded nanoparticles have various advantages against soluble (free) drug combination in terms of enhanced bioavailability, improved PK profile and diminished drug-associated toxicity.	[157]
14	Amide functionalized alginate NPs	HIV	Inhibits viral transcriptase	Effective antiviral delivery	[158]
15	Glycyrrhizic-acid-based carbon dots	Porcine reproductive and respiratory syndrome virus (PRRSV)	Gly-CDs can inhibit PRRSV invasion and replication, stimulate antiviral innate immune responses, and inhibit the accumulation of intracellular reactive oxygen species (ROS) caused by PRRSV infection.	Gly-CDs possess extraordinary antiviral activity with multisite inhibition mechanisms, providing a promising candidate	[159]

learned, immunity, financial loss and preparedness. The only complication of COVID-19 is a type of pneumonia called 2019 novel coronavirus-infected pneumonia (NCIP) in conjunction to ARDS, RNAaemia, acute cardiac injury, and secondary infection associated with other types of corona virus [142].

Sekowski et al reported the high chances of Posttraumatic Stress Disorder (PTSD) in COVID-19 survivors based on previous research on PTSD in epidemic survivors (e.g. SARS)[143]. PTSD is a serious mental disorder that negatively affects functioning and social life by reliving the traumatic event, emotional numbness and increased arousal. Preliminary report by Bo et al indicated that almost all clinically stable patients with COVID-19 in China experienced significant severity of post-traumatic stress symptoms [144]. Both the studies suggest to regularly screen for PTSD and pay attention on individuals at increased risk of complications, appropriate crisis psychological interventions and long-term follow up assessments should be started immediately for COVID-19 survivors. The issue of negative detrimental impact of significant posttraumatic stress prevalence of PTSD in individuals post COVID-19 remains a matter of future research as symptoms may develop up to 6 months after the traumatic event [143].

Immunity remains the cornerstone for post COVID−19 survival. The strength and duration of immune response in COVID−19 survivors remain as the major knowledge gap. There is no evidence at this point that people can't be reinfected with the virus and the development of an antibody response will be protective from secondary infection, according to WHO. Some countries suggested detection of antibodies to COVID−19, could serve as the basis for an 'immunity passport' or certificate of immunity assuming that they are protected against reinfection. But WHO said that issuing such certificate increases the severity of the disease. HERD immunity would be played an important role to address the devastating COVID-19, which is an indirect protection conferred to the susceptible ones by immune individuals against a specific pathogenic infestation in a given population [112]. It is possible only through vaccination. Vaccine approval may take up to a decade or more to win approval based on their ability to prevent disease in population. Typically, HERD immunity isn't achieved in a short time like year or two and would take several years to confer sufficient 'HERD immunity' to fight COVID-19 [145].

The lessons from unprecedented COVID−19 teach one about the importance of readiness, preparedness and response actions to combat sudden epidemics globally. In the battle of COVID-19 it is very crucial to maintain close watch of recovered patients, understand the long-term complications associated the risk of relapse and post discharge surveillance of COVID-19 survivors. Emergency response mechanisms, risk communication and public engagement case finding, contact tracing and management, surveillance, public health measures, laboratory testing are the various priority areas of work in the transmission of COVID as per the interim guidance document by WHO.

23. Conclusion and future perspective

The COVID-19 outbreak has been declared as a pandemic and represents one of the biggest risks globally, as the virus infects a large number of human populations, and the outbreak can cause severe medical complications with economic impact. This study presents the current status of the deadly infectious COVID-19 with special emphasis on the research agenda to fighting against COVID-19.The current review focuses on the possible particulate delivery approaches and the research agenda to combat COVID-19.The research agenda discussed in this context covers all the areas such as ground work, epidemiology, immunology, viral therapeutics and vaccine. The challenges, knowledge gaps and the research efforts are discussed in the specified areas. The major goals to combat COVID-19 are to identify, diagnose, treat and stop the transmission of virus due to its sudden spill over globally. Future perspective should focus on repurposing of antiviral drugs, development of animal models, in-vitro in-vivo studies to aid the screening of antiviral drugs, prevent transmission of disease, and develop vaccine as early as possible.

Author declaration template

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work.

[OR]

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author.

Declaration of competing interest

No conflict of interest was reported by the authors of this article.

Acknowledgment

The authors would like to acknowledge the Department of Pharmaceutics, National Institute of Pharmaceutical Education & Research (NIPER), Hyderabad for providing facilities for writing this manuscript.

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