Review article

In-line treatments and clinical initiatives to fight against COVID-19 outbreak

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1. Introduction

In December 2019, when the whole world is waiting for Christmas and New Year, the physicians of Wuhan, China, are astounded by clusters of patients suffering from pneumonia from unknown causes. The pathogen isolated from the respiratory epithelium of the patients is similar to previously known coronaviruses with some distinct features. The disease was initially called nCoV-2019 or SARS-nCoV-2 and later termed as COVID-19 by WHO. The infection is rapidly propagating from the day of emergence, spread throughout the globe and now became a pandemic which challenged the competencies of developed nations in terms of health care management. As per WHO report, 216 countries are affected with COVID-19 by August 5, 2020 with 18,142,718 confirmed cases and 691,013 deaths reports. Such huge mortality and morbidity rates are truly threatening and calls for some aggressive and effective measures to slow down the disease transmission. The scientists are constantly engaged in finding a potential solution to diagnose and treat the pandemic. Various FDA approved drugs with the previous history of antiviral potency are repurposed for COVID-19 treatment. Different drugs and vaccines are under clinical trials and some rapid and effective diagnostic tools are also under development. In this review, we have highlighted the current epidemiology through infographics, disease transmission and progression, clinical features and diagnosis and possible therapeutic approaches for COVID-19. The article mainly focused on the development and possible application of various FDA approved drugs, including chloroquine, remdesivir, favipiravir, nelfinavir mesylate, penciclovir, nitazoxanide, ribavirin etc., vaccines under development and various registered clinical trials exploring different therapeutic measures for the treatment of COVID-19. This information will definitely help the researchers to understand the in-line scientific progress by various clinical agencies and regulatory bodies against COVID-19.

In history, mankind experienced different types of coronavirus infections, affected specific regions of the world, among which SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) and MERS-CoV (Middle East Respiratory Syndrome Coronavirus) were considered as an epidemic. SARS-CoV and MERS-CoV affected a big population and

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myth busters to aware of the public with actual facts [6]. On the other predictions, WHO and many other Government bodies generated some vent the COVID-19, etc. Thus, to clarify the confusion and false pre-

responsible for a higher mortality rate throughout the world [1]. In December 2019, another dreadful coronavirus infection emerged in China initially diagnosed as pneumonia with an unknown cause. After preliminary investigations, it was called nCoV-2019 (novel coronavirus infection 2019) which was further officially named as COVID-19 (coronavirus infection disease-2019) by WHO. The first cases of novel coronavirus infection were reported in December 2019 in Wuhan city of China and spread to 216 countries of the world till date (August 5, 2020). The patients were prevalently observed with high fever, dry cough, dyspnea, and bilateral lung infiltrate upon imaging [2,3]. The origin of infection was linked to a wholesale seafood market of Wuhan city [4,5]. On March 11, 2020, COVID-19 is declared as a pandemic by WHO which is the first known pandemic in human history that supposed to be controlled by appropriate curative measures (WHO, March 11, 2020).

After the COVID-19 outbreak in Wuhan, China, more than 18,142,718 patients were identified positive with SARS-CoV-2 infection along with vaccines development and various clinical studies. We have discussed current therapeutic approaches used by the companies named Moderna Therapeutics, Bostan and Inovio Pharmaceuticals [6]. Although, the world has to wait for at least one and a half years to have some potential solutions to fight this threatful condition as soon as possible. These initiatives are also supported by various government bodies in terms of funding and other regulatory affairs [9]; The, 2020). The scientists and researchers around the globe are struggling to find a new drug or vaccine against any novel pathogenic species or completely new infection/disease always remains a challenging and lengthy process. The developmental process involves identification of the pathogenic strain, a detailed investigation of viral/microbial anatomy and genetic sequencing, thorough understanding of disease pathophysiology, in vitro model development, mode of invasion, product development, in vivo testing on animal models and human trials (phase I, phase II and phase III). The complete process including product approval is essential to ensure the safety and efficacy of the formulation and take around 10–15 years usually and a minimum of 1.5–2 years [8]. The good number of infected patients, government and many other Government bodies generated some myth busters to aware of the public with actual facts [6]. On the other hand, the lower CFR (case fatality rate) 3.80 on August 5, 2020 as compared to the previous coronavirus epidemic conditions, recovery of the good number of infected patients, government’s aggressive efforts to combat the disease and exhaustive research initiatives for developing various diagnostic tools, promising therapies, and vaccination, etc. gives some kind of assurance that we will fight and win this global issue.

The development of a new drug or vaccine against any novel pathogenic species or completely new infection/disease always remains a challenging and lengthy process. The developmental process involves identification of the pathogenic strain, a detailed investigation of viral/microbial anatomy and genetic sequencing, thorough understanding of disease pathophysiology, in vitro model development, mode of invasion, product development, in vivo testing on animal models and human trials (phase I, phase II and phase III). The complete process including product approval is essential to ensure the safety and efficacy of the formulation and take around 10–15 years usually and a minimum of 1.5–2 years [8]. The scientists and researchers around the globe are struggling to find some potential solutions to fight this threatful condition as soon as possible. These initiatives are also supported by various government bodies in terms of funding and other regulatory affairs [9]; The, 2020). Although, the world has to wait for at least one and a half years to have the first vaccine of COVID-19. Currently, two American based companies named Moderna Therapeutics, Bostan and Inovio Pharmaceuticals, Pennsylvania got approval for human trials of the vaccines. In this review, we have discussed current therapeutic approaches used by the physicians throughout the world to treat COVID-19 patients including different antiviral, antimalarial, anti-inflammatory drugs, immunosuppressants, nucleotide analogs, antibiotics, health-promoting agents, etc. along with vaccines development and various clinical studies. We have
also highlighted the latest epidemiology of the disease, the phases of disease progression, phase-wise transmission and spread of infection, its symptoms and diagnostic measures.

2. Epidemiology and infographics

As per the WHO update on August 5, 2020, in total, there are 18,142,718 confirmed cases of COVID-19 with 691,013 deaths reported throughout the world [10]. Around 216 countries got affected by this pandemic to August 5, 2020. The cases increasing day-by-day and the situations get worsens. The worst-case scenario is in the USA with 4,918,770 confirmed cases followed by Brazil with 2,808,076 cases, India with 1,910,681 cases, Russia with 866,627 cases, South Africa with 521,318 cases, Mexico with 449,961 cases, Peru 439,890 cases, Chile 362,962 cases, Spain with 349,894 cases and Colombia with 334,979 cases, as top ten countries of the world in respect to COVID-19 cases at early August. These are ten heavily burnt countries with COVID-19 pandemic while the China, the first hitted country is now showing flattening of growth curve with 84,491 cases [11]. The geographical representation of some worst affected countries is shown in Fig. 1.

For easy understanding and monitoring of the situation WHO has divided the whole world into 6 regions. The Region of Americas 9,741,727 cases and 365,334 deaths; European Region is identified with 3,425,017 confirmed cases and 214,238 deaths; South-East Asia Region with 2,242,656 cases and 47,574 deaths; Eastern Mediterranean Region with 1,574,551 cases and 41,202 deaths; African Region with 825,272 cases and 14,139 deaths and finally the Western Pacific Region with 332,754 cases and 8513 deaths (Fig. 2). Every day becomes crucial now, as initially, it took around 3 months to reach the number of one hundred thousand patients while this number gets doubled only in the next 3-6 days. WHO developed and approved a new protocol entitled “population-based age-stratified seroepidemiological investigation protocol for COVID-19 virus infection” for investigating the extent of infection in the general population by positive antibody test [6].

As per the unpublished data of the Chinese Government and Chinese media report, an unnoticed event of novel coronavirus infection was tracked back on November 17, 2019 in Wuhan city, Hubei province, China [12,13]. Rapid dissemination was noticed since the first day of the outbreak. By the end of 2019 i.e. 31st December 2019, China has 27 confirmed cases on records. The number gets doubled (59) within 5 days and remain constant till January 16, 2020. During this period, the Government of China and the rest of the world did not get the outrage of this situation. International traveling for personal, professional and
political purposes was frequent at that time. Chinese people continued to move transfrontier and went to many different places of the entire world, including the USA, European countries, South Africa, Western pacific region, other parts of Asia and all other places of the globe and China also allowed the cross-border travellers. Afterward, the number of infected patients quickly raised and reached 526 in the next 6 days by January 22, 2020 [14]. By this time, the Chinese Government initiated various strict measures to control this novel Coronavirus infection and established various Epidemic control and prevention councils at the state and national level [15]. Failing all the precautionary measures, a quick and widespread infection was observed in China which was uncontrollable till February 22, 2020 with 76,369 patients. Further, with aggressive, controlling measures, exhaustive screening, social distancing, and complete quarantine of suspects, a stagnancy was observed in the quick uprising curve of COVID-19 infection in the after 3 months in China [14]. On the basis of available statistics, by the end of March 2020, the whole world supposed that China came out from the containment stage and moved to the mitigation phase [16]. It was expected that China has completely overcome the outbreak by eradicating the infection but upon the appearance of some new cases of COVID-19 China fears about the second wave of infection which supposed to be more threatening than the previous version. Now, by early August, China has flattened the curve of COVID-19 spread and showed a stagnant situation with 84,079 cases [17]; Xu and Li).

In late January and February the epidemic was spread out from China and rapidly transmitted to different countries and now on August 5, 2020 COVID-19 is spread over 216 countries around the globe [14]. In the beginning, South Korea became the second most affected country after China with a quick and widespread infection. In South Korea, the first case was reported on 20th January and within one month it became 155 cases. Afterward, the number gets doubled on a daily basis and multiplied quickly thereof. By 8th March, the number of infected patients reached up to 7134. Thereafter, a stagnancy was observed in the growth curve which is maintained till date (May 22, 2020). The South Korean Government implemented an intensified testing model for high-risk groups or all. ‘Test, test and test’ or ‘triple T’ was the only formula of the South Korean Government. With strict preventive and control measures, the Government of South Korea succeeded in controlling the disease transmission (Alexis [18]).

With 4,918,770 confirmed cases and 160,318 death reports, now in August, unfortunately, United States of America maintained the first position in the COVID-19 statistic chart by WHO and other regulatory bodies with very little improvement in disease spread [6,11]. Initially, the disease transmission is lower in the USA than many other countries, including Italy, France, Spain, Japan, South Korea, etc. The very first case was reported on 21st January, while the 100th case on 3rd March. The great control was observed in February 2020. A faster multiplication and massive community spread were reported from 10th March and from then COVID-19 outbreak has erupted in the USA [14]. As per a report by William Haseltine in Project Syndicate, such a pandemic explosion is because of the initial casual response of US Government which did not bother about the contact tracing, extensive testing and imperative quarantine of suspects [19,20]; Michael D. [21]. After a huge number of deaths, the USA trying to respond to the pandemic situation and announced partial closing of business, universities, schools and other public premises for damage control and restraining of further spread [20,22]. Although, the situation is worst in the USA and seems out of control with these median steps. The fierceness is measured by the statement of the US President that ‘there will be a lot of death in the USA’ and ‘we will be lucky if it stopped in three hundred thousand deaths’ [23,24].

The worldwide scenario is changing day by day and various countries initially experiencing a modest spread of COVID-19 like Russia, India etc. are now becoming the centre of SARS-CoV-2 infection and struggling to combat the situation. COVID-19 not only affected the health of the human world but also put a question mark on the world economy and development. So, to balance the world economy, all the governments are now working on the concept of ‘learn to live with COVID-19’ and hence, most of the countries call-off the lockdown and trying to get back to the normal lives with essential precautions. The confirmed cases of COVID-19 from 22nd January to August 5, 2020, highlighting the case reports of ten worsely affected countries along with China is graphically displayed in Fig. 3. A detailed record of all the affected countries and timely disease spread has been given in

Fig. 3. Graph showing number of confirmed cases and rate of spread of COVID-19 in 10 worsely affected countries including USA, Brazil, India, Russia, South Africa, Mexico, Peru, Chile, Spain and Colombia along with the present data of China starting from January 19, 2020 to August 4, 2020 (Adapted from [25]).
supplementary file 1. A graphical data of daily new confirmed death reports on 3 days rolling average data is shown in Fig. 4, highlighting the daily new death reports of the aforementioned countries in comparison with world data.

3. Transmission and spread

The exact pathophysiology of COVID-19 is currently not clear, we have very limited information about the characteristics and clinical features of SARS-CoV-2 infection. The disease spread mechanism also has a higher degree of uncertainty. The current data is mostly based on the information of previous coronavirus infections including SARS-CoV and MERS-CoV which are transmitted from one person to another by respiratory content [27]. Usually, viral infections are transmitted from one to another during the symptomatic phase. Despite that current evidence suggests that COVID-19 transmission also takes place in the asymptomatic incubation phase of the virus which supposed between one to fourteen days [27, 28, 29]. As per various regulatory bodies, the community transmission or disease spread takes place in four stages (Fig. 5). When the infection is only found in individuals recently traveled from foreign countries or in imported cases, it is known as stage I. No community transmission is observed at stage I; hence it is easily controllable with proper preventive measures. At stage II community transmission takes by direct contact of a healthy individual with a person traveling the foreign country and carry the infection. The transmission mostly takes place in the family member or friend who came directly in contact with the primary infected person. At this stage, the primary source of transmission can be easily identified. Further, stage III is considered an advanced stage of disease transmission which is difficult to control. At this stage, community transmission takes place to a greater extent while the source of infection can’t be located and isolated. When community transmission gets started, the disease will spread faster and affect the bulk population. Stage IV is a very dreadful condition. A massive transmission among a cluster of the population is seen at this stage which is very difficult to control and treat. It is an epidemic condition for the affected country where the disease spread seems uncontrollable [30].

Once a person gets exposed to SARS-CoV-2, the disease progression can be understood in five categories based on the clinical symptoms and disease pathophysiology (Fig. 6). The period just after exposure to the
infection is known as the ‘asymptomatic phase’ or ‘incubation period’. This phase lasts from three to fourteen days which can be managed by keeping the infected person on isolation and observation. It is characterized by nasopharyngeal replication of viral strain with no significant clinical symptom. The second phase is ‘symptomatic’ or ‘prodromal stage’, which lasts up to seven days. The clinical symptoms include cough, fever, sore throat, myalgia, diarrhoea, vomiting, abdominal pain, etc. but no evidence of pneumonia [31]. The viral pathophysiology involves nasopharyngeal replication and ACE2 receptor binding. At this stage, the patients will be kept under observation and usually treated with chloroquine or hydroxychloroquine. Most of the COVID-19 patients retain at this stage and do not progress into further pneumonia phase. The third phase is ‘pneumonia’, usually appears from day eight of the symptomatic phase and lasts up to day ten. The viral pathophysiology is the same as the second phase and clinical symptoms include recurrent or persistent fever, cough, dyspnoea, CRP and reduced ALC. Usually, hydroxychloroquine is given at this stage but lopinavir and ritonavir are added to the dosage regimen when symptoms are progressive. Further, stage four is the advanced stage of pneumonia which also includes hypoxia along with the previous symptoms. It is also a phase of clinical deterioration featured with hypoxia, shortness of breath, progressive exertional dyspnoea, increased CRP, decreased ALC along with higher RR and lower SPO2 concentration. This phase can also be treated with hydroxychloroquine and lopinavir/ritonavir therapy. The last stage is the ‘immunological stage’ where the patients are critically ill and experience shock along with ARDS and MRF. The pathophysiology involves the cytokine storm with excessive interleukin and TH2 content in plasma. Chloroquine, hydroxychloroquine, lopinavir/ritonavir, ribavirin/interferon β and immunomodulators like IVIG, steroids, tocilizumab, etc. are preferred at this stage. The mortality rate is very high at this stage. Most of the COVID-19 related deaths are observed at the immunological stage only [32].

4. Pathophysiology

Usually, CoV is considered as a large (80–160 nm), non-segmented, enveloped, ssRNA viruses. However, SARS-CoV-2 differs from the already known CoV because of the presence of nucleocapsid protein and membrane protein-like spike glycoprotein (S-glycoprotein), which is responsible for a crown or spike-like structure at the outer membrane [33]. There are two subunits of S-glycoprotein, namely S1 and S2, from which S1 assists the entry of SARS-CoV-2 to the host cell by direct interaction with hACE (human angiotensin-converting enzyme-2) receptor [34]. The high pathogenicity and spread of SARS-CoV-2 may be attributed to the presence of modified RBD (receptor binding domain) of the S1 subunit, partially opened ‘S’ trimer and polybasic cleavage site (RRAR). Type-2 pneumocytes of the human lungs are decorated with hACE2 receptors. The receptor-binding domain of the S1 subunit of the spike glycoprotein tends to interact with the hACE2 receptor of pneumocyte 2 cells and results in the progressive suppression of the hACE2 receptor [35]. This downregulation of the hACE2 receptor facilitates the production of AT2 (angiotensin-2). Further, the increased AT-2 concentration which causes lung injury by increasing the permeability of pulmonary vasculature. Together, the APC (antigen-presenting cell) of SARS-CoV-2 binds to the host dendritic cells, and promotes the activation of macrophages and releases pro-inflammatory cytokines (different interleukins like IL-1β, IL-12, IL-18, IL-33 and interferons like IFN α and γ along with tumor necrosis factor (TNF-α) and tumor growth factor (TGF-β)) and chemokines (CCL-2, 3, 5 and CXCL-8, 9, 10). The macrophages and inflammatory mediators engender severe and extensive immunological reactions, which is termed as ‘cytokine storm.’ Such fierce inflammatory responses are considered as the primary pathophysiology of SARS-CoV-2 infection, which causes damage to the epithelial cell lining of lungs and other organs of the body by reaching to the blood circulation [35,36]. The pathophysiology of COVID-19 is graphically presented in Fig. 7.

Fig. 6. Phases of disease progression, pathophysiology, clinical symptoms, and management approaches.
5. Clinical features and diagnosis

Clinically COVID-19 is primarily characterized by fever, dry cough and fatigue, while other associated symptoms are vomiting, diarrhea, myalgia, dyspnea, headache, hemoptyis, etc. A person with multiple comorbidities, any disease condition, weaken the immune system, kidney disease/injuries and ARDS (Acute Respiratory Distress Syndrome) are prone to the infection [37, 38]. Various regulatory bodies like WHO and CDC (Centre for Disease Control and Prevention) issued guidelines for clinical and epidemiological investigations related to COVID-19 infection [39].

COVID-19 has an average incubation period of 5–6 days, after which the symptoms arose in the infected person [40]. After the onset of the symptoms, the diseased period to death may range from 6 to 41 days with an average of 14 days of survival [41]. The period of diseased phase depends upon the physiological condition, age and immune response of the patient. It becomes more severe and lethal in pediatric and geriatric patients and the person with lower immunity due to any other diseased condition like a cancer patient, patient with kidney injury, etc. [41]. The clinical symptoms of COVID-19 by chest CT scan indicates pneumonia. On the other hand, RNAemia, acute cardiac injury, ARDS and ground-glass opacity increases the severity of disease and led to death. The inflammation increases due to hyperactivation of both local and systemic immune responses which was observed when both the lungs get affected with multiple ground-glass opacity due to infection [42]. Unfortunately, in some cases, treatment with inhalable interferons doesn’t show any clinical effect and even worsens the condition and disease progression [43]. The symptoms at every stage of the disease progression are shown in Fig. 6. The primary symptoms of COVID-19 are similar to other beta coronavirus symptoms, including dry cough, dyspnea, fever and bilateral ground-glass opacity [38]. Unlike the previous coronavirus, COVID-19 affects the lower airways instead of the upper respiratory tract and hence, sneezing, rhinorrhea doesn’t indicate the COVID-19 [44, 45]. In addition, the COVID-19 patient also experiences some GI symptoms such as diarrhea which was not common in SARS-CoV or MERS-CoV. Thus, urine and fecal sample tests are also essential to confirm infection [42, 46].

The containment of disease spread and mortality rate without rapid and pervasive screening is been intricate for any government of this world. Hence, a prompt, effective and immense diagnosis of each and
Affordable test kits that produce quick responses, trained health care for SARS-CoV-2, a summary of which is shown in Table 1. Also detail of are working on the development of a quick and effective diagnostic tool ill cases. Sometimes repetitive tests are desirable if it gives negative sensitivity and accuracy of the RT-PCR assay are indecisive in critically choalveolar lavage is also a good option for diagnosis [51] but bron

[49]. However, strict precautionary measures are advised to avoid exposure to airborne contamination [50]. The analysis of bron

[48, 49]. RT-PCR assay is provided with emergency care and treatment [48, 49]. RT-PCR assay is

symptoms and individual diagnosed with pneumonia or severe acute respiratory illness. All these persons should be kept in quarantine and provided with emergency care and treatment [48,49]. RT-PCR assay is the prime technique for the SARS-CoV-2 diagnosis. Along with this, a sample taken from the lower respiratory tract like endotracheal aspirates and sputum is also recommended by WHO for diagnostic purposes [49]. However, strict precautionary measures are advised to avoid exposure to airborne contamination [50]. The analysis of bronchial lavage is also a good option for diagnosis [51] but bronchoscopy is usually avoided to protect the healthcare workers [52]. The sensitivity and accuracy of the RT-PCR assay are indecisive in critically ill cases. Sometimes repetitive tests are desirable if it gives negative results for suspicious patients [2,48,53]. Currently, different pharmaceutical and biotechnological companies and many research institutions are working on the development of a quick and effective diagnostic tool for SARS-CoV-2, a summary of which is shown in Table 1. Also a detail of initiatives taken by different Indian companies towards the development of COVID-19 testing kit or diagnostic tools is given in supplementary file 2.

6. In-line therapies and repurposed medicines

6.1. Repurposed medicines

Health care professionals and physicians throughout the world are trying some of the already existing drug molecules against COVID-19. Various FDA approved drugs previously intended for other pathophysiological conditions like antimalarial drugs (chloroquine, hydroxychloroquine), antiviral drugs (remdesivir, favipiravir, penciclovir, ribavirin, lopinavir), anticoagulant (nafamostat), antiprotozoal drug (nitazoxanide), antibiotic (teicoplanin), health-promoting agent (melatonin) and some immunosuppressant, etc. have been tested to treat COVID-19 (Table 2). These medicines resulted in positive response in some cases however, also fails sometimes depending upon the patient’s physiological condition, dosage regimen, and many other factors. A basic introduction of individual drugs, developmental aspects, and physiological condition, dosage regimen, and many other factors. A basic introduction of individual drugs, developmental aspects, and relevance of some frequently used active molecules in COVID-19 ther

apt are discussed in this section and also showed in Fig. 8.

6.1.1. Chloroquine and hydroxychloroquine

Chloroquine is a common antimalarial agent currently found effective in the treatment of the patients affected with COVID-19 [77]. Previous experiments proved its efficacy as an antiviral drug based on which it is presently explored for the treatment of COVID-19 infection. Both the phosphate and sulfate salt forms of chloroquine along with hydroxychloroquine are widely used for the treatment of malaria and also for some autoimmune disorders like rheumatoid arthritis, lupus,

Table 1

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<td>CE Mark</td>
</tr>
<tr>
<td>27</td>
<td>VIASURE SARS-CoV-2 Real-Time PCR</td>
<td>PCR</td>
<td>3</td>
<td>CerTest Biotech, BD</td>
<td>CE Mark</td>
</tr>
<tr>
<td>28</td>
<td>Logix Smart Coronavirus COVID-19 Test</td>
<td>PCR</td>
<td>1-2</td>
<td>Co-Diagnostics</td>
<td>CE Mark</td>
</tr>
<tr>
<td>29</td>
<td>VinaPCR SARS-CoV-2 Assay</td>
<td>PCR-PoC</td>
<td>&lt;1</td>
<td>Credo Diagnostics Biomedical</td>
<td>CE Mark</td>
</tr>
<tr>
<td>30</td>
<td>qCOVID-19, CLART COVID-19</td>
<td>PCR</td>
<td>5</td>
<td>Genomics/PharmMar Group</td>
<td>CE Mark</td>
</tr>
<tr>
<td>31</td>
<td>2019 Real-Time PCR Kit</td>
<td>PCR</td>
<td>4-6</td>
<td>Kogene Biotech</td>
<td>CE Mark</td>
</tr>
<tr>
<td>32</td>
<td>GeneFinder COVID-19 RealAmp Kit</td>
<td>PCR</td>
<td>4-6</td>
<td>OsangHealthcare</td>
<td>CE Mark</td>
</tr>
<tr>
<td>33</td>
<td>QIAstat-Dx Respiratory SARS-CoV-2 Panel</td>
<td>PCR</td>
<td>1</td>
<td>Qiagen (acq. by thermo Fisher)</td>
<td>CE Mark</td>
</tr>
<tr>
<td>34</td>
<td>Allplex 2019-nCoV Assay</td>
<td>PCR</td>
<td>4</td>
<td>Seegene</td>
<td>CE Mark</td>
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<tr>
<td>35</td>
<td>DiaPlexQ 2019-nCoV Detection kit</td>
<td>PCR</td>
<td>2</td>
<td>SolGent</td>
<td>CE Mark</td>
</tr>
<tr>
<td>36</td>
<td>SARS-CoV-2 Clinical Sequencing assay</td>
<td>NGS</td>
<td>&gt;12</td>
<td>Vision Medicals</td>
<td>CE Mark</td>
</tr>
<tr>
<td>37</td>
<td>Multiple Real-Time PCR Kit</td>
<td>PCR</td>
<td>4-6</td>
<td>Beijing Applied Biological Technologies (XABT)</td>
<td>CE Mark</td>
</tr>
<tr>
<td>38</td>
<td>Explify Respiratory</td>
<td>NGS</td>
<td>24-48</td>
<td>iDbyDNA</td>
<td>LDT</td>
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<tr>
<td>39</td>
<td>COVID-19 Home Test Kits</td>
<td>PCR</td>
<td>72-144</td>
<td>Carbon Health</td>
<td>Discontinued</td>
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<tr>
<td>40</td>
<td>At-home COVID-19 test</td>
<td>PCR</td>
<td>48</td>
<td>Everlywell</td>
<td>Discontinued</td>
</tr>
<tr>
<td>41</td>
<td>COVID-19 Home Test Kit</td>
<td>PCR</td>
<td>48</td>
<td>Nuru, Molecular Testing Labs</td>
<td>Discontinued</td>
</tr>
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</table>
Table 2
Current research and development towards the treatment of COVID-19 highlighting various drug molecules currently preferred or recommended by physicians or researchers against SARS-CoV-2 infection.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Therapeutic agents</th>
<th>Category</th>
<th>Indication</th>
<th>Development history</th>
<th>Available dosage form</th>
<th>Side effects</th>
<th>Clinical status against COVID-19</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
<td>Antimalarial</td>
<td>Malaria, Pneumonia, some viral infections and autoimmune disorders like rheumatoid arthritis, lupus, etc.</td>
<td>Discovered in 1934 by Hans Anderson and the team. Approved for clinical practices in 1947 for malaria treatment</td>
<td>A salt form like phosphate, sulfate &amp; hydrochloride available as an oral tablet</td>
<td>Blurred vision, nausea, vomiting, blurred vision, uncontrolled movements, deafness, headache, diarrhea, mood changes, sore throat, itchiness, etc.</td>
<td>Overdose cause chloroquine poisoning which may lead to cardiac arrest</td>
<td>Found effective in COVID-19 associated pneumonia and other symptoms Currently under clinical trial</td>
<td>[54-56]</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Antimalarial</td>
<td>Malaria and autoimmune disorder like rheumatoid arthritis, lupus erythematosus</td>
<td>Firstly, synthesized in 1934 and approved in 1955 by USFDA</td>
<td>Oral tablets</td>
<td>Nausea, vomiting, diarrhea, headache, reduced appetite, retinopathy, heart problems, etc.</td>
<td>Overdose may lead to heart failure</td>
<td>Effective in preliminary investigations against COVID-19</td>
<td>[57,58]</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>Antiviral (nucleoside analog)</td>
<td>Ebola, Marburg &amp; other viral infections</td>
<td>Developed by Gilead Sciences Designated as an orphan drug in Europe by Gilead</td>
<td>Intravenous injection</td>
<td>Nausea, Vomiting</td>
<td>Improvement of in vitro and in vivo SARS-CoV-2 model</td>
<td>Under phase III clinical trial by Gilead Sciences</td>
<td>[59,60]</td>
</tr>
<tr>
<td>Favipiravir</td>
<td>Antiviral (RNA polymerase inhibitor)</td>
<td>Influenza, also effective against Ebola infection</td>
<td>Developed by Toyama Chemicals, Japan, approved for clinical application in 2014 in Japan</td>
<td>Oral Tablet</td>
<td>Nausea, Vomiting, Sore throat</td>
<td></td>
<td>Effective in preliminary investigations against COVID-19</td>
<td>[61]; Mak, 10-03-2020; Xinhua, 17-03-2020)</td>
</tr>
<tr>
<td>Penciclovir</td>
<td>Antiviral (DNA polymerase inhibitor)/guanosine analog</td>
<td>Herpes virus disease</td>
<td>Launched in 2017 by Fujifilm Toyama Chemical</td>
<td>Topical (cream)</td>
<td>Headache, nausea, dyspepsia, increased serum lipase, abdominal pain, hyperbilirubinemia &amp; dizziness</td>
<td></td>
<td>No satisfactory response in in vitro SARS-CoV-2 model, Under investigation</td>
<td>[62,63]</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Antiviral (nucleoside analog)</td>
<td>hepatitis C, human orthopneumovirus and other hemorrhagic viral fevers including hantavirus, Lassa fever, and Crimean-Congo hemorrhagic fever</td>
<td>Patented in 1971 and approved 1986 for commercial use, launched by Valeant (now known as Rausch Health) as an inhalable powder dosage, 1999, it is manufactured as an oral capsule in combination with interferon α-2b by Schering-Plough (now known as Merck &amp; Co.)</td>
<td>Powder for inhalation and Oral capsule</td>
<td>Nausea, headache, muscle pain, fever, etc. RBC breakdown, allergic reactions and liver damage prohibited in pregnancy</td>
<td></td>
<td>Effective against COVID-19 in the preliminary investigation along with other drugs, Currently under clinical trial</td>
<td>[64,65,66]</td>
</tr>
<tr>
<td>Lopinavir-ritonavir</td>
<td>Antiretroviral (protease inhibitor) &amp; immune booster</td>
<td>HIV infection</td>
<td>Approved for clinical application by USFDA in 2000</td>
<td>Available as an oral capsule and oral solution</td>
<td>Headache, vomiting, abdominal pain, diarrhea, rash, hyperlipidemia, ischemic heart disease, etc.</td>
<td></td>
<td>Effective COVID-19 associated pneumonia, Under clinical investigation</td>
<td>[67,68]</td>
</tr>
<tr>
<td>Nafamostat mesylate</td>
<td>Anticoagulant (Serine protease inhibitor)</td>
<td>Cystic fibrosis</td>
<td>Launched in 1986 by y Tordil, Designated as Orphan drug by Mucokinetics in European Union in 2010</td>
<td>Intravenous injection</td>
<td></td>
<td></td>
<td>No significant improvement in in vitro SARS-CoV-2 model, currently under investigation</td>
<td>[69,69]</td>
</tr>
<tr>
<td>Nitazoxanide</td>
<td>Antiprotozoal</td>
<td>Diarrhea and other protozoal infections, Hepatitis C</td>
<td>Firstly introduced by Romark in 1996 for oral administration to</td>
<td>Currently marketed as an oral tablet and suspension as a licensed product</td>
<td>Headache, upset stomach, stomach pain, vomiting, skin rash, fever, itching, discoloration, etc.</td>
<td></td>
<td>Found effective against COVID-19 in in vitro study,</td>
<td>[70]; 2016 [60];</td>
</tr>
</tbody>
</table>

(continued on next page)
etc. These drugs show very mild adverse effects and hence considered a safer option for the aforementioned situations. Although there is a very narrow margin between the toxic and therapeutic dosage of the drug and the toxic dose results in chloroquine poisoning which may cause cardiac arrest led to death [78]. Hence, strict regulations are given for the use of chloroquine and self-medication is forbidden.

The in vitro antiviral potency of chloroquine has firstly been identified in the late 1960s [79]. Both the drugs, chloroquine and hydroxychloroquine significantly inhibits the growth of various virus species in the in vitro cell culture, including SARS coronavirus [80]. Further, investigations in mice model confirm its efficacy in numerous other viruses species like human coronavirus OC43 [81], zika virus [82], enterovirus EV-A71 [83], and influenza virus A H5N1 [84]. However, a randomized, double-blind, placebo-controlled clinical trial study
showed no effect in the treatment of influenza infection [85] and dengue patients in a clinical trial in Vietnam [86]. An ex vivo study indicates its activity in ebolavirus in mice model [87], influenza [88] and Nipah [89] in Ferrets. Various other preclinical studies indicate the efficacy of chloroquine in chikungunya and other viral infections [90,91] but in further clinical trials, no successful results were yet reported in acute viral infections in human being.

The drug was also tested for chronic viral diseases such as HIV and hepatitis C. No significant effect was observed in HIV therapy while only modest activity in treating hepatitis C. However, the activity was not sufficient to include the chloroquine into a standard therapeutic regimen of HIV and hepatitis C infection [92,93,94].

Upon the outbreak of COVID-19, based on the previous research data, scientists and researchers evaluated various existing FDA approved antiviral agents for their efficacy in SARS-CoV-2. In this sequence, Wang and his team studied two wide-spectrum antiviral agents and five different FDA approved drugs on clinically isolated SARS-CoV-2. They concluded that chloroquine effectively controls COVID-19 infection in vitro and based on its lower side effects and higher safety records it was assessed in individuals suffering from COVID-19 [60]. In past few weeks, many clinical trials have been registered in Chinese Clinical Trial Registry till February 23, 2020, in order to assess the safety and efficacy of chloroquine in the treatment of coronavirus. FDA released a clear statement after the briefings of US President that there are no FDA approved drug or therapy for treating COVID-19. The trial resulted, no reduction in the fatality of the patients 

Currently, it is used to treat COVID-19 patients owing to the anti-inflammatory and antiviral activity [95].

The available data represents chloroquine as the first successful therapeutically active agent for treating SARS-CoV-2 [78]. On the basis of various studies and trials, the President of USA announced during White house briefing on March 20, 2020, chloroquine as the first FDA approved drug for the treatment of COVID-19 with very encouraging results. However, as per the latest report of Fact First by CNN Politics, Washington, FDA has not approved chloroquine or any other drug for the treatment of coronavirus. FDA released a clear statement after the briefing of US President that “there are no FDA approved drug or therapies to cure COVID-19.” Although, chloroquine already has approval for other indications and the physicians are legally permitted to use it in the off-label or unapproved form to treat symptoms of coronavirus. Currently, the FDA can’t produce any statement regarding the safety and efficacy of the drug against coronavirus. Dr. Hahn (Commissioner FDA) in a post-briefing session of President Trump said that “the drug will be investigated in COVID-19 patients by a large pragmatic clinical trial.” Further, the studies are underway to generate sufficient proof for the safety and efficiency of the drug [97].

Hydroxychloroquine is a hydroxylated derivative of chloroquine, firstly synthesized in 1946 and reported 40% less toxicity in animal models than chloroquine [98,99]. Along with malaria, it also has wide applications in treatment of various autoimmune disorders like rheumatoid arthritis, systemic lupus erythematosus. Some scientists and physicians proposed the use of hydroxychloroquine as a promising candidate against SARS-CoV-2 infection owing to its similar chemical structure and mode of action like immunomodulation and pH modification, with chloroquine. In this aspect, around seven clinical trials were registered in the Chinese Clinical Trial Registry till February 23, 2020 for evaluating the efficacy of hydroxychloroquine against COVID-19. Liu et al. assessed the safety and efficacy of hydroxychloroquine in COVID-19 treatment using in vitro cell models and compared it with chloroquine performance [100]. As per the previous reports, both the drugs possess good pharmacokinetic profile i.e. good oral absorption and distribution and also found safe at the therapeutic dose [101]. The study also confirms the safety of hydroxychloroquine by cytotoxicity study. The drug also supposes to restrict viral replication by elevating the lysosomal and endosomal pH, necessary for maturation and function of viral endosome [102,103]. Along with the antiviral potency, it also supposes to mitigate the cytokine storm unleashed due to SARS-CoV-2 infection. The study of Liu and the team suggested that hydroxychloroquine lessen the SARS-CoV-2 infection and safer than chloroquine. Owing to a longer half-life and lesser toxicity hydroxychloroquine is considered a much safer and economic option in this pandemic situation. But still, sufficient clinical data and research evidence are needed to assure its applicability and safety in COVID-19 treatment [106].

Besides the aforementioned predictions about the success and safety of hydroxychloroquine against SARS-CoV-2 infection, some of the previous case studies and clinical data reported some toxicities or adverse effects due to prolonged administration or overdose of the drug. A case report by O’Laughlin et al. in 2016 reported severe life-threatening QT prolongation by hydroxychloroquine in systemic Lupus Erythematous (SLE) patients. They reported a case study of a 50-year-old lady who has a history of SLE from the past 20 years, ESRD (End-stage renal disease), atrial fibrillation was on hemodialysis and anticoagulation therapy and brought to the hospital upon a syncopal episode. The ECG showed a prolonged QT interval during the investigation. The medical history revealed she had been under hydroxychloroquine therapy for the past two years to treat SLE. A decrease in QT interval prolongation was observed after discontinuation of hydroxychloroquine therapy [104]. A similar adverse effect was also reported by [105] in a 41 years old African woman suffering from SLE, chronic kidney disease, hypertension and finally diagnosed with congestive heart failure [105]. Previously, another case reported QT prolongation in a 67 years old lady suffering from SLE and asthma and having hydroxychloroquine therapy from a longer period [106]. Such cases of adverse events call for a more exhaustive study on the safety and efficacy of hydroxychloroquine for COVID-19 treatment. Based on the positive results of preliminary investigations, FDA has issued an Early Use Authorization (EUA) in March 2020 for the use of hydroxychloroquine and chloroquine as the first line symptomatic treatment of COVID-19. Later on, various preliminary clinical trials reported no promising effect of these drugs against COVID-19 and hence, the agency has retreated the EUA [107]. Similarly, the WHO has announced a Solidarity Trial of hydroxychloroquine to treat COVID-19. The trial resulted, no reduction in the fatality of the COVID-19 patients under trial and hence further stopped the trial (WHO, 2020f).

6.1.2. Remdesivir

Remdesivir is a novel antiviral agent belongs to the category of nucleotide analog. It is a nucleoside derivative and RNA polymerase inhibitor developed by Gilead Sciences for the treatment of Ebola and Marburg viral infections [108]. It is reported as a spectrum antiviral drug found effective in various other acute viral infections caused by different single-stranded RNA viruses including the Junin virus, Nipah virus, respiratory syncytial virus, Hendra virus, Lassa fever virus and various coronavirus species like SARS and MERS viruses [109,110]. Based on the previous history of drug and positive effects on other coronaviruses, Gilead Sciences currently provided the samples of remdesivir to the medical professionals to treat the patients infected with SARS-CoV-2 in Snohomish County, Washington, USA [111,112] and also China to carry out some trials on the patients infected with COVID-19 [112,113].

Among different investigational drugs, remdesivir demonstrated significant inhibition of COVID-19 infection at lower molecular concentration, tested in the clinical isolate of in vitro cell culture model along with the in vivo mouse model [114,115]. Due to the preliminary
positive results, the whole world is looking towards Gilead Sciences for the treatment of COVID-19 with remdesivir. As per the latest report of Cory Renauer, three patients infected with COVID-19 were recently treated with Remdesivir with no negative effects [95]. However, safety is one major concern of the physician and researchers, as the patients were observed with significant GI symptoms and enhanced liver enzymes in the blood sample.

Cory’s report outlined a shallow view on the efficacy of Remdesivir based on preliminary investigations of the first 12 cases of COVID-19 in the US. Hence, it can’t be designated as a clinical trial and so, we are still not sure about the safety and efficacy of the drug [70]. At the same time, Gilead launched two different phase III clinical trials on patients infected with COVID-19 to generate sufficient proof of the efficacy of a drug in the treatment of this outbreak. The study is to be performed in 1000 patients to confirm the safety of Remdesivir [118]. By virtue of the efficacy of remdesivir, FDA has also issued EUA to the use of remdesivir to treat hospitalized patients of COVID-19 with severe conditions. However, it should not been given in combination with hydroxychloroquine sulfate or chloroquine phosphate, as such coadministration diminishes the antiviral potency of remdesivir. Although, the safety and efficacy of the drug is yet to be studied as the drug is not approved by FDA as therapy for COVID-19 [117].

6.1.3. Favipiravir

Favipiravir is a wide spectrum antiviral drug found effective against different life-threatening RNA virus infections. It is also termed as T-705, favilavir or Avigan, developed by Toyama Chemicals, Japan [118]. It is an RNA-directed RNA polymerase inhibitor that is effective against the influenza virus H1N1 [61]. The drug was firstly approved in 2014 in Japan for clinical application against influenza infection (Xinhua, 17-03-2020). Favipiravir has previously tested for human Ebola virus infection in 2014, during the Ebola virus outbreak in West Africa [119, 120].

The drug found to be effective against Ebola virus infection in the mouse model but similar results have not been observed in human Ebola infections [121]. As per the latest news report of Xinhua Net, China completed the clinical investigation on favipiravir which reported good therapeutic efficacy of the drug against COVID-19. Zhang Xinmin, the director of China National Centre for Biotechnology Development under the Ministry of Science and Technology stated that no significant adverse effect was observed in the clinical trial, hence it can be recommended for diagnosis and treatment of COVID-19 (Xinhua, 17-03-2020). Another report stated, Sihuan Pharmaceuticals Beijing conducted a clinical trial on Favipiravir used against COVID-19. Presently six clinical trials have been conducted in China to study its therapeutic efficacy in treating COVID-19 (Mak, 10-03-2020). The Sihuan Pharmaceuticals clinical trial involves 60 regular COVID-19 patients for a parallel dose exploration study for 10 days treatment (thepharmaletter, 02-03-2020).

6.1.4. Penciclovir

Penciclovir is a DNA polymerase inhibitor indicated for Herpes virus disease. It is a guanosine (nucleoside) analog having good selectivity and low toxicity profile. It is usually given for topical applications because of poor oral absorption [62].

The drug is commercially available as Denavir, fenvir, vectavir, and famciclovir (prodrug with improved oral absorption) [122]. In recent weeks, Xiaojun Liu’s team investigated various FDA approved antiviral drugs against clinically isolated COVID-19 cell culture models. The data showed no significant effect on inhibition of nCoV-19 and hence, it is still under investigation not approved for the treatment of COVID-19 [63].

6.1.5. Ribavirin

Ribavirin is a nucleoside analog also termed as tribavirin. It is an antiviral drug, commonly prescribed for hepatitis C, human orthopneumoviral infection and some other hemorrhagic viral fevers including hantavirus infection, Lassa fever, and Crimean-Congo hemorrhagic fever but not found effective in Marburg or Ebola viral infections. In hepatitis C, ribavirin is a part of the combined dosage regimen and given along with other medicines like sofosbuvir, simprevir, peginterferon α-2a and α-2b (Ribavirin, December 20, 2020; [123]. Apart from this, the drug also exerts significant side effects including nausea, headache, muscle pain, fever, etc. RBC breakdown, allergic reactions, and liver damage are some severe complications of ribavirin. It is also prohibited in pregnancy [124]. It is a guanosine analog which arrests the viral mRNA capping and RNA synthesis. It interrupts the RNA metabolism and hence stopped the viral growth [125]. It is an inosine-5’-monophosphate dehydrogenase enzyme inhibitor, patented in 1971 and approved 1986 for commercial use [126]. Ribavirin is included in WHO’s Essential Medicine list as a safe and effective medicine of essential in the health care system and provided as a generic medicine [127]. In 1986, it is launched by Valeant (now known as Bausch Health) as an inhalable powder dosage form to treat respiratory syncytial viral infection. Further, in 1999, ribavirin is manufactured as an oral capsule in combination with interferon α-2b by Schering-Plough (now known as Merck & Co.) for the treatment of hepatitis C [64].

A phase II clinical trial was conducted for its activity in metastatic breast cancer by Jewish General hospital. The study was terminated in 2015 without any conclusion [128]. A phase I clinical trial was registered by Behesht University to study the effect of ribavirin pediatric Crimean-Congo hemorrhagic fever. No recent updates are reported for this study [129]. ChronTech Pharma has conducted a preclinical study to test the potency of ribavirin to boost the immune response upon vaccine administration. No current development has been reported for this too [130]. A phase I/II clinical trials have also been carried out for the treatment of progressive metastatic prostate cancer in combination with docetaxel.

The drug is marketed as an oral tablet, capsule, oral solution and powder for nebulization. A tablet in combination with PEGinterferon α-2a is approved in Japan for commercial applications. Ribavirin in combination with PEGinterferon α-2a was also approved in Japan for the treatment of Hepatitis C [131]. In addition, injection for a week course in Japan and 24 weeks course in Europe in 2012 get approved for treating cirrhosis [132]. Currently, is licensed to Merck & Co. and also to Roche which was transferred to Chugai for manufacturing and development.

A team of Korean physicians (CPAM), having experience in the treatment of patients infected with previous SARS-CoV recommended the same dosage regimen for COIVD-19. They have recommended treatment of old age patients or patients with severe symptoms with a combination of antiviral drugs lopinavir, ritonavir and antimalarial drug, chloroquine. Ribavirin and interferon are recommended only when the above-mentioned therapy is not effective. Ribavirin is not considered as first-line treatment because of various side effects [95, 133]. Molecular docking on the SARS-CoV-2 RDRP model (RNA dependent RNA polymerase) demonstrated close binding of ribavirin and sofosbuvir with coronavirus RDRP. This result suggests the possible effect of sofosbuvir and ribavirin in the treatment of COVID-19 [65, 134]. Clinical trials on patients during previous SARS-CoV and MERS-CoV outbreaks use ribavirin in combination with a variety of drugs showed negative effects on the patients [135-137]. In a recent study by Zhou et al. (March 9, 2020), the patients were given antiviral, antibacterial, corticosteroid and other medicines followed by ribavirin. No improvements were observed in the initial 10 days thus, corticosteroid was stopped and ribavirin was continued with other medicines for further 14 days. Symptoms were improved in the next 25 days and infection found negative on the 30th day. However, the treatment regimen is still not confirmed and hence further clinical studies are needed to establish the facts [66].
6.1.6. Lopinavir-Ritonavir

Lopinavir and ritonavir are antiretroviral drugs belong to the category of protease inhibitor. Both drugs are used in a fixed-dose combination to treat HIV infection. Lopinavir/ritonavir got USFDA approval in the year 2000 for clinical application as an oral capsule and solution (manufactured and marketed by Abbott Laboratories) [68]. The combination of both the drug effectively reduces the HIV infection and boost-up the immune system of the body. The combined drug therapy only reduces the chances of further spread of the disease instead of curing the infection [138]; WebMD). The drugs were also used in the treatment of SARS-CoV [139] and MERS-CoV infections [140]. Ritonavir improves the plasma concentration of lopinavir by inhibiting CYP3A mediated metabolism. Based on the antiviral efficacy of lopinavir/ritonavir, combined drug therapy is also tested, COVID-19 patients. No in vitro studies were reported to date (April 21, 2020) for the efficacy of lopinavir/ritonavir against COVID-19 [1]. However, Considerable improvements in COVID-19 associated pneumonia symptoms were observed in three of four COVID-19 patients under lopinavir/ritonavir therapy (Wang et al., 2020e). As per the report of the Moscow City Health Department published on March 25, 2020, Russian doctors recommended lopinavir/ritonavir for treating mild COVID-19 [141]. Some of the clinical trials are also registered in the U.S. clinical trial and Chinese clinical trial register. On the other hand, a study by [67] reported no significant change in COVID-19 patients even after 14 days of treatment with these combined drug therapy [67]. Similar to hydroxychloroquine, WHO also revoked the solidarity trial of lopinavir/ritonavir in hospitalized patients of COVID-19 due to very minimum or no effect on the mortality of the patients in comparison with the standard care (WHO, 2020g).

6.1.7. Nafamostat mesylate

Nafamostat mesylate is a serine protease inhibitor, popularly used as an anticoagulant. It is a fast-acting, synthetic, proteolytic inhibitor that averts the proteolysis of fibrinogen to fibrin during hemodialysis [69]. It received Orphan drug designation by Mucokinetica in European Union and was indicated for the treatment of cystic fibrosis [142]. Nafamostat reduces the cathepsin B release and thus prevents membrane fusion. Attributed to these mechanisms it is currently tested for antiviral efficacy against influenza, Ebola and MERS-CoV [143,144]. [51] estimated the antiviral activity of five different FDA-approved drugs including nafamostat in clinically isolated in vitro COVID-19 culture. The study suggested nafamostat potentially inhibits MERS-CoV and also demonstrated inhibitive action against COVID-19 infection [115].

6.1.8. Nitazoxanide

Nitazoxanide is an antiprotozoal drug indicated for diarrhea and other protozoal infections. It also possesses antiviral activity against a wide range of viral species including animal and human coronaviruses [115]. The possible mechanism behind the anti-protozoal activity is the interference of PFOR (pyruvate ferredoxin oxidoreductase enzyme) dependent electron transfer which is essential energy metabolism for anaerobic organisms. In combination with pyruvate synthase inhibition, the drug also possesses hemagglutinin inhibition (in virus), c-Myc (Myc Proto-Oncogene Protein) inhibition, PI3/A3 (Protein Disulfide-Isomerase A3) inhibition activity. The cellular mechanisms involve signal transduction modulation, viral fusion and viral maturation inhibition [145].

Nitazoxanide was firstly introduced by Romark in 1996 for oral administration to treat pediatric diarrhea. Initially, it was intended for children less than 11 years, later the drug was indicated also for the patient above 12 years of age [70]. It is currently marketed as an oral tablet and suspension as a licensed product by Cardinal Health [146]. Various clinical studies have been conducted to assess the efficiency of nitazoxanide in treating different viruses and protozoa originated diseases. Another phase II/III clinical trials are ongoing to study the efficacy of oral dosage in hepatitis C infection and also for clostridium associated diarrhea (Kohla, September 9, 2010). Romark is performing a phase II/III clinical study to evaluate its efficacy in acute influenza infection [147]. In addition, Cornell University is underway to phase II clinical study to treat pulmonary tuberculosis [148].

However, Genfit is in the process of phase II clinical trial to assess its activity in fibrosis induced by non-alcoholic steatohepatitis (NASH). In 2009, Romark granted Chugai pharmaceuticals received license for manufacturing and distribution of oral formulation of nitazoxanide in Japan to treat hepatitis C. Further, in 2013, Romark issued exclusive rights to Lupin for the promotion, marketing, and distribution of oral suspension Alina (R) in the United States to treat diarrhea in the patient of 1 year age and older [149]. Based on the previous clinical records and ongoing clinical trials towards the treatment of acute viral infections, nitazoxanide is currently explored by the scientists to treat COVID-19 outbreak. An in vitro study by [51] demonstrated that nitazoxanide has effectively inhibited COVID-19 at low molecular concentration. They proposed further in vivo evaluation to confirm the activity of this drug against COVID-19 [115]. Presently, nitazoxanide is approved for the treatment of diarrhea and hepatitis C while under investigation for human and animal coronavirus [70,150,151].

6.1.9. Teicoplanin

Another positive hope in COVID-19 treatment was observed with glycopeptide antibiotics, teicoplanin which actively inhibits the SARS-CoV infection in vitro [152]. The drug is eventually prescribed for gram +ve bacterial infections specifically the infection caused by Staphylococcal strain. It is also found effective in the treatment of different viral infections like influenza, Ebola, Hepatitis C, flaviviral infection, HIV and different coronavirus including SARS-CoV and MERS-CoV [153,154]. The activity of teicoplanin in the treatment of MERS-CoV has already patented in 2016 [154]. Studies stated that the teicoplanin act at the initial stages of the viral life cycle. It averts the release of genomic viral RNA and thus the viral replication by inhibiting the cleavage of viral spike protein by reducing endosomal pH [154]. It is supposed that the drug reproduces a similar activity on SARS-CoV-2 as the virus contains similar cathepsin L among the spike protein which is a probable target for teicoplanin [152]. The study by Alexandra et al. on the in vitro SARS-CoV-2 model demonstrated IC50 (concentration of drug required to inhibit 50% of the virus) of teicoplanin was found 1.66 μM which is much lesser than the concentration in human blood (8.78 μM) [155]. These are very preliminary investigations and hypothesis based on the previous history. However, further investigations and clinical trials are essential to evaluate the antiviral activity and safety of teicoplanin in COVID-19 treatment.

6.1.10. Melatonin

Melatonin is a bioactive agent with a lot of health-promoting properties. It is also found effective in radiation, bacteria or virus-induced acute respiratory syndrome [156]. Based on the evidence, it is supposed to show some positive effects in the treatment of COVID-19 induced acute lung injury, acute respiratory distress syndrome, and pneumonia. Melatonin does not have any viricidal property but owing to anti-oxidant, anti-inflammatory, and immune-enhancing activity, it exerts anti-viral effect [157]. Some studies on the anti-inflammatory, antioxidant, immunomodulating effect and attenuation of higher cytokine levels support the hypothesis of melatonin activity and safety against COVID-19 infection. However, no such evidence or scientific findings are reported [158].

Here, we have discussed some of the most explored drugs, currently under investigation to eradicate the SARS-CoV-2 infection. Apart from the preceding molecules, some other therapeutic candidates have been investigated for the treatment of COVID-19 [47]. Ivermectin is one such molecule that was also tested by a group of Australian researchers. They have investigated the efficacy of ivermectin in impeding the replication of the SARS-CoV-2 virus through an in vitro study [159]. Ivermectin is an FDA approved drug for the treatment of various parasitic infections. It is also included in the list of FDA essential medicines which assures the
wide availability and safety profile of the drug [160,161,162]. They have evaluated the anti-viral efficacy of the drug in the Vero/hSLAM cell culture model by using SARS-CoV-2 isolate. The study depicted that the drug can reduce the replication of viral RNA more than 5000 folds within 48 h while no further reduction was observed in the next 72 h. This study generates proof in support of the anti-viral activity of ivermectin [159]. However, this is only one investigation of its kind and hence, furthermore, studies are warranted to establish its efficiency against COVID-19. List of all the drug candidates currently under clinical investigation and their development status is given in Table 3.

### 6.3. Interferons and antibodies

Interferons broadly belong to the class of cytokines. These are signaling proteins, usually produced by the infected host cell to communicate a signal to the neighboring cells to boost up the immune system and heighten the defense mechanism against the virus or pathogen [165]. A promising antiviral therapy is highly desirable in this pandemic situation to exacerbate the SARS-CoV-2 virus. Among different investigational approaches, IFN-1 (Interferon type-I) supposed to be a potential option because of its unspecific antiviral efficacy [95, 166]. The IFN-1 is currently under investigation to evaluate its antiviral potency against COVID-19 [167,168]. IFN-1 is the first cytokine released a viral infected cell. The IFN-1 interacts with the IFNAR receptor on the plasma membrane of other cells and activate ISG (interferon stimulating gene). This ISG triggers the inflammatory reactions and adaptive immunity to interfering with viral replication and slow down the spread to eradicate the disease [169]. Owing to the immunomodulatory effects, IFN-1 is used in various viral infections and other diseases like multiple sclerosis [170]. It is also found effective in SARS and MERS infections [171] in various *in vitro* or *in vivo* studies either in combination or not with many other drugs including ribavirin [166,172], lopinavir-ritonavir [173,174], corticosteroid, remdesivir [136], etc. Based on the previous experimental data, IFN-1 is tested against SARS-CoV-2. An *in vitro* study displayed a sensitivity of SARS-CoV-2 for IFN-1 [175]. However, it cannot suppress viral replication. IFN-1 found more effective in SARS-CoV-2 than SARS-CoV. Another study showed IFNα2a can reduce the rate of infection of SARS-CoV-2 [176]. These studies provided the shreds of evidence that IFN could be a safe and effective option for COVID-19 treatment. However, proper clinical studies are essential to assuring its safety and efficacy [177].
6.4. Vaccines

Now in August 2020, its been more than seven months of COVID-19 outbreak and still no significant diminution is observed due to the prolonged incubation period of SARS-CoV-2, frequent dissemination and propagation and scarcity of potential treatment line and vaccines [178]. The development of an effective vaccine is an essential need as vaccination is the only way to protect the human being from getting sick. More than 160 vaccine candidates by different pharma industries and research institutions are currently in the race to discover a COVID-19 vaccine among which approximately 140 candidates are in the preliminary stage of development while more than 20 are under human trials. The vaccine candidates currently in phase I to III clinical trials are reported in Table 4. Moderna Therapeutics, Boston, is a first biotech firm producing a COVID-19 vaccine and currently going to perform a human trial to evaluate its safety and efficacy [179]. These exceptionally fast research outcomes are because of the early efforts of Chinese scientists to identify and define the genetic sequencing and structure of SARS-CoV-2 and sharing the details with the rest of the world [47]. A well-defined genetic sequence of the virus allowed in vitro culture of viral strain and facilitates the study of its pathophysiology. These preliminary scientific data promote the vaccine and drug development against COVID-19. In February 2020, CEPI (Coalition for Epidemic Preparedness Innovation) and World bank took an initiative to fund the vaccine development for COVID-19 and also launched a Vaccine Development Taskforce which makes strategies for finance and manufacturing the vaccines for global application [180]. The vaccine is a global need and a fair distribution of the available resources is also essential. Unlike the 2009H1N1 pandemic, the supply must not be monopolized by the high-income group or the developed countries. There should be an adequate distribution among the global population which should further prioritize as per the need and severity of the condition [181,182]. G7 also committed to supporting the joint research project for treatment and vaccination development for COVID-19 on March 16, 2020 (Yamey et al.). After all such initiatives and efforts, development and launching of the COVID-19 vaccine for public use will surely take a minimum of 12–18 months period. The industrial scale-up of the laboratory technique is a prime challenge for the researchers. Even after product approval, bulk production to meet the public demand will also be a major challenge [179].

Impact of BCG vaccination policy of disease spread rate.

It seems that COVID-19 has varying impacts on different countries which may be because of different environmental conditions, healthcare facilities, cultural norms and mitigation efforts. After the outbreak in Wuhan, China, the pandemic quickly spread all over the world. However, in some of the countries, COVID-19 behaves differently in terms of the spread and mortality rate. Like Italy, Spain, France other European countries, the United nation, etc. has to struggle more even after taking strict measures and having world-class health facilities to control COVID-19. These nations are presently at a very crucial stage with the highest number of infected population and mortality rate. On the other hand, Japan, India and many developing nations with similar preventive measures have better control over disease spread and lesser mortality rate than others (WHO, 2020e). Based on such statistics, experts come out with a hypothesis that India, Japan, and other countries who followed a universal policy of BCG vaccination in newborns have a population with already ‘trained immunity’ [183]. While the developed nations discontinued the universal BCG vaccination policy due to the lower risk of M. Bovis infection. BCG vaccines demonstrate a protective action to respiratory tract infection. A comparative analysis of morbidity and mortality rates of different countries, it was observed that countries with long term universal BCG vaccination policy have the lesser infected population, lower mortality and better control over disease spread than the countries without proper BCG vaccination policy. So, it is expected that BCG vaccination reduces the mortality and morbidity rate of COVID-19 while no significant proof or clinical data is available which showed the efficacy of the BCG vaccine in the treatment of COVID-19 [184].

7. Clinical studies

Along with the aforementioned therapeutics, various other drugs, vaccines, and bioactive are currently underway of clinical trials, based on their previous success history on SARS-CoV, MERS, Ebola, Hepatitis C, and other viral infections. Numerous institutions, research laboratories, hospitals and scientific fraternity including China, USA, European region and rest of the world are contentiously making efforts to find an effective solution of COVID-19 and save mankind. In this sequence, various clinical studies are registered in the past three months in different government agencies which are discussed in Table 5. Complete

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Detail of COVID-19 vaccines currently approved for clinical trials along with the respective agencies/companies/institutions (adapted from [132,158]).</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. N.</td>
<td>Vaccine</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------</td>
</tr>
<tr>
<td>1</td>
<td>AZD1222</td>
</tr>
<tr>
<td></td>
<td>mRNA-1273</td>
</tr>
<tr>
<td>2</td>
<td>Ad5-CoV</td>
</tr>
<tr>
<td>3</td>
<td>BNT162a1, b1, b2, c2</td>
</tr>
<tr>
<td></td>
<td>BNT162-CoV</td>
</tr>
<tr>
<td>5</td>
<td>INO-4800</td>
</tr>
<tr>
<td></td>
<td>AG0301-COVID19</td>
</tr>
<tr>
<td>7</td>
<td>LV-SMENP-DC</td>
</tr>
<tr>
<td>8</td>
<td>LNP-CoVsaRNA</td>
</tr>
<tr>
<td>9</td>
<td>NVX-CoV2373</td>
</tr>
<tr>
<td>10</td>
<td>Gam-COVID-VacLyo</td>
</tr>
<tr>
<td></td>
<td>GX-19</td>
</tr>
<tr>
<td>11</td>
<td>SCB-2019</td>
</tr>
<tr>
<td>12</td>
<td>COVAX-19</td>
</tr>
<tr>
<td>13</td>
<td>CVnCoV</td>
</tr>
<tr>
<td>14</td>
<td>Sars-CoV-2</td>
</tr>
</tbody>
</table>


ARTICLE IN PRESS
Presently registered clinical studies for exploring the efficiency of various bioactives and therapeutic measures towards the treatment of COVID-19.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Title</th>
<th>Design</th>
<th>Condition</th>
<th>Population</th>
<th>Intervention types</th>
<th>Registration no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC-09F and Ritonavir</td>
<td>A Randomized, Open, Controlled Clinical Study to Evaluate the Efficacy of ASC-09F and Ritonavir for 2019-nCoV Pneumonia</td>
<td>Randomized, single-blind clinical study</td>
<td>Pneumonia; SARS-CoV-2 infection (COVID-19)</td>
<td>Patients aged 18–55 years with 2019-nCoV Pneumonia (n = 60)</td>
<td>Drug therapy</td>
<td>NCT04261270</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia</td>
<td>Double-blind, placebo-controlled, randomized clinical study</td>
<td>SARS-CoV-2 infection (COVID-19); Pneumonia</td>
<td>Patients aged 18 y and older with 2019 novel coronavirus (2019-nCoV) pneumonia (n = 140)</td>
<td>Drug therapy</td>
<td>NCT04264533</td>
</tr>
<tr>
<td>Bromhexine Hydrochloride</td>
<td>Evaluating the Efficacy and Safety of Bromhexine Hydrochloride Tablets Combined with Standard Treatment/Standard Treatment in Patients with Suspected and Mild Novel Coronavirus Pneumonia (COVID-19)</td>
<td>Comparative, open, randomized clinical study</td>
<td>Pneumonia; SARS-CoV-2 infection (COVID-19)</td>
<td>Patients aged 18 to 80 y with suspected and clinical symptoms confirmed case of mild, or common novel coronavirus pneumonia (COVID-19) (n = 60)</td>
<td>Drug therapy, Immunotherapy</td>
<td>NCT04273763</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Chloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting</td>
<td>Double-blind, placebo-controlled, randomized clinical study</td>
<td>SARS-CoV-2 infection (COVID-19)</td>
<td>Healthy Volunteers Aged 16 Years and older (n = 10000)</td>
<td>Drug therapy, Prevention</td>
<td>NCT04303507</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>Fingolimod in COVID-19</td>
<td>Open clinical study</td>
<td>Pneumonia, viral; SARS-CoV-2 infection (COVID-19)</td>
<td>Patients aged 18 to 85 y with viral pneumonia/2019 novel coronavirus (2019-nCoV) infection (n = 30)</td>
<td>Drug therapy</td>
<td>NCT04280588</td>
</tr>
<tr>
<td>Immunoglobulin</td>
<td>Treatment of Acute Severe 2019-nCoV Pneumonia with Immunoglobulin From Cured Patients</td>
<td>Open clinical study</td>
<td>SARS-CoV-2 infection (COVID-19); Pneumonia, viral</td>
<td>Patients aged 18 y and older with 2019 novel coronavirus (2019-nCoV) pneumonia (n = 10)</td>
<td>Drug therapy</td>
<td>NCT04264858</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir, Ribavirin and IFN-beta</td>
<td>Lopinavir/Ritonavir, Ribavirin and IFN-beta Combination for nCoV Treatment</td>
<td>Open, randomized clinical study</td>
<td>SARS-CoV-2 infection (COVID-19)</td>
<td>Patients aged 18 y and older with 2019 novel coronavirus (2019-nCoV) infection (n = 70)</td>
<td>Drug therapy</td>
<td>NCT04276688</td>
</tr>
<tr>
<td>Anti-CD147 Humanized Meplazumab</td>
<td>Clinical Study of Anti-CD147 Humanized Meplazumab for Injection to Treat With 2019-nCoV Pneumonia</td>
<td>Open clinical study</td>
<td>SARS-CoV-2 infection (COVID-19)</td>
<td>Patients aged 18 to 75 y with 2019 novel coronavirus (2019-nCoV) infection (n = 20)</td>
<td>Drug therapy, Immunotherapy</td>
<td>NCT04275245</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Efficacy and Safety of Corticosteroids in COVID-19</td>
<td>Open, randomized clinical study</td>
<td>SARS-CoV-2 infection (COVID-19); Pneumonia</td>
<td>Patients aged 18 y or older with 2019 novel coronavirus (2019-nCoV) pneumonia (n = 400)</td>
<td>Drug therapy</td>
<td>NCT04273321</td>
</tr>
<tr>
<td>Pirfenidone</td>
<td>A Study to Evaluate the Efficacy and Safety of Pirfenidone With Novel Coronavirus Infection</td>
<td>Multicenter, open, randomized clinical study</td>
<td>Pneumonia, viral; SARS-CoV-2 infection (COVID-19); Hospitalization</td>
<td>Hospitalized adult patients aged 18 y and older with severe type novel coronavirus pneumonia (n = 294)</td>
<td>Drug therapy</td>
<td>NCT04282902</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>Drug therapy</td>
<td></td>
<td></td>
<td></td>
<td>NCT04292730</td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)
At this crucial stage, we are hopeful to have some promising tool in the mission rate, the government of all the affected countries has taken algorithms to predict the outbreak of COVID-19 should be fully explored the world are making their extreme efforts in finding some promising solution to fight with such a pandemic situation by COVID-19 infection.

8. Conclusion and recommendation

Pharmaceutical industries, government organizations, research institutions, scientists, researchers and medical professionals throughout the world are making their extreme efforts in finding some promising solution to fight with such a pandemic situation by COVID-19 infection. Based on currently using therapeutic regimen by the physicians of China, USA, Europe, Asia and the rest of the world, some of the drugs gives positive results in improving the COVID-19 symptoms. Among these drugs remdesivir and some other anti-viral drugs appears as promising molecules for the treatment of symptoms of COVID-19 with more successful cases. Both these drugs are under clinical investigations to assure the safety and efficacy against SARS-CoV-19 infection. Along with this, various companies like BioNTech, Moderna, CureVac, etc. are also trying to develop a suitable vaccine for COVID-19. In addition, one of the primary challenges is to control the further spread of disease. Application of artificial intelligence techniques, machine learning algorithms to predict the outbreak of COVID-19 should be fully explored to develop the forecasting system to assess the magnitude of the disease spectrum and also to take necessary control measures well in advance. At this crucial stage, we are hopeful to have some promising tool in the near future to fight against COVID-19 and save mankind.

In response to the current COVID-19 pandemic and its faster transmission rate, the government of all the affected countries has taken various strict measures including, home quarantine of the suspect, complete isolation of the patients, complete lockdown of the countries, extensive screening and case identification, social distancing, contact tracing, etc, to control and manage the disease spread. After all these preventive measures global statistics on new cases and death reports doesn’t match the expectations. Hence, more concerns and efforts are desirable for the containment of this pandemic situation. It is also very important to fetch more funds for clinical research and development to face this type of condition in the future. This pandemic event has challenged the capabilities of developed countries in terms of medicine and healthcare management. This means that more research is required for the scale-up of diagnostic facilities, vaccines, and PPE kit. Along with this, it is highly recommended to reform separate wing-like disaster management to handle epidemic and pandemic situations. This requires proper training and facility to handle such situations in the future for a large group of population. The government must support research institutions and entrepreneurs for innovations aligned to this situation in terms of sufficient financial support. In the present scenario looking upon the current statistics worldwide in terms of new cases detected and confirmed deaths, only two strategies have been worked to control this outbreak up to a certain limit. The first is testing and tracking the suspected cases and the second is a complete lockdown. In addition to this, strict implementation of the regulation framed by the Government authorities is also required.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary data

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M. Agrawal et al. Respiratory Medicine xxx (xxxx) xxx

Appendix A. Supplementary data

18


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