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Review article

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

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ABSTRACT

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 SARS-CoV-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, nefamostate 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.

1. Introduction

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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Abbreviation

ACE2	Angiotensin Converting Enzyme 2
ALC	Alternate Level of Care
APC	antigen-presenting cell
ARDS	Acute Respiratory Distress Syndrome
AT2	Angiotensin-2
BCG	*Bacillus Calmette–Guérin* Vaccine
CDC	Centre For Disease Control And Prevention
CDSCO	Central Drug Standard Control Organization
CEPI	Coalition for Epidemic Preparedness Innovation
CFR	Case Fatality Rate
CGHS	Central Government Health Scheme
c-Myc	Myc Proto-Oncogene Protein
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CPAM	Congenital Pulmonary Airway Malformation
CPR	Cardiopulmonary Resuscitation
CRP	*C*-Reactive Protein Test
CT scan	Computerized Tomography Scan
CXR	Chest X-Ray
CYP3A	Cytochrome P450
DCGI	Drugs Controller General of India
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ESRD	End-Stage Renal Disease
EUA	Early Use Authorization
FDA	Food and Drug Administration
GI	Gastro Intestinal Tract
hACE	human angiotensin-converting enzyme-2
HIV	Human Immunodeficiency Virus
ICMR	Indian Council of Medical Research
IFN-1	Interferon Type-I
IFNAR	Interferon-A/B Receptor
IL-6	Interleukin-6
ISG	Interferon Stimulating Gene
IVIG	Intravenous Immunoglobulin
LAV	Live Attenuated Virus
MERS	Middle East Respiratory Syndrome
MRF	*Medical* Response Force
mRNA	Messenger RNA
NASH	Non-Alcoholic Steatohepatitis
nCoV	Novel Coronavirus Infection
OPD	Outpatient Department
PDIA3	Protein Disulfide-Isomerase A3
PFOR	Pyruvate Ferredoxin Oxidoreductase Enzyme
PPE	Personal Protective Equipment
R&D	Research and Development
RBC	Red Blood Cell
RBD	Receptor Binding Domain
RCGM	Review Committee on Genetic Manipulation
RDRP	RNA-Dependent RNA Polymerase
RNA	Ribonucleic Acid
RNAaemia	Serum SARS-CoV-2 Viral Load
RRAR	polybasic cleavage site
RR	Respiratory Rate
RT-PCR	Reverse Transcription Polymerase Chain Reaction
S-glycoprotein	Spike-glycoprotein
SARS	Severe Acute Respiratory Syndrome
SLE	Systemic Lupus Erythematosus
SPO2	Peripheral Capillary Oxygen Saturation
TGF	tumor growth factor
TNF	tumor necrosis factor
TH2	T Helper Cell Type 2
USA	United States of America
VRDLs	Viral Research & Diagnostic Laboratories
WHO	World Health Organization

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 and supposed to spread from the animal species (possibly bats, snakes, fish or any other) consumed by the affected population [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 691,013 confirmed death reports throughout the globe till date [6, 7]. Such huge mortality and morbidity reports create too much chaos among the world population which originated various myths like high temperature kill SARS-CoV-2 virus, ability to hold your breath for more than 10 s without difficulty is a test to confirm the infection, drinking alcohol protects against COVID-19 infection, a hot water bath will prevent the COVID-19, etc. Thus, to clarify the confusion and false predictions, WHO 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

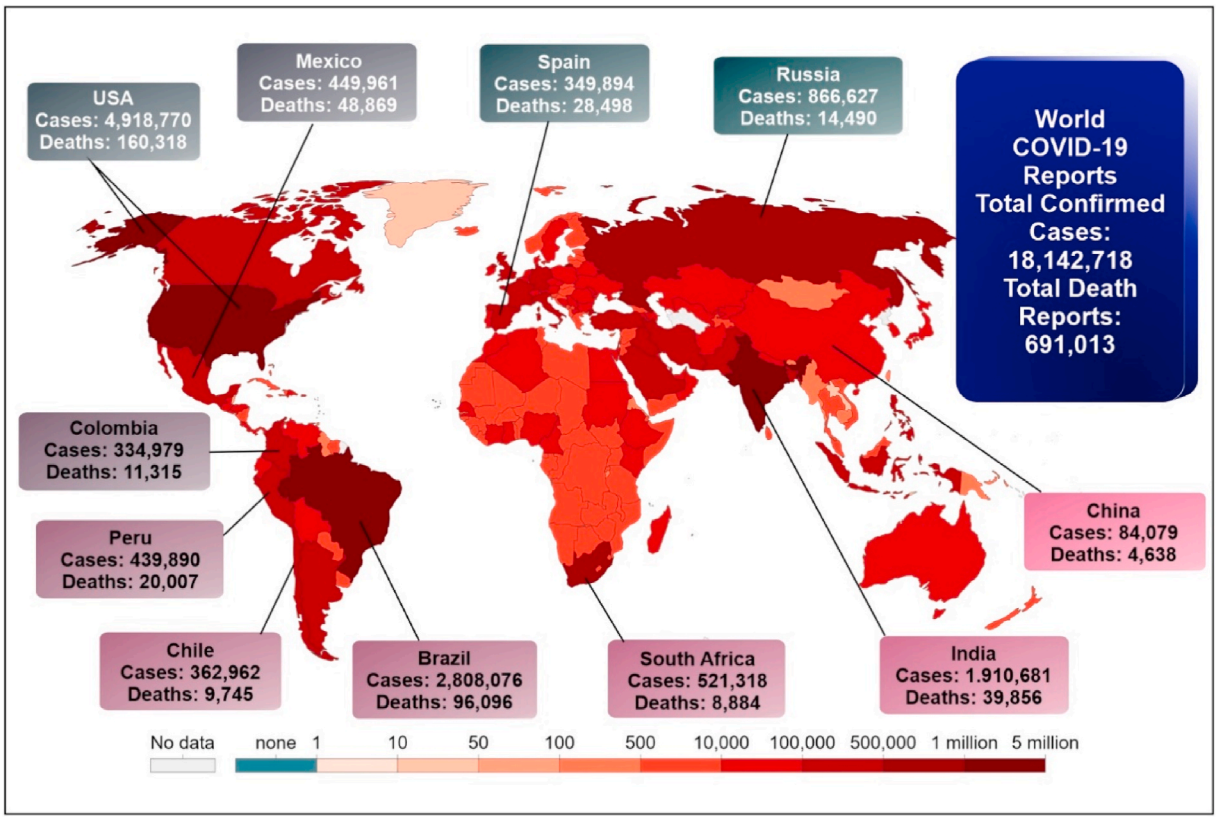

Fig. 1. Geographical representation of COVID-19 epidemiology, showing the current statistics of 10 worsely affected countries including USA, Brazil, India, Russia, South Africa, Mexico, Peru, Chile, Spain and Colombia along with the present data of China (confirmed cases and death reports in these countries till August 5, 2020).

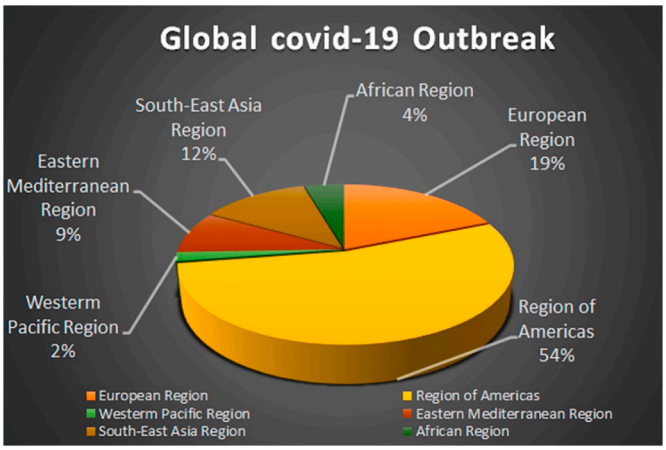

Fig. 2. Epidemiology of COVID-19 infection showing the number of confirmed cases in a different region of the Globe as per WHO COVID-19 Situation report 197 [6].

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

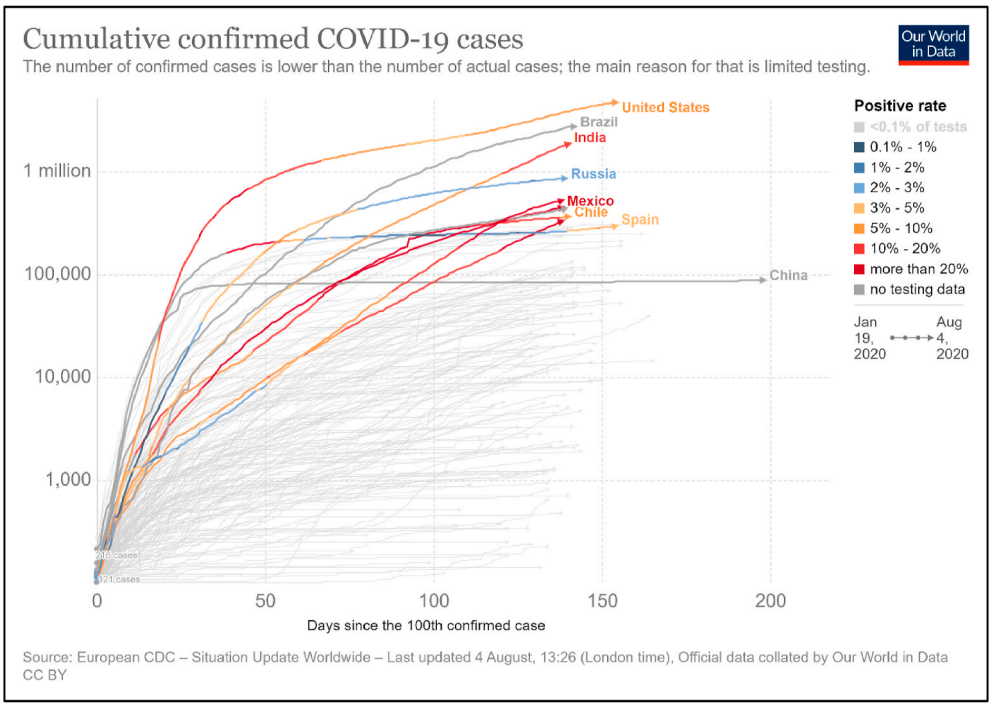

Fig. 3. Graph showing number of confirmed cases and rate of spread of COVID-19 in 10 worsely affected countries including USA, Brazil, India, Russia, South Africa, Mexico, Peru, Chile, Spain and Colombia along with the present data of China starting from January 19, 2020 to August 4, 2020 (Adapted from [25]).

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

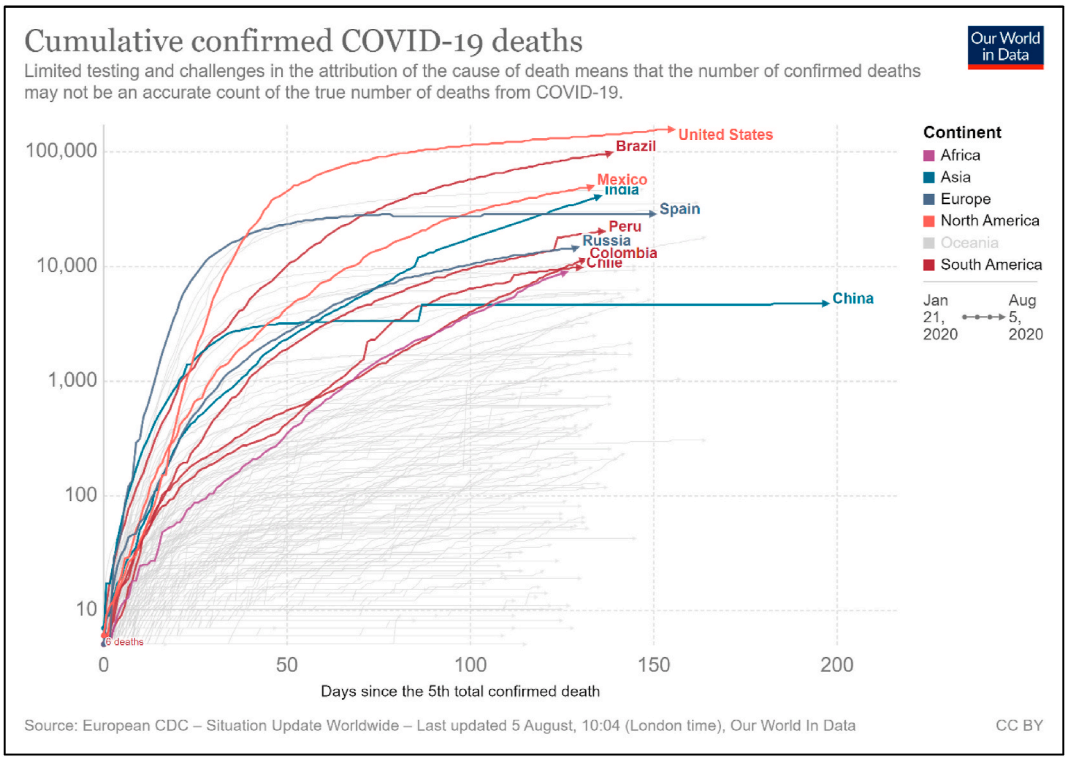

Fig. 4. Graph showing cumulative confirmed death due to COVID-19 in 10 worsely affected countries including USA, Brazil, India, Russia, South Africa, Mexico, Peru, Chile, Spain and Colombia along with the present data of China starting from January 21, 2020 to August 5, 2020 (adapted from [26]).

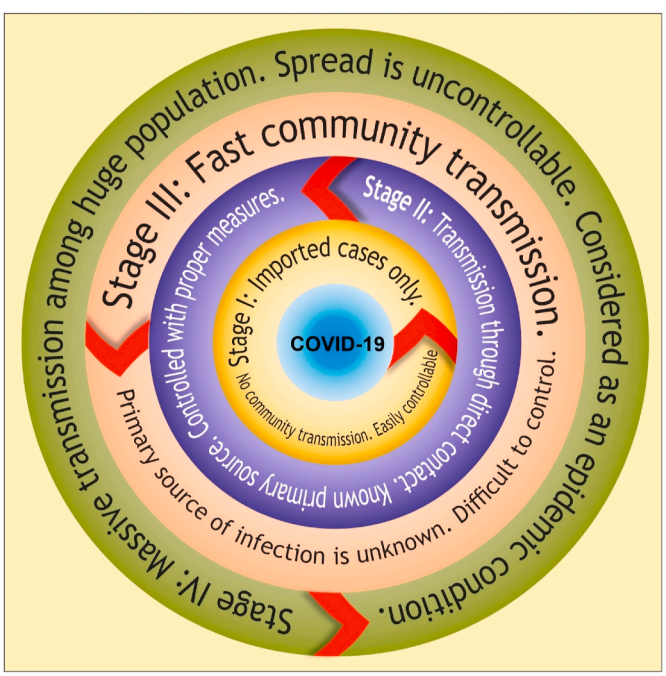

Fig. 5. Different phases of disease transmission or spread in the community according to its mode of spread and severity.

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

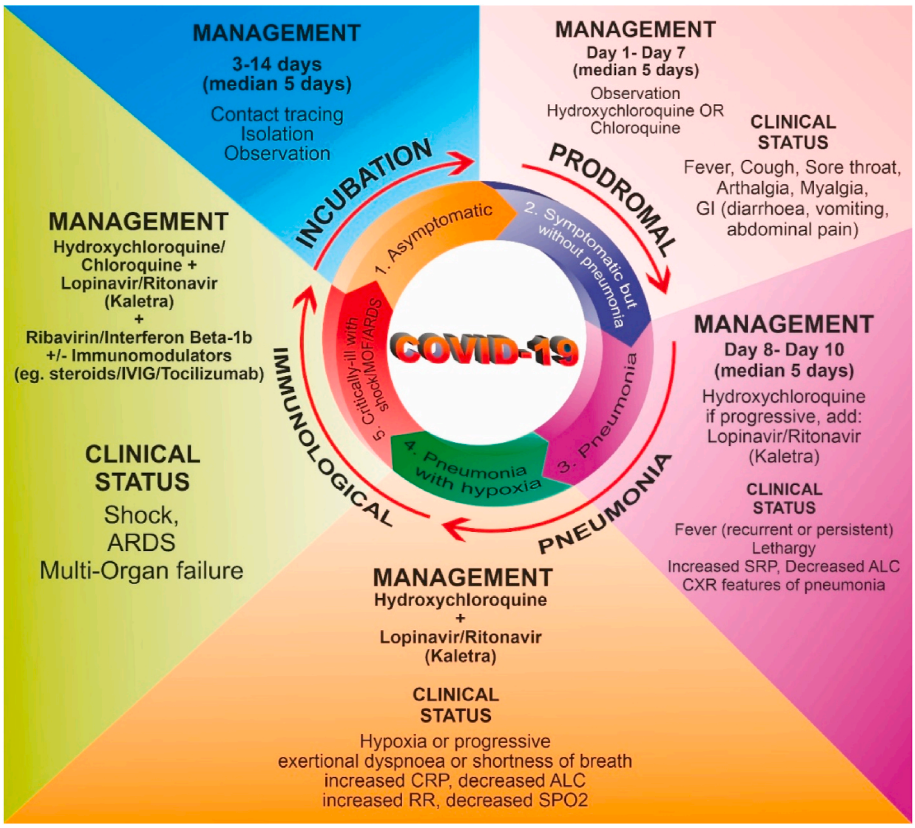

Fig. 6. Phases of disease progression, pathophysiology, clinical symptoms, and management approaches.

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, diarrhea, 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, lethargy, CXR features of pneumonia, increased CPR 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 dyspnea, increase 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 [33,36]. The pathophysiology of COVID-19 is graphically presented in Fig. 7.

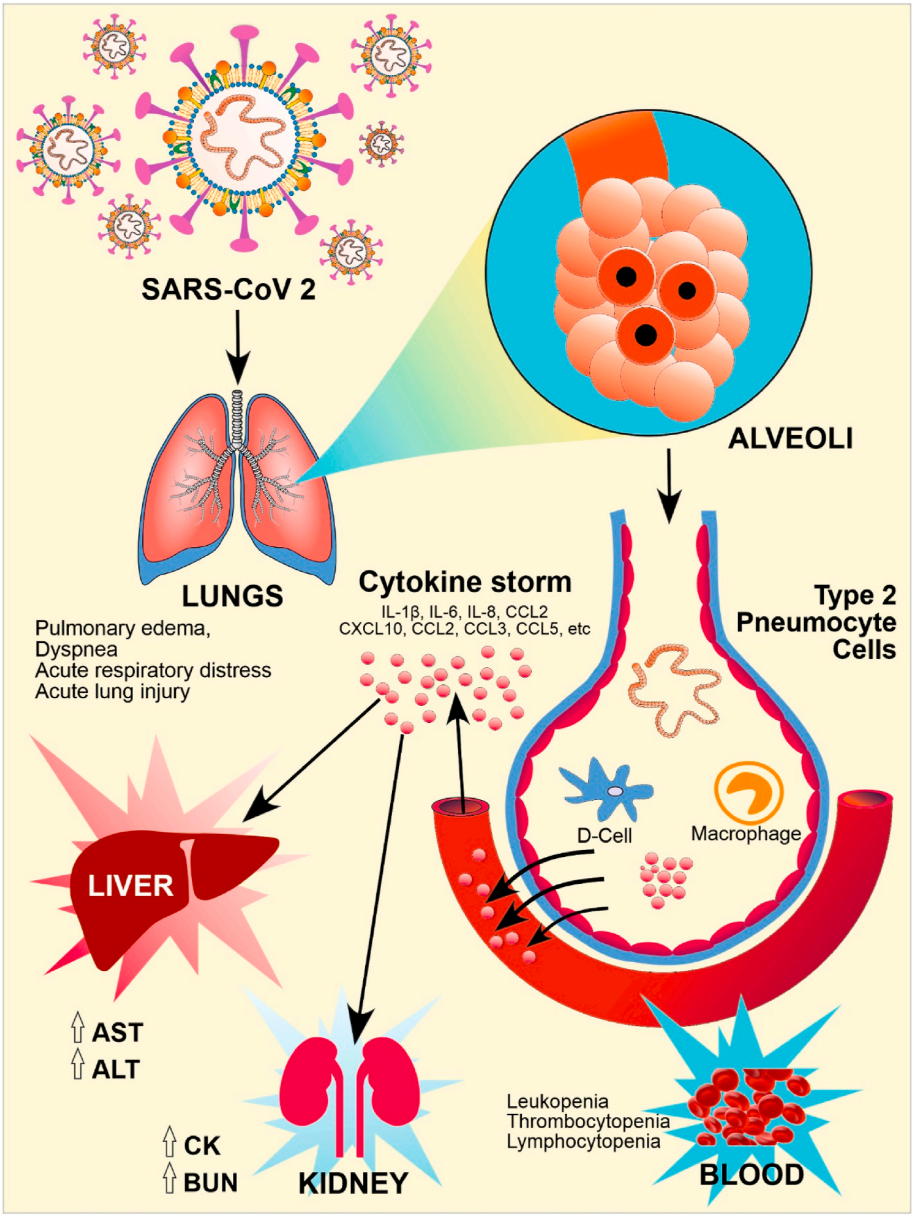

Fig. 7. The figure demonstrates a brief overview on the pathophysiology of COVID-19. When SARS-CoV-2 entered into the lungs, it binds to the hACE2 receptor of type-2 pneumocyte cells of the alveoli and activates the macrophages and other inflammatory mediators like different cytokines and chemokines. These inflammatory mediators result in rigorous immunological reactions and bring 'cytokine storm' which causes damage to lung tissues and other organs by entering into the general circulation (Adapted with permission from [33]).

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, dyspnoea, headache, hemoptysis, 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, RNAaemia, 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, rhinorrhoea 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

Table 1
List of different COVID-19 diagnostic tools under development along with the respective companies and their approval status [47]].

S·N.	Product name	Test Type	Result time (h)	Company/Institution	Approval status
	RealTime SARS-CoV-2	PCR	4–6	Abbott	FDA-EUA
	ID NOW COVID-19 Test	Isothermal amp.-PoC	<1	Abbott	FDA-EUA
	AvellinoCoV2	PCR	24–48	Avellino Labs	FDA-EUA
	Real-Time Fluorescent RT-PCR kit	PCR	3	BGI	FDA-EUA
	BIOFIRE COVDI-19 test	PCR	<1	Biomerieux-BioFire Defense	FDA-EUA
	2019-nCoV Real-Time RT-PCR Dx Panel	PCR	24–72	CDC	FDA-EUA
	Xpert Xpress SARS-CoV-2 Test	PCR-PoC	<1	Cepheid	FDA-EUA
	Simplexa COVID-19 Direct	PCR	1	DiaSorin Molecular	FDA-EUA
	ePlex SARS-CoV-2 Test	PCR	2	GenMark Diagnostics	FDA-EUA
	Panther Fusion SARS-CoV-2 Assay	PCR	3	Hologic	FDA-EUA
	COVID-19 RT-PCR Test	PCR	24	LabCorp	FDA-EUA
	NxTAG CoV Extended Pannel Assay	PCR	4	Luminex Molecular Diagnostic	FDA-EUA
	Accula SARS-CoV-2 Test	PCR-PoC	<1	Messa Biotech	FDA-EUA
	New Coronavirus RT-PCR Test	PCR	4–6	Perkin Elmer	FDA-EUA
	COVID-19 genesig Real-Time PCR assay	PCR	2	Primerdesign	FDA-EUA
	Quest SARS-CoV-2 rRT-PCR	PCR	96–120	Quest	FDA-EUA
	Lyra SARS-CoV-2 Assay	PCR	4–6	Quidel	FDA-EUA
	Cob as SARS-CoV-2 Test	PCR	24	Roche	FDA-EUA
	TaqPath COVID-19 Combo Kit	PCR	4	Thermo Fisher	FDA-EUA
	NY SARS-CoV-2 Real-time RT-PCR	PCR	24–72	Wadsworth Centre, NY State	FDA-EUA
	SARS-CoV-2 + Influenza A & B RT-qPCR Kit	PCR	4–6	3D Medicine	CE Mark
	RAELQUALITY RQ-2019-nCoV	PCR	4–6	AB Analytica	CE Mark
	Bosphore 2019-nCoV Detection Kit	PCR	2	Anatolia Geneworks	CE Mark
	SARS-CoV-2, Influenza, RSV panel	PCR	4–6	AusDiagnostics	CE Mark
	AccuPower COVID-19 Real-Time RT-PCR Kit	PCR	8	Bioneer	CE Mark
	Q-Sens 2019-nCoV Detection Kit	PCR	2	CancerRop	CE Mark
	VIASURE SARS-CoV-2 Real-Time PCR	PCR	3	CerTest Biotech, BD	CE Mark
	Logix Smart Coronavirus COVID-19 Test	PCR	1–2	Co-Diagnostics	CE Mark
	VitaPCR SARS-CoV2 Assay	PCR-PoC	<1	Credo Diagnostics Biomedical	CE Mark
	qCOVID-19, CLART COVID-19	PCR	5	Genomica/PharmMar Group	CE Mark
	2019 Real-Time PCR Kit	PCR	4–6	Kogene Biotech	CE Mark
	GeneFinder COVID-19 RealAmp Kit	PCR	4–6	OsangHealthcare	CE Mark
	QIAstat-Dx Respiratory SARS-CoV-2 Panel	PCR	1	Qiagen (acq. by Thermo Fisher)	CE Mark
	Allplex 2019-nCoV Assay	PCR	4	Seegene	CE Mark
	DiaPlexQ 2019-nCoV Detection kit	PCR	2	SolGent	CE Mark
	SARS-CoV-2 Clinical Sequencing assay	NGS	>12	Vision Medicals	CE Mark
	Multiple Real-Time PCR Kit	PCR	4–6	Beijing Applied Biological Technologies (XABT)	CE Mark
	Explify Respiratory	NGS	24–48	IDbyDNA	LDT
	COVID-19 Home Test Kits	PCR	72–144	Carbon Health	Discontinued
	At-home COVID-19 test	PCR	48	Everlywell	Discontinued
	COVID-19 Home Test Kit	PCR	48	Nurx, Molecular Testing Labs	Discontinued

every citizen of the affected country is the prime need at this time. Affordable test kits that produce quick responses, trained health care persons and PPE kit are the key elements to curb the pandemic [47]. WHO suggested the list of COVID-19 suspects including the patients with ARDS and high fever, a person with travel history to the infected area or international travel history after the pandemic outbreak, a person with an exposure to the hot spots of COVID-19, in contact with other suspect or confirmed patients within 14 days before the onset of 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 bronchoalveolar 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 relevance of some frequently used active molecules in COVID-19 therapy 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 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.

S. No.	Therapeutic agents	Category	Indication	Development history	Available dosage form	Side effects	Clinical status against COVID-19	Reference
	Chloroquine	Antimalarial	Malaria, Pneumonia, some viral infections and autoimmune disorders like rheumatoid arthritis, lupus, etc.	Discovered in 1934 by Hans Anderson and the team. Approved for clinical practices in 1947 for malaria treatment	A salt form like phosphate, sulfate & hydrochloride available as an oral tablet	Blurred vision, nausea, vomiting, blurred vision, uncontrolled movements, deafness, headache, diarrhea, mood changes, sore throat, itchiness, etc. Overdose cause chloroquine poisoning which may lead to cardiac arrest	Found effective in COVID-19 associated pneumonia and other symptoms Currently under clinical trial	[54–56]
	Hydroxychloroquine	Antimalarial	Malaria and autoimmune disorder like rheumatoid arthritis, lupus erythematosus	Firstly, synthesized in 1946 and approved in 1955 by USFDA	Oral tablets	Nausea, vomiting, diarrhea, headache, reduced appetite, retinopathy, heart problems, etc. Overdose may lead to heart failure	Effective in preliminary investigations against COVID-19 Under clinical trial	[57,58]
	Remdesivir	Antiviral (nucleotide analog)	Ebola, Marburg & other viral infections	Developed by Gilead Sciences Designated as an orphan drug in Europe by Gilead	Intravenous injection	Nausea, Vomiting	Improvement of *in vitro* and *in vivo* SARS-CoV-2 model Under phase III clinical trial by Gilead Sciences	[59,60]
	Favipiravir	Antiviral (RNA Polymerase inhibitor)	Influenza, also effective against Ebola infection	Developed by Toyama Chemicals, Japan, approved for clinical application in 2014 in Japan	Oral Tablet	Nausea, Vomiting, Sore throat	Effective in preliminary investigations against COVID-19 Under clinical trial	[61]; Mak, 10-03-2020; Xinhua, 17-03-2020)
	Penciclovir	Antiviral (DNA polymerase inhibitor)/ guanosine analog	Herpes virus disease	Launched in 2017 by Fujifilm Toyama Chemical	Topical (cream)	Headache, nausea, dyspepsia, increased serum lipase, abdominal pain, hyperbilirubinemia & dizziness	No satisfactory response in *in vitro* SARS-CoV-2 model, Under investigation	[62,63]
	Ribavirin	Antiviral (nucleoside analog)	hepatitis C, human orthopneumo virus and other hemorrhagic viral fevers including hantavirus, Lassa fever, and Crimean-Congo hemorrhagic fever	Patented in 1971 and approved 1986 for commercial use, launched by Valeant (now known as Bausch 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 & Co.)	Powder for inhalation and Oral capsule	Nausea, headache, muscle pain, fever, etc. RBC breakdown, allergic reactions and liver damage prohibited in pregnancy	Effective against COVID-19 in the preliminary investigation along with other drugs, Currently under clinical trial	[64,65,66]
	Lopinavir-ritonavir	Antiretroviral (protease inhibitor) & immune booster	HIV infection	Approved for clinical application by USFDA in 2000	Available as an oral capsule and oral solution	Headache, vomiting, abdominal pain, diarrhea, rash, hyperlipidemia, ischemic heart disease, etc,	Effective COVID-19 associated pneumonia, Under clinical investigation	[67,68]
	Nafamostat mesylate	Anticoagulant (Serine protease inhibitor)	Cystic fibrosis	Launched in 1986 b y Toril, Designated as Orphan drug by Mucokinetica in European Union in 2010	Intravenous injection	Anaphylaxis, Hyperkalemia, dyspnea, anaphylaxis, etc.	No significant improvement in *in vitro* SARS-CoV-2 model, currently under investigation	[60,69]
	Nitazoxanide	Antiprotozoal	Diarrhea and other protozoal infections, Hepatitis C	firstly introduced by Romark in 1996 for oral administration to	Currently marketed as an oral tablet and suspension as a licensed product	Headache, upset stomach, stomach pain, vomiting, skin rash, fever, itching, discoloration, etc.	Found effective against COVID-19 in *in vitro* study,	[70]; 2016 [60];

(*continued on next page*)

Table 2 (*continued*)

S. No.	Therapeutic agents	Category	Indication	Development history	Available dosage form	Side effects	Clinical status against COVID-19	Reference
				treat pediatric diarrhea	by Cardinal Health		Under clinical investigation	
	Teicoplanin	Glycopeptide antibiotics	Staphylococcal infection, effective in some viral infections like influenza, Ebola, Hepatitis C, HIV, etc.	–	Intramuscular & intravenous injection	Fever, erythematous rash, etc.	Effective against SARS-CoV-2 in preliminary investigations, Clinical investigations are needed to assess the safety and efficacy	[71,72,73]
	Melatonin	Health-promoting agent (Anti-inflammatory & antioxidant)	Atherosclerosis, delirium, sleep disorders, respiratory diseases, and different viral infections	Firstly discovered in 1917 Carey P. McCord & Floyd P. Allen while the antioxidant property was discovered in 1993	Fast dissolving tablet	Headache, bedwetting, dizziness, diarrhea, Nausea, high risk of seizure, etc.	Suppose to be effective in COVID-19 but no clinical shreds of evidence are available	[74–76]

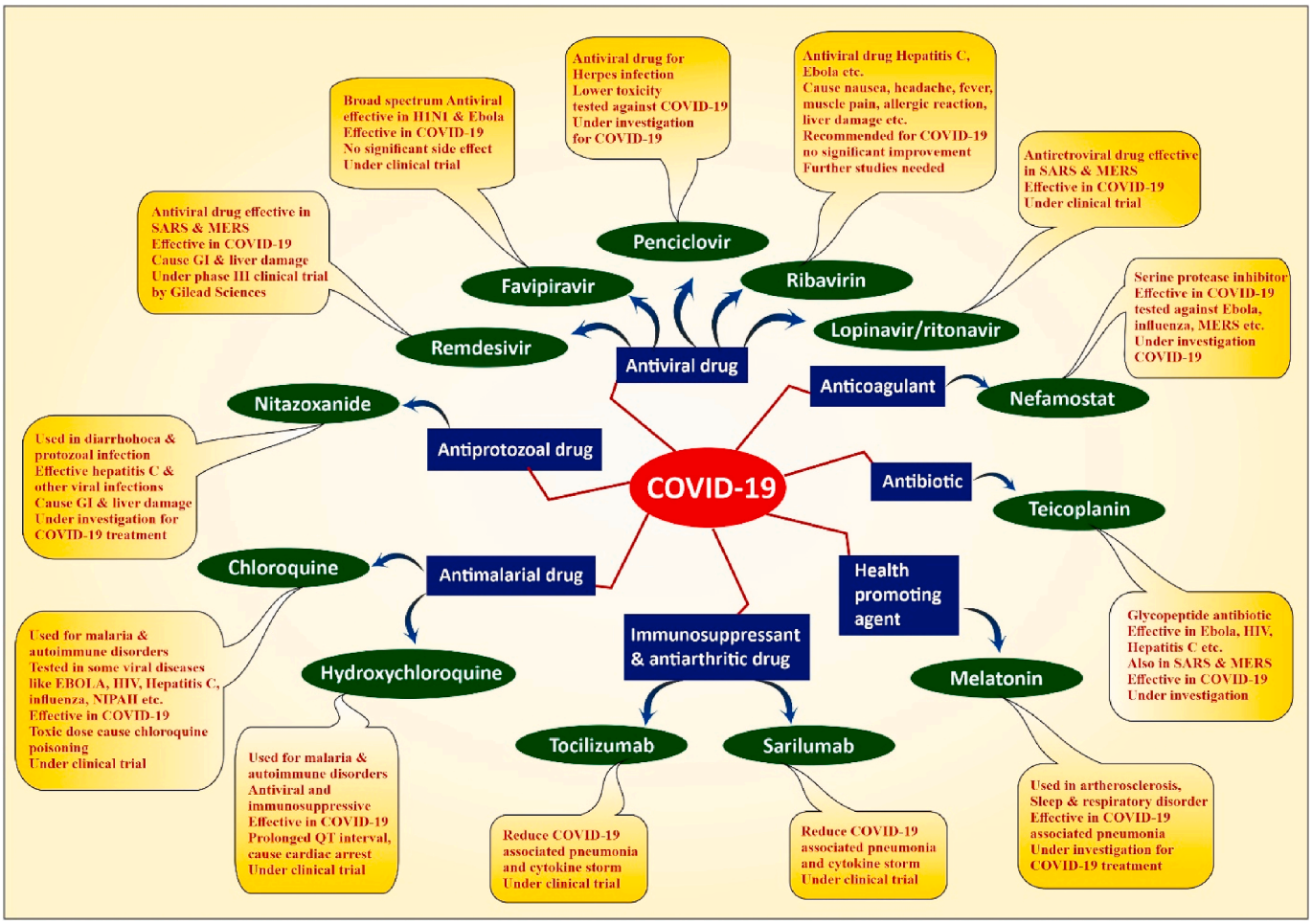

Fig. 8. Developmental aspects of different therapeutic agents currently under investigation for COVID-19 treatment.

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 Register (ChiCTR2000029939, ChiCTR2000029837, ChiCTR2000029899, ChiCTR2000029935, ChiCTR2000029868, ChiCTR2000029803, ChiCTR2000029760, ChiCTR2000029609, ChiCTR2000029762, ChiCTR2000029741, ChiCTR2000029559, ChiCTR2000029898, ChiCTR2000029826, ChiCTR2000029542, ChiCTR2000029761, ChiCTR2000029740, etc.) proposing the application of chloroquine against COVID-19 [78]. [95] stated, as per the current report, chloroquine phosphate showed better control in the treatment of pneumonia, inhibiting its exacerbation, promoting negative conversion of virus and shortening the disease period [95]. Various studies reported that chloroquine increases the endosomal pH which facilitates the viral growth by cell fusion thus showed broad-spectrum antiviral activity. It also interferes with glycosylation of SARS-CoV cell receptors [84,96]. 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 therapeutics 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 application in the 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 [100].

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 Erythematosus (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 retracted 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 coronavirus diseases 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 [116]. 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 cobination 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, favilavi 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, fenivir, vectavir, and famciclovir (prodrug with improved oral absorption) [122]. In recent work, Xiao and the 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, simeprevir, 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 Beheshti 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 Europen Union 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 in 2010, 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, PDIA3 (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 IC_{50} (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 impending 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

Table 3
List of drugs along with their respective agencies/companies currently under clinical development as new treatment line for COVID-19 (Adapted from [47]]).

S·N.	Brand Name	Generic name	Company/agency	Mode of action	Treatment goal	Stage of clinical trial
	Kaletra	Lopinavir-ritonavir	Abbvie	HIV protease inhibitor	Anti-viral growth	Failed trial
	Arbidol	Umifenovir	Pharmstandard	Broad-spectrum antiviral agent	Anti-viral growth	Failed trial
	Ganovo + ritonavir	Danoprevir	Ascletis	Hep C/HIV protease inhibitor	Treat pneumonia	Phase IV
	Actemra	Tocilizumab	Roche	IL-6 inhibitor	Anti-inflammatory	Phase III
	Lenzilumab	Lenzilumab	Humanigen	Anti-GM-CSF	Anti-inflammatory	Phase III
	CD24FC	–	OncoImmune	IL-6 inhibitor	Anti-inflammatory	Phase III
	Prezcobix	Prezcobix	Shanghai Public Health Clinical Centre	HIV protease inhibitor, a CYP3A inhibitor	Treat pneumonia	Phase III
	Colchicine	Colchicine	Montreal Heart Institute	Tubulin disruption	Anti-inflammatory	Phase III
	Kevzara	Sarilumab	Regeneron, Sanofi	IL-6 inhibitor	Anti-inflammatory	Phase II/III
	Chloroquine/ Hydroxychloroquine	Chloroquine/ Hydroxychloroquine	Univ of Minnesota	ACE-2 inhibitor	Anti-viral growth	Phase II/III
	Avigan	Favipiravir	Fujifilm	RNA polymerase inhibitor	Anti-viral growth	Phase II/III
	Avastin	Bevacizumab	Roche	VEGF inhibitor	Treat pneumonia	Phase II/III
	Remdesivir	Remdesivir	Gilead	Adenosine analog	Anti-viral growth	Phase II
	Leronlimab	Leronlimab	CytoDyn	CCR5 antagonist	Anti-inflammatory	Phase II IND failed
	Aviptadil	Aviptadil	NeuroRx	IL-6 inhibitor	Anti-inflammatory	Phase II
	SNG001	–	Synairgen	IFN-β-1a	Treat respiratory illness	Phase II
	Gilenya	Fingolimod	Novartis	Sphingosine-1-phosphate modulator	Anti-inflammatory	Phase II
	AiRuika	Camrelizumab	South East University, China	PD-1 inhibitor	Treat pneumonia or sepsis	Phase II
	Mesenchymal Stem Cells	–	VCANBIO Cell & Gene Engineering	Tissue regeneration	Anti-inflammatory, Tissue regeneration	Phase I/II
	Losartan	Losartan	University of Minnesota	ATiR inhibitor	Reduce organ failure	Phase I
	Gimsilumab	Gimsilumab	Roivant	Anti-GM-CSF	Anti-inflammatory	Phase I
	Sylvant	Siltuximab	EUSA pharma	IL-6 inhibitor	Anti-inflammatory	Observational
	Plasmapheresis	–	Mount Sinai	Antibodies from recovered patients	Anti-viral, Anti-inflammatory	Emergency use

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.

6.2. Immunosuppressants and anti-arthritic drugs

In some cases, the damage by the virus is lower than the damage caused by the hyperactivated immune system of the person itself. As the individual gets exposed to the virus, sometimes the immune system gets overexcited and releases excessive cytokines (cytokine storm) for the frontal attack to the antigen in order to protect the body. This over-exploitation of the immune system causes severe damage to the internal tissues and eventually leads to death. Thus, physicians are using immunosuppressant, tocilizumab to pacify such a storm of cytokine. This drug is approved by the FDA for the treatment of rheumatoid arthritis. It acts by blocking IL-6 (interleukin-6) binding cell receptors and hence reduces the cytokine rage [163]. On March 19, 2020, Roche announced to launch a trial to study the effect of tocilizumab in the symptoms of COVID-19 pneumonia or COVID-19 associated risk factors. The drug will be tested along with other standard drugs in a group of patients and results will be compared with the placebo group. At the same time, Regeneron is planning to conduct a clinical trial on another IL-6 inhibitor sarilumab (marketed as Kevzara) to treat COVID-19 associated pneumonia [164].

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 IFNα2α 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].

Table 4
Detail of COVID-19 vaccines currently approved for clinical trials along with the respective agencies/companies/institutions (adapted from [132,158]).

S·N.	Vaccine	Technology	Current development stage	Developer
	AZD1222	Modified chimp adenovirus vector (ChAdOx1)	Phase II-III	University of Oxford, AstraZeneca
	mRNA-1273	Lipid nanoparticle dispersion containing mRNA	Phase III	Moderna, NIAID, BARDA
	Ad5-nCoV	Recombinant adenovirus type 5 vector	Phase II	CanSinoBIO, Beijing Institute of Biotechnology of the Academy of Military Medical Sciences
	BNT162 a1, b1, b2, c2	mRNA	Phase II-III	BioNTech, Fosun Pharma, Pfizer
	CoronaVac	Inactivated SARS-CoV-2	Phase I-II	Sinovac, Instituto Butantan
	INO-4800	DNA plasmid delivered by electroporation	Phase I-II	Inovio, CEPI, Korea National Institute of Health, International Vaccine Institute
	AG0301-COVID19	DNA plasmid	Phase I	Shenzhen Genoimmune Medical Institute
	LV-SMENP-DC	Lentiviral vector with minigene modifying DCs	Phase I	Shenzhen Genoimmune Medical Institute
	LNP-nCoVsaRNA	mRNA	Phase I	MRC clinical trials unit at Imperial College London
	NVX-CoV2373	SARS-CoV-2 recombinant spike protein nanoparticle with adjuvant	Phase I	Novavax
	Gam-COVID-Vac Lyo	Non-replicating viral vector	Phase I	Gamaleya Research Institute
	GX-19	DNA	Phase I	Genexine consortium, International Vaccine Institute
	SCB-2019	Spike protein trimeric subunit with GSK adjuvant	Phase I	Clover Biopharmaceuticals
	COVAX-19	Recombinant protein	Phase I	Vaxine Pty Ltd
	CVnCoV	mRNA	Phase I	CureVac, CEPI
	SARS-CoV-2 Sclamp	Molecular clamp stabilized spike protein with MF59	Phase I	UQ, Syneos Health, CEPI, Seqirus

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 5
Presently registered clinical studies for exploring the efficiency of various bioactives and therapeutic measures towards the treatment of COVID-19.

Drug	Title	Design	Condition	Population	Intervention types	Registration no.
Arbidol	A Randomized multicenter Controlled Clinical Trial of Arbidol in Patients With 2019 Novel Coronavirus (2019nCoV)	Double-blind, multicenter, randomized clinical study	SARS-CoV-2 infection (COVID-19)	Patients with 2019 novel coronavirus (2019-nCoV) infection ($n = 500$)	Drug therapy	NCT04246242
ASC-09F and Ritonavir	A Randomized, Open, Controlled Clinical Study to Evaluate the Efficacy of ASC-09F and Ritonavir for 2019-nCoV Pneumonia	Randomized, single-blind clinical study	Pneumonia; SARS-CoV-2 infection (COVID-19)	Patients aged 18–55 years with 2019-nCoV Pneumonia ($n = 60$)	Drug therapy	NCT04261270
Vitamin C	Vitamin C Infusion for the Treatment of Severe 2019nCoV Infected Pneumonia	Double-blind, placebo-controlled, randomized clinical study	SARS-CoV-2 infection (COVID-19); Pneumonia	Patients aged 18 y and older with 2019 novel coronavirus (2019-nCoV) pneumonia ($n = 140$	Drug therapy	NCT04264533
Bromhexine Hydrochloride	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)	Comparative, open, randomized clinical study	Pneumonia; SARS-CoV-2 infection (COVID-19)	Patients aged 18 to 80 y with suspected and clinical symptoms confirmed case of mild, or common novel coronavirus pneumonia (COVID-19) ($n = 60$)	Drug therapy, Immunotherapy	NCT04273763
Human Umbilical Cord Mesenchymal Stem Cells	Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Novel Coronavirus Severe Pneumonia	Open, placebo-controlled, randomized clinical study	SARS-CoV-2 infection (COVID-19)	Patients aged 18 to 65 y with 2019 novel coronavirus (2019-nCoV) infection ($n = 48$)	Transplantation/ cell therapy	NCT04273646
–	Treatment of Mild Cases and Chemoprophylaxis of Contacts as Prevention of the COVID-19 Epidemic	Open, randomized clinical study	SARS-CoV-2 infection (COVID-19)	Healthy subjects aged 18 y and older ($n = 2900$)	Drug therapy, Prevention	NCT04304053
Chloroquine	Chloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting	Double-blind, placebo-controlled, randomized clinical study	SARS-CoV-2 infection (COVID-19)	Healthy Volunteers Aged 16 Years and older ($n = 10000$)	Drug therapy, Prevention	NCT04303507
Hydroxychloroquine and azithromycin	Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial	Open-label non-randomized clinical trial	SARS-CoV-2 infection (COVID-19)	Patients above 12 years age with confirmed COVID-19 and PCR documented SARS-CoV-2 carriage	Drug therapy	
Fingolimod	Fingolimod in COVID-19	Open clinical study	Pneumonia, viral; SARS-CoV-2 infection (COVID-19)	Patients aged 18 to 85 y with viral pneumonia/ 2019 novel coronavirus (2019-nCoV) infection ($n = 30$	Drug therapy	NCT04280588
Immunoglobulin	Treatment of Acute Severe 2019-nCoV Pneumonia with Immunoglobulin From Cured Patients	Open clinical study	SARS-CoV-2 infection (COVID-19); Pneumonia, viral	Patients aged 18 y and older with 2019 novel coronavirus (2019-nCoV) infection pneumonia ($n = 10$)	Drug therapy	NCT04264858
Lopinavir/Ritonavir, Ribavirin and IFN-beta	Lopinavir/Ritonavir, Ribavirin and IFN-beta Combination for nCoV Treatment	Open, randomized clinical study	SARS-CoV-2 infection (COVID-19)	Patients aged 18 y and older with 2019 novel coronavirus (2019-nCoV) infection ($n = 70$)	Drug therapy	NCT04276688
Anti-CD147 Humanized Meplazumab	Clinical Study of Anti-CD147 Humanized Meplazumab for Injection to Treat With 2019-nCoV Pneumonia	Open clinical study	SARS-CoV-2 infection (COVID-19)	Patients aged 18 to 75 y with 2019 novel coronavirus (2019-nCoV) infection ($n = 20$	Drug therapy, Immunotherapy	NCT04275245
Corticosteroids	Efficacy and Safety of Corticosteroids in COVID-19	Open, randomized clinical study	SARS-CoV-2 infection (COVID-19); Pneumonia	Patients aged 18 y or older with 2019 novel coronavirus (2019-nCoV) infection/pneumonia ($n = 400$)	Drug therapy	NCT04273321
Pirfenidone	A Study to Evaluate the Efficacy and Safety of Pirfenidone With Novel Coronavirus Infection	Multicenter, open, randomized clinical study	Pneumonia, viral; SARS-CoV-2 infection (COVID-19); Hospitalization	Hospitalized adult patients aged 18 y and older with severe type novel coronavirus pneumonia ($n = 294$	Drug therapy	NCT04282902
Remdesivir	Adaptive COVID-19 Treatment Trial	Double-blind, multicenter, placebo-controlled, randomized clinical study	SARS-CoV-2 infection (COVID-19)	Patients aged 18–99 y with 2019 novel coronavirus (2019-nCoV) infection (COVID-19) ($n = 394$	Drug therapy	NCT04280705
Remdesivir					Drug therapy	NCT04292730

(*continued on next page*)

Table 5 (*continued*)

Drug	Title	Design	Condition	Population	Intervention types	Registration no.
	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Participants with Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment	Open, randomized clinical study	SARS-CoV-2 infection (COVID-19)	Patients aged 18 years and older with 2019 novel coronavirus (2019-nCoV) infection (n = 600)		
Remdesivir	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Participants With Severe Coronavirus Disease (COVID-19)	Open, randomized clinical study	SARS-CoV-2 infection (COVID-19)	Patients aged 18 y and older with 2019 novel coronavirus (2019-nCoV) infection (n = 400)	Drug therapy	NCT04292899
Ritonavir and danoprevir	Clinical Trial of Ganovo and Ritonavir Combination Therapy on Novel Coronavirus Pneumonia	Open clinical study	SARS-CoV-2 infection (COVID-19)	Patients with 2019 Novel Coronavirus Pneumonia (2019-nCoV)	Drug therapy	
Shengjimycin, lopinavir/ritonavir, umifenovir and chloroquine	The Clinical Study of Carrimycin on Treatment Patients with COVID-19	Multicenter, open, randomized clinical study	SARS-CoV-2 infection (COVID-19)	Patients aged 18 to 75 y with 2019-nCoV infection (n = 520)	Drug therapy	NCT04286503
Sildenafil	A Pilot Study of Sildenafil in COVID-19	Open clinical study	SARS-CoV-2 infection (COVID-19)	Patients aged 18 y and older with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19) (n = 10)	Drug therapy	NCT04304313
Thalidomide	The Efficacy and Safety of Thalidomide in the Adjuvant Treatment of Moderate New Coronavirus (COVID-19) Pneumonia	Double-blind, placebo-controlled, randomized clinical study	SARS-CoV-2 infection (COVID-19)	Patients aged 18–75 years with 2019 novel coronavirus (2019-nCoV) infection (n = 100)	Drug therapy	NCT04273529
Thalidomide	The Efficacy and Safety of Thalidomide Combined with Low-dose Hormones in the Treatment of Severe COVID-19	Double-blind, placebo-controlled, randomized clinical study	Infection, viral	Patients aged 18 to 75 y with confirmed diagnosis of CoVID-19 (n = 40	Drug therapy	NCT04273581

detail of all the ongoing and registered clinical trials on COVID-19 is given in supplementary file 3a and 3b. All the clinical data were collected from Integrity database.

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 suspects 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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Appendix A. Supplementary data

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