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Review Article

TREATMENT MODALITIES OF THE COVID-19 PANDEMIC THROUGH REPURPOSED DRUGS AND STATUS OF VACCINES

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ABSTRACT

Respiratory diseases are the leading source of morbidity and death for millions around the world of all ages. A 2019 coronavirus outbreak has occurred in China and is spread quickly throughout nearly all across the world. To introduce prevention measures that have contributed to a sudden upturn in the rate of cases around the globe, several nations responded too late. It has prompted nations to close the borders, halted companies, kept people inside their homes, and numerous other measures to prevent their spread.

We systematically searched on Google scholar, PubMed, LitCovid, and MedRxiv using the search terms coronavirus, severe acute respiratory syndrome, 2019-nCoV, SARS-CoV-2, SARS-CoV, MERS-CoV, COVID-19, and vaccine for published articles. Present or performed clinical studies were found on the ClinicalTrials. gov, the Chinese Clinical Trial Registry, and the International Clinical Trial Registry site using the disease searches phrase coronavirus infection.

Many repurposed drugs, including antivirals, antibiotics, monoclonal antibodies, corticosteroids, and others, were found to be effective against the novel COVID-19. Governments, private firms, researchers, and non-profit organizations are working hard to create a COVID-19 vaccine.

In addition to the new medicines and old drug clinical testing, SARS-CoV-2 vaccines must also be designed and developed. Moreover, positive news in the development of vaccines suggests that new vaccines will be available on the market soon and a bowl of immunity against this virus can be established, thus limiting the spread and eradication of this deadly virus from the surface of the world as with so many viruses.

Keywords: SARS-CoV-2, COVID-19, Repurposed drugs, Vaccines, Clinical trials

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INTRODUCTION

The lives of over one billion populations globally are affected by respiratory illnesses and the main reason for death and morbidity [1]. A wide variety of severe disorders are defined by chronic respiratory diseases (CRD), i.e. chronic airway diseases and other structures of the lungs [2]. Unfortunately, the public awareness of CRDs and research funding are proportionately lower than that of other diseases such as cardiovascular, tumors, heart attack, diabetes, and Alzheimer's [3]. In both developed and developing countries, CRDs pose a public health threat because of their incidence and economic implications [4].

The novel coronavirus 2019 (2019-nCoV) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as it is now known, is expanding quickly from its origin (Wuhan, China) since December to the rest of the world [5]. A swift response team to assist the province of Hubei and the Wuhan City health agencies and perform epidemiological investigations was sent out on December 31st, 2019, by the Chinese Center for Disease Control and Prevention (China CDC) [6]. The World Health Organisation (WHO) has reacted promptly by preparation of the production of diagnostic systems; issuing patient surveillance, test selection, and care guidelines; and updating epidemic information [7]. On 12 January 2020, the isolated pathogen was named 2019-CoV after quick isolation from a patient. And the International Taxonomy Committee for Viruses reported on 11 February that its official classification is SARS-CoV-2. On the same day, the WHO declared Corona Virus Disease-19 (COVID-19), the official name of the virus causing the disease [8, 9]. The WHO declared a pandemic on March 11, 2020 [10]. COVID-19 is a modern disorder that has distinct biological features, clinical signs, and manifestations of the imaging, while important clinical management advancements have been achieved [11]. Tyrell and Bynoe, who grown the pathogen from patients with common colds, i.e., first identified coronavirus in 1966 [12]. Bats are thought to be a natural storehouse for SARS-CoV-2, but human infection has been proposed by an intermediate host like pangolins [13].

The COVID-19 epidemic features high contagious levels and comparatively high death rates, especially among elderly people over 80 y of age [14]. China, the first COVID-19 affected country, shows an 8 percent fatality rate in 70–79 y, and almost double for people aged 80 or over. An analogous pattern is observed in Italy, 42.2% of those who died of COVID-19 were in the 80 to 89-year age group, and 32.4% were in the 70 to 79-years group, whereas the worldwide average fate rate is 3.4 percent. The aging population is, therefore a serious worry in estimating death and morbidity during the coronavirus pandemic in the world [15].

Experiences with outbreaks like Middle East Respiratory Syndrome (MERS), pandemic influenza, and others demonstrated the immediate need to extend public health efforts to shed light on and classify the epidemiology of the emerging viruses [16]. The epidemic has been somewhat slowed, due to drastic safety precautions taken in China. However, it quickly spread throughout the globe, causing extreme worry [17]. Many nations have responded too late for mitigation steps that have led to a sudden rise in cases globally [18].

A reverse transcription chain reaction (RT-PCR) assay has been produced and is currently in use for COVID-19. Whilst RT-PCR remains the reference standard for making a conclusive diagnosis of COVID-19, the high false negatives, as well as the inaccessibility of the RT-PCR assay, limited easy diagnosis for infected patients in the early stages of the epidemic. In combating this infectious disease, radiological exams, especially thin-slice chest CT, plays an important role [19]. Personal and environmental hygiene maintenance are the key measures to protect from the current virus infection [20]. Timeline of SARS-CoV-2 first case registered to the pandemic declaration by WHO shows in fig. 1.

Different strains OF CoV

COVID-19 is the 7th coronavirus that has been identified to infect humans [21]. Six various CoV strains are known to infect humans before SARS-CoV-2. HCoV229E (229E), HCoV-OC43 (OC43), HCoV-NL63 (NL63), HCoV-HKU1 (HKU1), SARS-CoV, and MERS-CoV are also

included in these groups. The different types of CoV strains that affect humans are listed in table 1 [22-24]. SARS-CoV is a pathogenetic agent that caused over 8,000 human infections and 774 deaths in China during a 2002–2003 serious respiratory illness outbreak and since 2012, the MERS-CoV causes 2458 infections and 848 deaths by 2019 as the disease-causing pathogen for the outbreak of serious breathing diseases in the Middle East [21, 22, 25]. The SARS and MERS coronavirus are indicative of a major danger to public health [26].

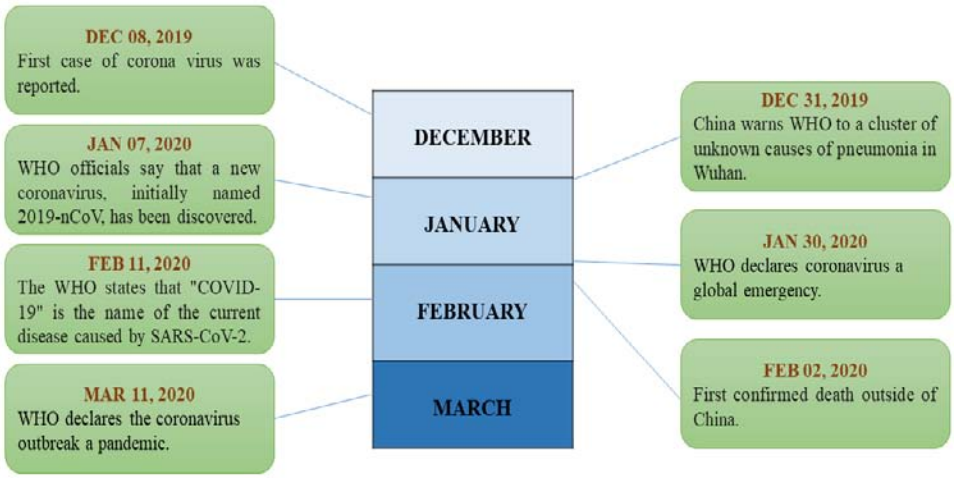

Fig. 1: Shows the timeline of coronavirus from the first case registered to the declaration of a pandemic by WHO

Table 1: Different strains of CoV affecting humans

S. No.	Type of strain
1	Alpha coronavirus-229E
2	Beta coronavirus-OC43
3	Alpha coronavirus-NL63
4	Beta coronavirus-HKU1
5	SARS-CoV
6	MERS-CoV
7	SARS-CoV-2

Table 2: List of top 5 countries having maximum cases registered along with their classification of transmission as of 11th December 2020

Country	Cases–cumulative total	DEATH-cumulative total	Case fatality rate (%)	Transmission classification
United States	15,203,208	287,384	1.89%	Community transmission
India	9,796,769	142,186	1.45%	Clusters of cases
Brazil	6,728,452	178,995	2.66%	Community transmission
Russia	2,569,126	45,280	1.76%	Clusters of cases
France	2,283,752	56,280	2.46%	Community transmission

Up to December 11, 2020, the top 5 countries with the most COVID-19 cases and other information are listed in table 2. CoV is common in all species of bats but can also be found in many other species, such as cats, dogs, horses, humans, mice, pigs, and whales. They can cause the variable intensity of respiratory, gastrointestinal, liver, or neurological conditions [24]. The positive-sense, uniform RNA virus of the genus beta coronavirus was found to be SARS-CoV-2 [27]. CoV's ability to propagate rapidly is the deadliest feature [28]. In early transmission studies, the linkage between the fish market and the sea creatures market in China with many early infections was reported. Later, new infections were spread by the virus mainly through transmission between humans [29]. Globally, the CoV incubation period is 3-7 d. About 80% of infectious case scenarios persist mild or asymptomatic, 15% are severe or 5% are critical, and ventilation is required [30].

Epidemiological results indicate that the most common form of transmission is droplets expelled through face-to-face contact, coughing, or sneezing. Extended exposure to a person that has been infected (within at least 6-feet for 15 min) and short-term exposures to people that are symptomatic (e. g. coughing) are more likely to spread and are less likely to result in short exposures to asymptomatic contacts [31]. As smaller particles (aerosols) and large particles (droplets) are all clustered within a few meters, with physical distancing, and increased ventilation, the probability of transmission reduces. The respiratory-particle transmission (where an individual<2 m from an infected individual) spreads the bulk of SARS-CoV-2 infections over a small distance [32].

They invade the host cells via their viron spike protein and virus replication can also be closely linked to an angiotensin-converting enzyme 2 (ACE 2). The surface of pulmonary epithelial cells is heavily expressed by ACE2, which explains the recurrent lung involvement in SARS-CoV-2 [33-35].

COVID-19 encompasses a full variety of signs ranging from elevated respiratory infections to dangerous pneumonia consistent with acute respiratory distress syndrome. Breathlessness, common cold, confusion, cough, diarrhea, fever, myalgia, runny nose, sneezing, vomiting, and wheezing are primary indicators of SARS-CoV-2 [34, 36, 37]. Popular signs include in-hospital patients are breathlessness (53-80 percent), diarrhea (15-39 percent), dry cough (60-86 percent), exhaustion (38 percent), fatigue (25 percent), fever (70-90 percent), myalgias (15-44 percent), nausea or headache, or

rhinorrhea (7 percent). In approximately 3 percent of individuals with SARS-CoV-2, anosmia or ageusia can be the only symptom [38]. The fast development of respiratory collapse immediately after dyspnea and hypoxemia is a striking characteristic of SARS-CoV-2 [39]. Fig. 2 represents the severity of COVID-19 symptoms according to a cohort study of>44,000 people.

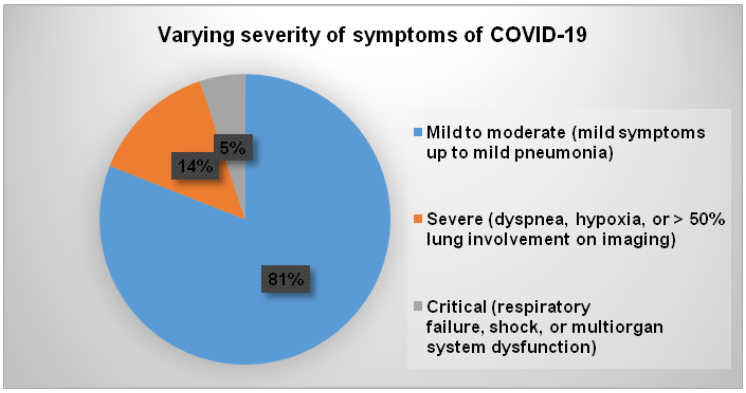

Fig. 2: A visual representation of a cohort of>44,000 patients in China and their varying illness severity [40]

Treatment modalities

Various Treatment options for Coronavirus disease (COVID-19) are being explored; apart from finding new treatment re-purposing or reprofiling of drugs, to treat COVID-19 is one of the centers of attention. Many drugs are under clinical trials, whereas Remdesivir has been approved by the United States (US) Food and drug administration and given emergency use authorization (EUA) on May 1 2020 to treat coronavirus disease [41]. Generally, treatment for COVID-19 focuses on relieving symptoms by use of supportive symptom care as well as general care [42]. Moieties attaching to the virus as well as the inhibiting molecules which can affect replication or transcription of the virus can be the prominent treatment options available. Several proteins of the virus can be targeted by molecules such as helicase as well as essential proteases [43]. Because of the whole genome sequenced and protein structure designing connected information, scientists have been able to fig. out possible drugs for the treatment of COVID-19 [44].

Anti-viral drugs

What has been understood from previous virus outbreaks like SARS-CoV-1 and middle east respiratory syndrome suggests the use of anti-virals like lopinavir-ritonavir and ribavirin and also other drugs like redeliver, arbidol, immunoglobulins, and interferons have been tried in the treatment of the coronavirus disease and found varying degrees of success [45]. Like antibiotics, the anti-viral agents do not directly target pathogens, rather they harm the growth and development of the viruses [46]. Through drug repurposing, various drugs have been suggested for COVID-19 potential treatment [47]. World Health Organization has begun the International Solidarity trial to assess the potential drugs for COVID-19 treatment which are already used for the anti-viral purpose [48].

Remdesivir

This drug was initially identified for Ebola and Marburg viral infections [49]. It works by the cessation of viral transcription by attacking the RNA-dependent RNA polymerase (RdRp) of viral origin and viral chain cessation [50]. This drug has an expansive spectrum of activity against other viruses like SARS-CoV and the Middle East respiratory syndrome [51,52]. This is the reason that it's used against these two above viruses that it has been tested for use in the case of COVID-19. Remdesivir has found to be effective in decreasing the viral lung load, checking the disease development as well as considerable bettering of the function of lungs in a mouse model used to inspect pathogenesis of SARS-CoV, prophylactic and post-exposure administration of remdesivir [53]. Data from rhesus monkeys acknowledge that intravenous administration of remdesivir 10 mg/kg dose can bring about immense concentrations of active triphosphate form intracellularly for a 24-hour period, which encourages the possibility of the use of remdesivir in COVID-19 treatment [49]. On a benevolent basis, 53 serious patients infected with SARS-CoV-2 infection, were administered with remdesivir and Grein *et al.* described 68% of patients exhibited a decrease in need of O_2 requirement and thus shown substantial betterment and 57% of patients were no longer in need of ventilator support [54]. As per the Adaptive COVID-19 Treatment Trial in which 1063 participants (COVID-19 patients that were hospitalized) were administered with remdesivir and it was found that this drug reduced the recovery period for hospitalized patients suffering from pneumonia in COVID-19 [55]. In another trial analogous effectiveness was reported concerning remdesivir when it was given for 5 d in place of 10 d in serious COVID-19 patients with no need for ventilation regimen. Based on data from the Ebola outbreak and two trials, remdesivir received emergency use authorization by US-FDA [56]. As per another report with participants as patients having manifestations from ten days or less administered with remdesivir found better medical improvement than those receiving placebo but no analytically clinical advantage [57]. A case was recorded, which was found to have extreme betterment in the condition of the patient within one day after administering remdesivir [58].

Lopinavir-ritonavir

Lopinavir and ritonavir both are protease inhibitors utilized to reduce the infectivity of HIV-1 lopinavir are used in consolidation with ritonavir which leads to enhancement in the bioavailability because of protection from mitigation due to metabolic processes [59]. Apart from chloroquine and chlorpromazine, lopinavir has been shown to constrain duplication of MERS-CoV and SARS-CoV [60]. Acute respiratory distress syndrome was found to be reduced in subjects suffering from severe acute respiratory syndrome-related to SARS-CoV, which were managed with the consolidation of lopinavir-ritonavir and ribavirin [61]. Because of the capability of lopinavir-ritonavir for use against SARS-CoV and MERS-CoV, these drugs have been proposed and tried for COVID-19. In China, lopinavir, ritonavir was endorsed for pneumonia treatment due to COVID-19 infection [62]. In another incidence, the subject was suffering from mild pneumonia due to COVID-19, which was administered with lopinavir-ritonavir and it was found that viral load was significantly reduced and viral titers were undiscoverable [63]. A clinical trial conducted in China where lopinavir-ritonavir was used showed no advantages in comparison to definitive classic care, and viral load was not declined in infected individuals with COVID-19 infection [64], but a decreased mortality was recorded in comparison to definitive classic care [53].

Favipiravir

This drug constrains the RdRp of viral RNA and has expansive anti-viral actions for RNA viruses [65]. Favipiravir is authorized in japan for influenza treatment and it is opinionated to be a beneficial

treatment for COVID-19 Infection. In a limited sample size study of severe COVID-19 patients administered with combinations of favipiravir, heparins, and corticosteroid, it was found that favipiravir could somewhat restrain the mediators of inflammation but not completely. Findings report that favipiravir can have some advantage in COVID-19 infection treatment [66]. In another controlled open-label study, which in comparison to lopinavir-ritonavir found that favipiravir had a swift clearance of viral load and a better pace of improving as found in the chest examination, in comparison to lopinavir-ritonavir it had enhanced effectiveness concerning the advancement of disease [67]. In a cohort study which was multicentered, of comparison of favipiravir and umifenovir, and it found that favipiravir had exceptional potency with recovery at 7th day and fever as well as cough extent was reduced [68].

Ribavirin

It also inhibits the Viral RdRp, because of its action against other novel coronaviruses, it is considered to be utilized in the management of SARS-CoV-2 infection [69]. Largely in the SARS epidemic, it was utilized but was bothered for, causing embryonic development disruptions in the fetus and hemolytic anemia [70]. In a phase II trial, consolidation of lopinavir-ritonavir, ribavirin, and interferon-β-1b lead to a contraction in the period of viral clearance [71]. The anti-viral actions *in vitro* of ribavirin were found at a concentration of 50 μg/ml, counteracting SARS-CoV infection [72].

Umifenovir (Arbidol hydrochloride)

It is a wider spectrum Anti-viral drug having effectiveness against influenza and parainfluenza etcetera [73]. A study including 111 patients who were suffering from pneumonia-related to COVID-19 was administered with an anti-viral regimen with including arbidol or not including arbidol, and it was reported that patients for those, arbidol was included along with anti-viral had a lower requirement of oxygen therapy and it was also noted that mildly symptomatic subjects were most helped with arbidol [74]. In another study including fifty patients' effects of arbidol only and lopinavir-ritonavir treatment were observed and it was reported that patients only administered with arbidol, had untraceable viral load after a duration of two weeks of admitting them in contrast to 44% observed in patients who received lopinavir-ritonavir [75].

Oseltamivir

It is also used against influenza and it is potent neuraminidase inhibiting drug. In 1099 sufferers of COVID-19 of guan *et al.* showed the use of oseltamivir in 35.8 % of patients [76], and in 93% of 41 sufferers of COVID-19 of Huang *et al.* were given oseltamivir [77] but no compelling findings were present to prove the efficacy of the drug oseltamivir.

Nelfinavir

This drug can be a potential drug for the treatment of SARS-CoV-2 because it restricts the duplication, and also the cytopathogenic consequences of the COVID-19 causing virus *in vitro*. This drug acts by constraining the HIV protease [78, 79].

Hydroxychloroquine (HCQ) or chloroquine (CQ)

For the past 70 y, HCQ and CQ are being utilized in malaria treatment and both these drugs have been found to have an action against the synthesis of protein of viruses as well as on access of the virus into and out of the host cell [80]. Various studies found that CQ decreases Angiotensin-converting enzyme-2 glycosylation and this way CQ inhibits attaching of SARS-CoV-2 to the host cell surface [81-83]. *In vitro* CQ and HCQ were found to have restrictive actions for mRNA synthesis of novel Coronavirus 2019, whereas the HCQ is reported to have a better effect than CQ [84, 85]. As per a Chinese news broadcast of about 10 health care centers, for one hundred patients CQ strongly helped treat and decrease the advancement of COVID-19 [86]. In a study trial conducted on 36 subjects, Azithromycin and HCQ were given to patients either HCQ only or in a merger with azithromycin and it was found that all the subjects treated with the consolidation of azithromycin and HCQ had an untraceable load of SARS-CoV-2 and viral load was 57.1 % in those who were administered with HCQ alone [87]. As per a Chinese report, out of one hundred sufferers of COVID-19 those who were administered HCQ found to have better clinical results than the control subjects. HCQ is secure and competent for pneumonia associated with SARS-CoV-2 therapy as described by Gao *et al.* [86]. In a study, CQ was reported to decrease the viral concentration by the 6th day of treatment and lowered the need for oxygen as well as the requirement to shifted in ICU [88, 89]. In a Randomized trial of 491 mild COVID-19 patients administered with HCQ and placebo, this study reported that there was not great differentiation between, alteration of the seriousness of patient condition by 14 d between placebo and HCQ group and it was reported that HCQ does not alleviate symptom seriousness in non-hospitalized less severe COVID-19 patients [90]. World health organization terminated trials being conducted for determining the effectiveness of HCQ because of no reduction in death rate by the drug in the sufferers of COVID-19 [91].

Antibiotics and antiparasitics

Carrimycin

National Medical Products Administration, china authorized carrimycin for use in the treatment of upper respiratory tract infections this drug was formed for this purpose [92]. On 520 COVID-19 sufferers in Beijing youan health care center, randomized open-labeled multiple center trial is being conducted to assess clinical effectiveness and safety [93].

Azithromycin

It is an Antibiotic belonging to the Macrolides category, it works by preventing the growth of bacteria, apart from antibacterial actions it has antiviral actions as well. It has been utilized in the treatment of infections related to viruses in the upper respiratory tract [94]. Moreover, azithromycin has been thought to be preventive against serious respiratory infection, in nursey children when given it is given to sufferers of virus-related infections [95]. The latest study revealed that for treating 20 serious SARS-CoV-2 infections sufferer's azithromycin considerably strengthened the effectiveness of HCQ, there was increased virus clearing efficiency after giving these two drugs [96]. As per Masahi *et al.* macrolides only or when given together with HCQ are efficacious to treat COVID-19 [97].

Ivermectin

In 1975 this drug was unearthed and its utilization was started in 1981 [98, 99]. This is a US-FDA authorized drug and utilized in the treatment of various diseases like scabies, malaria, enterobiasis, etc. This drug is also acknowledged to have anti-viral actions against some viruses *in vitro* [100-103]. As per a study, conducted it was found that ivermectin constrains the duplication of SARS-CoV-2 virus in the *in vitro* conditions [104]. In a study on 100 COVID-19 patients treated by administering ivermectin and doxycycline together, and this was reported that when these two drugs given together were very competent in eliminating viral load in less severe as well as moderately affected COVID-19 sufferers [105]. In a pilot trial conducted to assess the efficacy of ivermectin as an additional treatment with HCQ and azithromycin on 87 COVID-19 sufferers, it was reported that administration of additional ivermectin therapy to HCQ and azithromycin regimen leads to a lesser hospital stay, greater efficacy, and better safety in comparison to control group [106]. As per a randomized controlled trial conducted in Baghdad, Iraq on 70 COVID sufferers administered with ivermectin and doxycycline and other 70 COVID sufferers, treated with standard therapy and it was reported that ivermectin along with doxycycline decreased time to recover and also death rate was declined in the serious patients [107].

Interferons

Interferons are existing by nature proteins, which are formed by immune cells of the body. Interferons can be of alpha, beta, and gamma types, immune responses are furthered opposing attacking antigens [108]. Because of distinct cell surface molecules, toll-like receptors get stimuli and thus a-helical cytokines are secreted called interferons. For hepatitis, interferon-alpha (IFN-α) is extensively utilized, it's a wide scope anti-viral drug. IFN-α is reported to decrease the replication of SARS-CoV-2 in the *in vitro* conditions [109]. Interferon-beta (IFN-β) is a naturally existing protein

molecule that puts together the anti-viral bodily responses [70]. IFN-α and IFN-β two together have adverse effects on severe acute respiratory syndrome coronavirus 2 in the *in vitro* conditions [110, 111]. Interferon-beta showed compelling activity versus the MERS-CoV *in vitro* [112]. IFN-α and IFN-β showed synergism with ribavirin against SARS-CoV as well as both alpha and beta interferons shows synergistic effects against SARS-CoV [113-116]. Using Recombinant Type-I IFN-α in an *in vitro* condition study, it was found that there was a considerable reduction in the reproduction of the SARS-CoV-2 [117]. The guidelines given by the National health commission and state administration of Traditional Chinese medicine suggested various drugs for SARS-CoV-2 treatment, along with other drugs IFN-α is also suggested [118].

Monoclonal antibodies

Monoclonal antibodies made synthetically at laboratory scale mimes the antibodies existing in nature. As per studies conducted on SARS-CoV and MERS pathogenesis, and it was advised that during a severe illness, interleukin-6 (IL-6) and other pro-inflammatory cytokines are released [119]. In COVID sufferers' antibodies can bring about the rapid effect.

Tocilizumab

It is a monoclonal antibody that acts in opposition to IL-6, utilized as an agent that suppresses immunity. Considerable harm to the lungs is brought about by the activation of the immune response as well as the release of cytokines, and in the cytokine storm, IL-6 seems to have a leading role as found in a Chinese case series [120]. Because tocilizumab can bar the release of IL-6 it can be protective for COVID-19 sufferers [121]. In a small sample-sized trial conducted in china on 21 serious COVID-19 sufferers, and they were administered with tocilizumab, and it was reported that fever was controlled in every patient, whereas for 75% of patient's oxygen requirement was decreased, and in 90.5% of patient's lung lesions were resolved, C-reactive proteins were lowered and came to regular levels in 84.2 % of the COVID-19 patients [122]. In a reflective study, it was reported that C-reactive protein was considerably lowered after giving tocilizumab to fifteen COVID-19 patients [123]. In Civic health care centers, Mumbai tocilizumab was used to treat patients and it was found to be quite efficacious [121].

Sarilumab

It is also an IL-6 receptor inhibitor utilized for rheumatoid arthritis. As per a phase II trial, for whom result data is given in a press release, and it was disclosed that in comparison to the placebo, sarilumab was related to the lesser death rate, increased hospital discharges, and better clinical improvement [124].

Corticosteroids

Corticosteroids belong to the category of steroidal hormones, and they act as key aspects related to inflammation and immune responses. Because of the effectiveness of the corticosteroids on various interleukins like IL-6, interleukin 1(IL-1), etc. these have been extensively utilized in the SARS-CoV epidemics [125, 126], But the researches involving corticosteroids in the treatment of MERS and SARS reported no considerable effect on death rate and infection clearance was also found to be disrupted [127]. RECOVERY (Randomized Evaluation of COVid-19 therapy) trial regarding dexamethasone, its primary results have shown that dexamethasone decreased the death rate in patients who were on mechanical respiratory support [128, 129]. Recovery trial data about dexamethasone shows strong proof that the drug can be utilized in those sufferers who are at mechanical respiratory support; also this trial gives firm proof about the use of glucocorticoids which also lead to approval of dexamethasone by the National Health Service, England [130]. Dexamethasone also received authorization from the world health organization for very serious patients [131].

Angiotensin receptor blockers

For novel coronavirus 2019 Angiotensin-Converting Enzyme-2 (ACE2) is a site of binding, and the attachment with ACE2 lead to a reduction of ACE2, which in turn leads to increased production of angiotensin by angiotensin-converting enzyme, and elevated angiotensin leads to elevated excitation of angiotensin receptor 1, as a consequence of that there can be lung damage, and speculation is that angiotensin receptor 1 blocker such as losartan can be a potential treatment for Lung damage in COVID-19 infection [132].

Convalescent plasma

In various disease conditions like influenza as well as SARS and serious ebolavirus infection, convalescent plasma has been utilized as a concluding alternative to cause betterment in the condition of severe sufferers [133, 134]. The proposed reasoning for the effectiveness of the plasma is because of the presence of immunoglobulin antibodies in the blood of patients successfully treated and recovered from COVID-19, which can lead to the elimination of viral presence in the bloodstream [53]. As per the case series by Shen *et al.*, Convalescent plasma therapy, when given to five severe SARS-CoV-2 patients, resulted in the betterment of clinical outcomes [134]. In other proven treatments, convalescent plasma has previously been used, but it has been tried and found to be effective in this case, and the procedures at different facilities have shown that it demonstrates the same high degree of effectiveness and protection [135]. Further clinical trials and studies are needed to evaluate the usage of convalescent plasma in COVID-19 treatment.

Herbal therapy

Because of the previous usage in SARS and swine flu, traditional Chinese herbal medicine was also considered as a therapy for the management of COVID-19, whereas strong proof that justifies the effectiveness of these drugs in the current pandemic is still not available. Traditional Chinese medicines like Huangqi, Gancao, and fangfeng, etc. were utilized in china in the SARS-CoV-2 pandemic [136, 137]. A chemical constituent obtained from roots of licorice called Glycyrrhizin is reported to restrict duplication of SARS-CoV in vitro [138]. Another flavonoid, Baicalin also found to have activity against SARS-CoV in vitro [139]. In India Ayurvedic experts via the government of India, gave precautionary measures to build immunity against COVID-19 such as taking lukewarm water, rinsing the mouth with oil, use of ghee in the nose, etc. [140]. Arsenic album, which is a homeopathic medicine, has been suggested in managing the COVID-19 [141].

Miscellaneous agents

Because of the pulmonary microthrombi in severely sick SARS-CoV-2 sufferers, thus anti-coagulation agents expected to be used in the treatment of the disease, COVID-19 is related to excessive abnormal blood clot formation, which in turns is the reason for the greater death rate. Heparin has been found to decrease the death rate in serious COVID-19 sufferers [142]. Low molecular weight heparins have been endorsed in the prevention of development of thrombosis and as a prophylactic treatment for COVID-19 patients [143, 144].

Nitazoxanide has a potent wide spectrum, anti-viral actions as it has anti-viral actions against various kinds of viruses like coronaviruses, hepatitis c, and b as well as influenza viruses. In the *in vitro* conditions, this drug has been found to constrain the novel coronavirus 2019 at low concentrations [99]. Apart from having anti-viral activities, nitazoxanide inhibits inflammatory cytokines like IL-6 and IL-1, etc. In a study on mice, it was reported that nitazoxanide reduced plasma concentrations of IL-6 after administration of nitazoxanide in comparison to the vehicle [145]. Nitazoxanide is proposed to do the betterment in the cytokine storm, which is faced by serious COVID-19 sufferers [146].

Camostat mesylate restricts the protease serine 2 of the host, thus averts the access of the novel coronavirus 2019 to the cell of the host *in vitro* [147]. But more studies are required to show anti-viral actions against novel coronavirus 2019.

A cough suppressing agent, Bromhexine hydrochloride, which is a mucus clearing agent from upper respiratory airways, it is accepted that bromhexine inhibits firmly the protease serine 2, which has an important part in the entry of novel coronavirus 2019, so clinical studies and trials are required to assess its efficiency [148].

Janus kinase inhibitor Baricitinib is authorized for utilization in rheumatoid arthritis; this drug can be efficacious in treating the

COVID-19 to constrain the inflammatory activity as well as access of virus to host cell [149,150]. Baricitinib has a strong inclination towards AP2-associated protein kinase 1 (AAK1), which governs the endocytosis [151]. Interruption of endocytosis can lead to the prohibition of access of virus into the host cell [152]. Janus kinase inhibitors are found to be efficacious opposite the effects of cytokine levels as found in SARS-CoV-2 sufferers [77].

Valproate has anti-viral and anti-inflammatory abilities; because of that, this drug may avert lung damage due to the effects of COVID-19 [153].

Intravenous gamma globulins (IVIGs) were utilized broadly in the SARS outbreak in Singapore by Thomas *et al.* [154]. Few case series reported that a greater dose of IVIG can alleviate the further advance of the disease and make the clinical outcomes better [155]. In critical SARS-CoV patients, IVIG as an adjuvant therapy can decrease the requirement of respiratory support, decrease the death rate, and also decrease the time spent at the hospital [156]. Bacillus Calmette–Guérin (BCG) vaccine can persuade metabolic and epigenetic alterations to cause innate immunity its efficacious act in case of SARS, for COVID-19 this vaccine has been suggested [157].

Vitamins and supplements: Because of the immunomodulation properties of Vitamin D, versus the COVID-19 as reported in few clinical trials, it was able to avert the infection in the beginning stages, as well as in more inflammatory levels during COVID-19 infection [158].

Vitamin C also has immunity modulating, anti-oxidant as well as anti-viral actions; this supplement has various mechanisms related to immune responses and has direct activities against viruses. Vitamin C drastically decreases the pro-inflammatory cytokines, which are related to crucial COVID-19 condition [159].

Also, supplements like iron, selenium, zinc, and other trace elements are suggested for use in the treatment of COVID-19 disease [73].

Vaccines

Vaccines are amongst the most economic and therefore important public health initiatives. Vaccines are indeed very unique because they improve health, defend people, families, and whole societies, and speedily help to save lives [160]. Vaccines are now important in preventing the spread of disease and prevention of SARS-COV-2 contamination. In its development phase, nearly 100 vaccines have been developed and 10 are being clinically assessed according to the recent update from the WHO [161]. Table 3 shows the lists of advanced vaccines and their information.

Table 3: List of advanced COVID-19 vaccines that are in Phase 3 and approved by some countries

Manufacturer	Vaccine name	Type	Efficacy	Clinical phase
Pfizer-BioNTech	BNT_162_b2	mRNA	95%	Phase 3
University of Oxford-AstraZeneca	ChAdOx1 nCoV-19	Adenovirus	90%	Phase 3
Moderna-US National Institutes of Health	mRNA-1273	mRNA	94.5%	Phase 3
CanSino Biologics-Academy of Military Medical Sciences	Ad5-nCoV	Adenovirus	Unknown	Phase 3
Gamaleya Research Institute	Sputnik V	Adenovirus	Unknown	Phase 3
Sinopharm	BBIBP-CorV	Inactivated	86%	Phase 3
Zydus	ZyCov-D	DNA	Unknown	Phase 3
CureVac	CVnCoV	mRNA	Unknown	Phase 3
Sinovac	CoronaVac	Inactivated	Unknown	Phase 3
Bharat Biotech, Indian Council of Medical Research, and National Institute of Virology	Covaxin	Inactivated	Unknown	Phase 3

Pfizer-BioNTech vaccine

This vaccine is also named BNT_162_b2, is the earliest vaccine to be referred to US-FDA for emergency use authorization. On November 20, it was submitted to US-FDA after completion of the phase-3 trial [162]. The Pfizer-BioNTech vaccine is not given approval by US-FDA but Emergency use authorization has been granted [163]. As per conclusions given in the press-release, this vaccine was found to be 95% efficacious after administering the first dose after 28 d in 170 COVID-19 sufferers. The vaccine is expected to be priced at £15 for each dose. Pfizer has stated that this vaccine can be made accessible to increased risk populations in the US [164].

University of oxford-astra zeneca vaccine

ChAdOx1 nCoV-19 vaccine has various trials in different countries of the world, whereas trials were initiated in the United Kingdom, and in Brazil, US, and South Africa trials have branched out. Provisional results of the phase 3 trial on 131 patients advised 90 % effectiveness of the vaccine [165]. The company intends to make the vaccine available in the whole world and not just in the developed countries and is estimated to be priced at £3 for each dose, it can be stored at a temperature range of 2-8 degrees Celsius [164].

Moderna-US national institutes of health vaccine

US biotechnology company Moderna, in association with the US National Institute of health, prepared mRNA-1273 vaccine, which is found to be 94.5% efficacious as per provisional results from phase 3 trial in the US [166]. Soon, Moderna aims to receive emergency use authorization from US-FDA and apply for the same in the near future. The per-dose price is quite high than the other two late phase vaccine candidates, it is expected to be £25 for each dose [164].

CanSino biologics-academy of military medical sciences vaccine

CanSino Biologics in partnership with an academy of military medical sciences, institute of biology, made a vaccine named Ad5-nCoV, this vaccine candidate asserts whole length spike, a glycoprotein from viral strain Wuhan-Hu-1. Phase 1 trial on 108 patients gave promising results. Neutralising antibodies were elevated at day 14 considerably, and antibodies were highest at day 28 after vaccination [167]. In the phase 2 trial, it was showed that the vaccine persuades the immune response in most of the patients [168]. In June 2020, before the commencement of the phase 3 trial, this vaccine became approved and it was declared as approved by CanSino Biologics and institute of biology, academy of military medical sciences, china [169]. From August, the phase 3 trial was initiated in countries like Pakistan, China, and Saudi Arabia.

Gamaleya research institute vaccine

A unit of the Russian Health Ministry, Gamaleya Research Institute, developed a vaccine, sputnik V with an effectiveness of 91.4 percent as per announcement in a press release [170]. In the randomized phase 1/2 trial two studies, including 76 patients, 38 in each found that vaccine has effectiveness in generating immune responses in patients [171]. Initial data from the phase 3 trial was provided and it was announced that the vaccine is efficacious. Phase 3 trial results are under review by a few countries, including India [172].

Sinopharm

Presently, Sinopharm working on two vaccine candidates, which are attenuated virus, out of the two one was developed by the Beijing Institute of Biological Products. As per the phase 1/2 trial, the BBIBP-CorV vaccine is secure at all dosages tested. On day 42,

immune responses were persuaded in all patients who received vaccine dose [173]. The United Arab Emirates gave emergency approval to the vaccine to be administered to health care people [174]. On December 9 Beijing institute vaccine candidate received full authorization to be used in the United Arab Emirates, the vaccine being at efficacy 86% [175]. Bahrain also approved the vaccine on basis of data, it also participated in phase 3 trials [176]. Another vaccine by Sinopharm was made by the Wuhan Institute of Biological Products. The phase 1/2 trial reported that the vaccine was able to induce antibodies in patients. In various countries, the vaccine is under phase 3 trials [177].

CONCLUSION

With COVID-19 appearing to spread, more infections are likely to occur in various regions, parts of the globe within the general public. The society and their family members, as well as the general public and health service providers, therefore need to be informed as accurately as possible. Since we still have the COVID-19 epidemic worldwide, we need to efficiently and effectively make preparations ourselves. Our objective should be to provide adequate clinical care and patient support whilst adequately protecting healthcare professionals.

In the last two decades, we have been alerted thrice. First, in 2002, the SARS-CoV spread rapidly to 32 nations around the globe then in 2012 a MERS-CoV outbreak was later experienced worldwide. The newly developed SARSCoV-2 is certainly a warning in recent times. SARS-CoV-2 is confirmed by its binding with ACE2 in the lung. ACE2 is highly expressed in other tissues, such as the bile duct, esophagus, gastrointestinal organ, liver, kidneys, and testis as well as in pulmonary tissue.

In addition to new medicines and old drug clinical testing, SARS-CoV-2 vaccines must also be designed and developed. SARS-CoV and MERS-CoV lessons indicate that SARS-CoV-2 research should focus on the creation of animal models to summarize the different aspects of human disease and the vaccine safety and effectiveness determinants. Moreover, positive news in the development of vaccines suggests that new vaccines will be available on the market soon and a bowl of immunity against this virus can be established, thus limiting the spread and eradication of this deadly virus from the surface of the world as with so many viruses.

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