Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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OUTBREAK of novel corona virus disease (COVID-19): Antecedence and aftermath

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ABSTRACT

Outbreak of Coronavirus disease 2019 (COVID-19) started in mid of December 2019 and spread very rapidly across the globe within a month of its outbreak. Researchers all across the globe started working to find out its possible treatments. However, most of initiatives taken were based on various hypotheses and till date no successful treatments have been achieved. Some strategies adopted by China where existing antiviral therapy was initially used to treat COVID-19 have not given very successful results. Researchers from Thailand explored the use of combination of anti-influenza drugs such as Oseltamivir, Lopinavir and Ritonavir to treat it. In some cases, combination therapy of antiviral drugs with chloroquine showed better action against COVID-19. Some of the clinical studies showed very good effect of chloroquine and hydroxychloroquine against COVID-19, however, they were not recommended due to serious clinical toxicity. In some cases, use of rho kinase inhibitor, fasudil was found very effective. In some of the countries, antibody-based therapies have proved fairly successful. The use of BCG vaccines came in light; however, they were not found successful due to lack of full-proof mechanistic studies. In Israel as well as in other developed countries, pluristems allogeneic placental expanded cell therapy has been found successful. Some phytochemicals and nutraceuticals have also been explored to treat it. In a recent report, the use of dexamethasone was found very effective in patients suffering from COVID-19. Its effect was most striking among patients on ventilator. The research for vaccines that can prevent the disease is still going on. In light of the dynamic trends, present review focuses on etiopathogenesis, factors associated with spreading of the virus, and possible strategies to treat this deadly infection. In addition, it attempts to compile the recent updates on development of drugs and vaccines for the dreaded disease.

1. Introduction

Though research on coronavirus disease 2019 (COVID-19) was going on at global level since last two decades, highly virulent transmission of COVID-19 came into existence as highly fatal human pathogen during June 2012 in Arabian Peninsula (https://www.business-standard.com/article/international/china-suspends-public--trans-port-in-wuhan-confirms-571-cases-of-coronavirus-120012300122_1.html). At that time, it was christened as Middle East Respiratory Syndrome Coronavirus (MERS-CoVs). Corona virus is an enveloped, positive sense ribonucleic acid (RNA) virus found in various species mainly in mammals and birds (Lee, 2015). The World Health Organization (WHO) named the coronavirus (CoVs) as severe acute respiratory syndrome coronavirus-2(SARS-CoV-2) recently.

The components of SARS-CoV-2 are spike glycoprotein (S), membrane protein (M), nucleocapsid protein (N) and envelope protein (E). The spikes present on the virus consist of a single-pass trans membrane anchor, a large ectodomain and short intracellular tail. The ecto domain contains two subunits S1 and S2 (Li, 2016). The homo trimers of S-protein help in building of spikes on the viral surface which play a key role in its attachment with host receptors (Beniac et al., 2006; Delmas and Laude, 1990). The M glycoprotein performs three major functions i.e. it provides shape to the virions, aids in promoting curvature of membrane, and facilitates binding to the nucleocapsid (Nal et al., 2005;

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Abbreviations

CoVs	Coronavirus
COVID-19	Coronavirus Disease 2019
E	Envelope protein
hDPP-4	Human Dipeptidyl Pentidase-4
HIV	Human Immunodeficiency Virus
LPV	Lopinavir
M	Membrane protein;MAVS,O-mitochondrial antiviral signalling protein
MERS-CoVs	Middle East Respiratory syndrome coronavirus
N	Nucleoprotein
NOX2	nicotinamide adenine dinucleotide phosphate hydrogen oxidase 2
nsp-3	Non-structural protein-3
RBD	Receptor Binding Domain
RNA	Ribonucleic Acid
S	Spike protein
SARS	Severe Acute Respiratory Syndrome
URT	Upper Respiratory Tract
VLPs	Virions Like Particles
WHO	World Health Organization
RT-PCR	Reverse transcription polymerase chain reaction

Neuman et al., 2011). The E-glycoprotein plays a key role in the assembly and pathogenesis of virus (DeDiego et al., 2007; Nieto-Torres et al., 2014). The N- glycoprotein consists of two domains which bind to the RNA genome of the virion. It is also believed that N-glycoprotein bind stonon-structural protein 3 (nsp-3) which, in turn helps in tying the genome to replication-transcription complexes (RTCs) and helps in packaging of enfolded genome into virions (Chang et al., 2006; Fehr and Perlman, 2015; Hurst et al., 2009). The structure of SARS-CoV-2 is shown in Fig. 1.

2. Symptomatic features of COVID-19

The main symptoms of COVID-19 include runny nose, sneezing, common cold, cough, confusion, myalgia, diarrhea, vomiting, shortness of breath, wheezing and fever (Nassar et al., 2018; Tyrrell and Myint, 1996).The virus enters the respiratory tract through nose and stays there for three days. Afterwards, it starts infecting upper respiratory tract (URT) with above-mentioned symptoms. COVID-19 causes URT illness including acute exacerbation of chronic obstructive pulmonary disease, bronchitis and pneumonia, with co-morbidities in digestive, cardiac (Zheng et al., 2020), renal (Cheng et al., 2020) and circulatory systems as well (Huang et al., 2020).

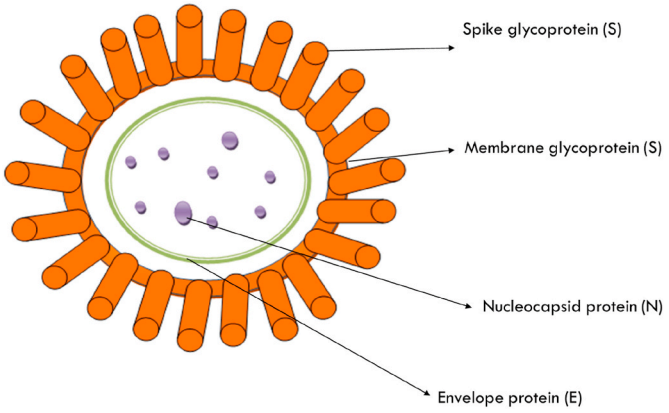

Fig. 1. Structure of SARS-CoV-2. SARS-CoV-2 binds with ACE-2 receptor and influxes host cells through receptor-mediated endocytosis. Inside the cell, SARS-CoV-2 forms a layer called capsid vesicle. Microtubules transport viruses to the cytoplasm. Viral RNA is involved in transcription process in the cytoplasm and conversion into viral genome mRNA. It also affects translation processes and develops viral protein. Viral RNA and viral proteins form new viruses. Thus virus multiplies and forms capsulated nucleoprotein. The multiplied viruses cause apoptosis in the cell and affect other cells also (Bleibtreu et al., 2019).

The risk factor for COVID-19 infection is higher in both infants as well as in geriatric age group. Also, diabetic patients are more prone to COVID-19 with higher rate of mortality and co-morbidity. The risk factors associated with the COVID-19 are obesity, smoking, low blood pressure, impaired gas exchange, leukopenia, anemia, disturbance in liver and kidney functions etc.

3. Life cycle of SARS-CoV-2 in host cell

The life cycle of COVID-19 begins when virion enters the host and gets attached to the host cells by interaction between glycoprotein "S" and host receptors human angiotensin converting enzyme-2 (ACE-2) leading to tropism of virus. The virion enters the cytosol with the help of capthesin and transmembrane protease, serine 2 (TMPRSS2) which results in cleavage of "S" protein from two sites (Hoffmann et al., 2020). The first cleavage helps in separation of receptor binding domains (RBD) and fusion domain of "S" protein while second cleavage exposes fusion peptides to endosomes. Six helical bundles are formed, which release virions into the cytoplasm. After attachment, the replication cycle begins, during which, translation of replica gene in virion genomic RNA takes place. This is encoded by two large open reading frames ORF1a and ORF1b that give rise to poly protein 1a and 1b (pp1a and pp1b) and are expressed by slippery sequence 5′UUU AAC-3′ and RNA pseudo-knot. This results in ribosomal shifting and stops the ribosomal elongation. It also acts as mRNA for expression of structural and accessory proteins. Finally, virus spreads to different parts of the body. During this phase, "S1", "M" and "E" are translated, which help the virion to enter into endoplasmic reticulum and endoplasmic reticulum-golgi intermediate compartments. "M" leads to protein-protein interaction, which further combines with "E" to activate virus-like particles (VLPs), which in turn, lead to formation of corona envelope. Then "N" protein promotes formation of VLPs and fusion of encapsidate with endoplasmic reticulum golgi intermediate compartment (ERGIC) (Shereen et al., 2020).This gives rise to assembly of COVID-19. The exocytosis of virions takes place as a result of interaction between normal and affected cells. Finally the giant cells are formed and virus spreads to other cells (https://www.antibodies-online.com/resources/18/5410/sars-cov-2-life-cycle-stages-and-inhibition-targets/) (Fig. 2).

4. Diagnosis of COVID-19 infection

The detection of SARS-CoV-2 is done by performing antibody testing such as enzyme-linked immune sorbent assay (ELISA) for Immunoglobulin G(IgG), and Immunoglobulin A (IgA) or plaque reduction neutralization test (PRNT) in blood or airways fluid (Fig. 3). Distal lung sampling results in its satisfactory diagnosis (Bleibtreu et al., 2019; Oh, 2016). SARS-CoV-2 kits are very important tools for easy and fast diagnosis in coronavirus pandemic. Various biopharmaceutical companies are working on virus kit research and development. Various kits made by different countries are mentioned in Table 1.

4.1. Real time reverse transcription polymer chain reaction (RT-PCR)

It is the most widely used nuclear derived method to detect the genetic material present in the pathogen. In this technique, radioactive isotope markers were conventionally used to identify the desired target genetic material. But now a days these radioactive isotopes are being replaced by fluorescent dyes. In RT-PCR, the sample is taken mainly from the patient's throat and nose. The collected sample is treated with

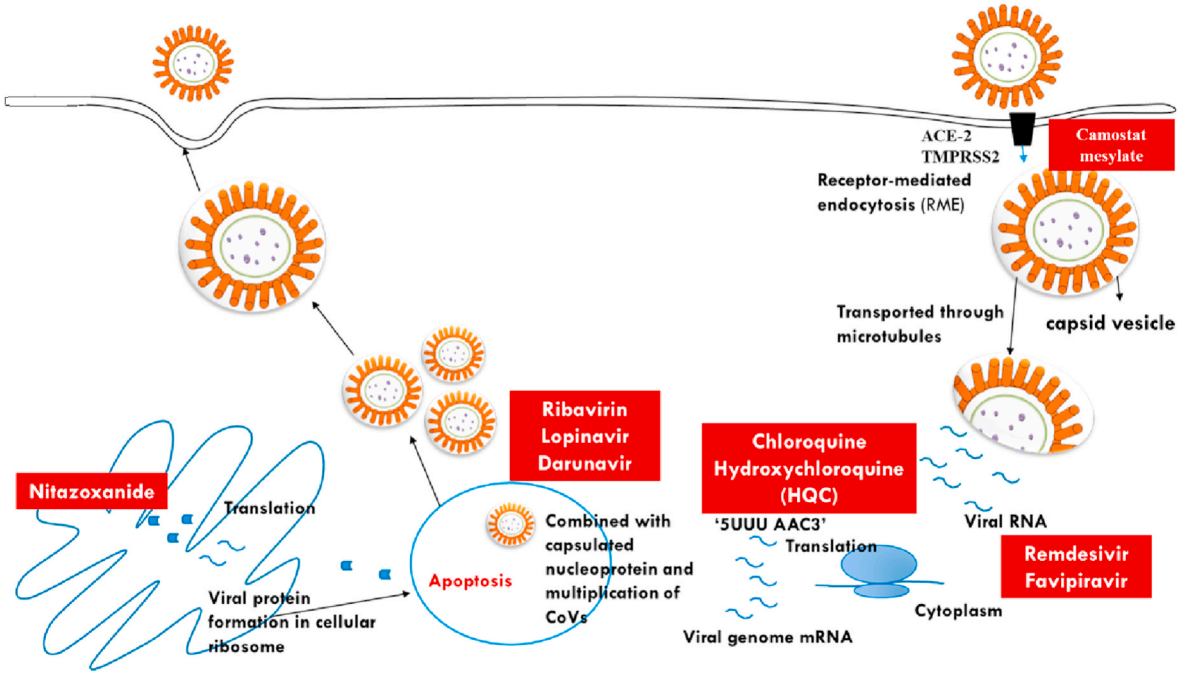

Fig. 2. Viral cycle of SARS-CoV-2 in target host cell and target drug.

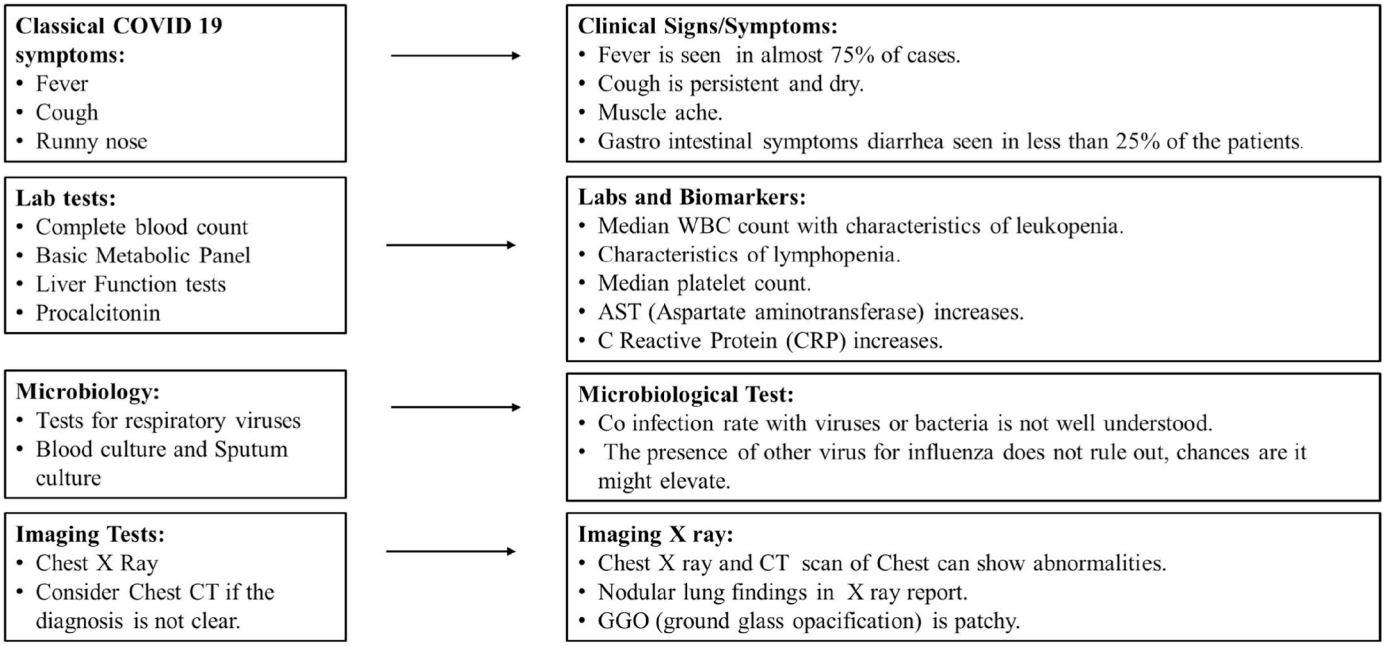

Fig. 3. Tests used for diagnosis of SARS-CoV-2 infection.

Table 1
Diagnostic kits used to detect SARS-CoV-2 infection.

Sr. No.	Pathokit	Country	Reference
1.	GenMarkDx – Multiplex Diagnostics	Canada	(https://www.startus-insights.
2.	XCR Diagnostics – Quantitative Polymerase Chain Reaction (qPCR	United states of America	com/innovators-guide/5-top-diagnostic-test-kits-to-use-during-the-coronavirus-pandemic/)
3.	SensDx – Ultrasensitive Electrodes	Poland	
4.	Aperiomics – Deep Metagenomic Sequencing	United states of America	
5.	MiRXES – MicroRNA Diagnostics	Singapore	
6.	Truenat Beta CoV test	India	(https://www..gov.in/team-india-blogs/truenat-beta-test-covid-19-detection-indiainvestindia)

solvents to remove fats and proteins and extract only RNA. The obtained RNA consists of mixture of infected person's genetic material as well as coronavirus RNA. Then the RNA is reverse transcribed to DNA with help of enzymes. Additional short fragments of DNA that are complementary to specific parts of the transcribed viral DNA are then added. The added fragments attach to the target site of viral DNA if sample consists of virus. The added genetic material acts as a builder for DNA strands during amplification, while the labels added help in detecting the virus. The mixture is then placed under the RT-PCR machine. The machine cycles through heating and cooling of sample so that chemical reaction takes place and forms new copies of viral DNA. These cycles take place 35 times, so that at the end of the cycle, about 35 billion identical copies of viral DNA formed. The fluorescence emission by sample is measured by machine and helps in assessing presence or absence of virus (https://www.iaea.org/newscenter/news/how-is-the-covid-19-virus-detected-using-real-timert-pcr).

4.2. Computed tomography (CT) imaging

It has been found that chest CT imaging is more steady, practical and expeditious technique to diagnose and assess COVID-19. In some of the studies, it has been found that computed tomography is more sensitive tool than RT-PCR to assess COVID-19. The sensitivity of CT and RT-PCR was reported to be 98% and 71% respectively (https://www.itnonline.com/content/ct-provides-best-diagnosis-novel-coronavirus-covid-19). Ai et. al., 2020, studied the comparison between RT-PCR and chest CT for the diagnosis of COVID-19. In the study total 1014 patients underwent RT-PCR and chest CT. The results revealed that out of 1014 patients, 601 (59%) showed positive results with RT-PCR while 888 (88%) patients showed positive CT scans results. So, it was concluded that chest CT is more reliable technique for the diagnosis of COVID-19 (Ai et al., 2020; An et al., 2020).

5. Treatment strategies

With the prevalence of COVID-19 reaching a new hight every day, there is an immediate need to find safe and efficacious measures to diagnose, treat, mitigate and combat the disease. Looking at the alarming dimensions that the disease is acquiring, treatment strategies among various systems of medicines are being investigated. Based on the treatments offered so far and clinical findings, the treatment strategies can be categorized into three classes.

5.1. Synthetic drugs

Antibiotics, for obvious reasons, are not expected be effective in the treatment and a combination of antiviral drugs is being used. Studies also confirm that flu shots are not efficient in the fight against COVID-19 as the patients continue to suffer despite the treatment (https://www.com/articles/gilead-sciences-offers-experimental-drug-for-coronavirus-treatments-testing-11580511519wsj). In the meantime, Thai health officials claimed to have successfully handled the infection with acocktail of antiviral drugs that include lopinavir and ritonavir under the name "*Kaetra*" along with flu medication oseltamivir. However, a lot more studies need to be conducted to declare this combination as a treatment for COVID-19. Randomized clinical trials using combination of antiviral drugs are already being conducted (Hung et al., 2020). Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19 has been tried. The possibility of successful treatment exists because the same combination was successfully used to treat SARS outbreak in 2002 and SARS-CoV-2 is reported to be a strain similar to the earlier one with the genomic sequence of COVID-19 being about 75–80% similar to that of SARS. Lopinavir was used as major antiviral drug to treat during the SARS outbreak. Lopinavir has been reported to treat COVID-19 (https://www.antibodies-online.com/resources/18/5410/sars-cov-2-life-cycle-stages-and-inhibition-targets/),(https://clinicaltrials.gov/ct2/show/NCT03301090?term=NCT03301090#wrapper). However, its efficiency to mitigate COVID-19 is yet to be fully established. To analyze antiviral effect of inferferon-α2b (IFN- α2b) and ribavirin, SARS-CoV-2 was isolated from hCoV-Emc/2012 replication process by Vero and LLC-MK2 cells. Combination of IFN- α2b and ribavirin achieved comparable remission in low concentration. As per Falzarano et al. (2013), combination of IFN- α2b and ribavirin may also prove to be useful (Falzarano et al., 2013). Anti-ebola and anti-HIV drugs combination (remdesivir + galidesivir) showed significant action against the enzymes responsible for virus replication. These drugs have been able to alleviate the symptoms of COVID-19 similar to that in SARS and MERS (Li and De Clercq, 2020). In an *invitro* cell line study, this drug also showed very good antiviral effect (Wang et al., 2020).

The Gilead biotechnology company, USA reported preclinical trials of Remdesivir (a nucleotide analogue) which led to remission in animal models (Sheahan et al., 2020). Later, it was reported to be effective in the treatment of COVID-19 patients also (Holshue et al., 2020). Another study, conducted on 760 patients in placebo-controlled trials also proved the effectiveness of remdesivir. This drug has now received emergency use authorization by USFDA on 1st May 2020 (https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment).

Frequently used antimalarial drug, Chloroquine (CQ) and Hydroxychloroquine (HCQ) have also been explored and found to be quite effective against COVID-19 (Wang et al., 2020). CQ and HCQ increase endosomal pH and interfere with the glycosylation of cellular receptor of SARS-CoV-2. Thereby they have the potential to block viral infection (Wang et al., 2020). Moreover, they change the pH of lysosomes and likely inhibit cathepsins, that leads to the formation of the autophagosome which cleaves SARS-CoV-2 spike protein. It is also reported that CQ and HCQ through the inhibition of MAP-kinase interfere with SARS-CoV-2 molecular crosstalk, besides altering the virion assembly, budding and interfering with the proteolytic processing of the M protein. It is reported that they interfere with ACE-2 receptor's glycosylation. Since, SARS-CoV-2 utilizes the similar surface receptor ACE-2, it is believed that CQ and HCQ can also thus prevent SARS-CoV-2 attachment to the target cells (Zhou et al., 2016). Some studies have also been initiated and showed very good effect of CQ and HCQ against SARS-CoV-2 (Gautret et al., 2020; Singh et al., 2020).; Gao et al. (2020); (Millán-Oñate et al., 2020). However, due to reported potential clinical toxicity issues such as retinal toxicity, the use of CQ and HCQ is not recommended by WHO.

An antiviral drug favipiravir (Avigan), got approval in Japan in 2014. In 2016, this drug was used as an emergency aid for the Ebola virus outbreak. A clinical trial involving 80 participants (in Shenzhen city) demonstrated chest symptoms improvement in patients of COVID-19 treated with favipiravir. The drug was able to shorten the recovery time from 11 days to 4 days in mild and regular cases. Another trial showed that the drug shortened fever duration from an average of 4.2 days–2.5 days. Favipiravir has been reported to be effective, without any obvious side-effects, in helping coronavirus patients recovery. In another study carried out in China, two mild and two severe COVID-19 associated pneumonia patients were treated with combined Western and Chinese medicine treatment (Lopinavir/ritonavir/arbidol/ShufengJiedu Capsule). Three of the four patients showed significant improvement in pneumonia associated symptoms. The remaining patient with severe pneumonia showed signs of improvement; however, the efficacy of this combination treatment warrants further investigation (https://www..nlm.nih.gov/pubmed/32037389ncbi).

In a recent study, Rho kinase (ROCK) inhibitor, Fasudil has been explored to treat COVID-19. In patients with COVID-19, activation of

ROCK causes burst in inflammatory features, immune cell migration, apoptosis, coagulation, contraction, and cell adhesion in pulmonary endothelial cells, leading to endothelium barrier dysfunction and edema as hallmarks of lung injury. Fasudil attenuates this effect due to its excellent anti fibrotic activity (Abedi et al., 2020). It has been found that angiotensin-converting enzyme-2 (ACE-2) is the receptor required for the cellular entry of SARS-CoV-2 (Hoffmann et al., 2020). Envelope spike protein of SARS-CoV-2 mediates its attachment and fusion into the human cells through binding ACE-2 with super-affinity and efficiency. ACE-2 is widely expressed in alveolar epithelial cells and converts angiotensin 2 to angiotensin (1–7). Angiotensin 2 triggers a number of adverse effects like interstitial fibrosis, increased coagulation, interference with adaptive immunity by activating macrophages and other cells of the immune system, with consequent increased production of IL-6, TNFα and other inflammatory cytokines. ROCK inhibitors upregulate the axis of ACE-2, and are thereby found effective in treating COVID-19.

In one of the studies, a 53-year-old woman suffering from COVID-19 was treated with a combination of moxifloxacin and oseltamivir. She was treated with moxifloxacin 400 mg intravenously once a day for eight days and antiviral drug oseltamivir 75 mg orally twice a day for 5 days. After seven days treatment, patient's symptoms got reduced and she tested negative (Ding et al., 2020).

In recent clinical studies the use of steroidal drug Dexamethasone has been very effective to treat patients suffering from COVID-19. It easily diffuses through the host cell membranes and bind to the glucocorticoid receptor in the cell cytoplasm. This receptor binding triggers a cascade of reactions that end up suppressing pro-inflammatory cytokines IL-1, IL-2, IL-6, IL-8, TNF, and IFN-gamma and reduce the severity of Covid-19. Dexamethasone also inhibits the overaction of macrophages in patients suffering from COVID-19. A British research team found that Dexamethasone's (2 mg tablet) effect was most striking among patients on ventilators. Those who were receiving oxygen therapy but were not on ventilators also saw improvement: their risk of dying was reduced by 20%. The steroid had no effect on people with less severe cases of COVID-19 — those not receiving oxygen or ventilation (Ledford, 2020).

Table 2 summarizes various antiviral drugs which may have potential to treat COVID-19 with their mechanism of action. Table 3 summarizes possible drugs with dose to mitigate COVID -19 and Table 4 provides update about recent clinical trials on COVID-19 with possible targets.

5.2. Phytochemicals

Saikosaponins are triterpene glycosides isolated from medicinal plants like *Bupleurum spp, Heteromorpha spp and Scrophularia scorodonia* which possess potent antiviral activity (Li et al., 2005). Extracts belonging to *Lindera aggregata, Lycoris radiata, Artemisia annua and Pyrrosia lingua* have been recorded to show antiviral activity especially against SARS. An Amentoflavone isolated from *Torreya nucifera* (belonging to the family Taxaceae), a native of southern Japan and South Korea has been shown to inhibit SARS-CoV 3 CL protease. *Isatis tinctoria,* known as *Asp of Jerusalem* belonging to the family Brassicaceae, has been shown to have SARS-CoV 3CL protease inhibition acivity (Lin et al., 2014). With 99% of small molecules failing to be effective, it remains to be seen what can be used in the fight against COVID-19. Fig. 4 exhibits the patents granted on drugs and small molecules which might be effective against COVID-19.

Lianhuaqingwen (LH) is a traditional Chinese medicine that has been used previously to combat SARS, influenza virus and enhance immunomodulatory effects. Runfeng et. al. (2020), studied the antiviral and anti-inflammatory effect of LH against SARS-CoV-2. In this study, African green monkey's kidney epithelial cell (Vero E6 cells) was used as an *invitro* cell line. The cytopathic effect (CPE) and plaque reduction assay was used to assess the antiviral activity of LH in Vero E6 cells. The results revealed that the LH helped in inhibition of SARS-CoV-2 replication. It has been also found that LH showed significant reduction in pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrotic factor-α (TNF- α) and chemokine (C–C motif) ligand 2/monocyte chemo attractant protein 1 (CCL2/MCP-1).

5.3. Vaccines

In 1986, US patent (US 4567043A) was granted for Canine Corona vaccine which on parenteral administration provided humoral protection from virulent canine corona virus that mostly affect the intestinal tract of dogs (Acree et al., 1986). A novel vaccine was developed using cDNA that is encoded with structural antigens such as spike (S) protein, membrane (M) protein, envelope (E) protein and nucleocapsid (N) protein for SARS caused by COVID-19. Among the developed vaccines, (M) and (N) DNA vaccines showed cytotoxic T Lymphocytes (CTL) activity and human T-cell proliferation in SCID-PBL/hu mice and in vivo human model (Okada et al., 2007). Recently, a new strategy has been developed based on the immunogenetics and immunogenomics. Molecular docking technique was employed for predicting the combination effect of B- and T-cell epitope on the nonstructural protein 4 coronavirus. To target the virus, two peptide sequences from the nonstructural protein 4 of beta coronavirus (IRNTTNPSAR and PTDTYTSVYLGKFRG) were selected and were found to be potent T-cell epitopes. They were found to interact perfectly with epitope grooves of major histocompatibility complex (MHC) allelic protein (HLA-A*01:01 and HLA-DRB5*01:01) that formed a stable MHC complex. It can, therefore, be considered as potential peptide for development of peptide based corona virus vaccine (Basu et al., 2020). In another study, computational approach along with bioinformatics tools was adopted for vaccine design. Based on the docking score as well as antigencity scores, natural inhibitors such as tanshinoneIia and methyl tanshinonate were identified as effective drugs and FVFLVLLPL (MHC class-I allele) and FVFLVLLPL(MHC class-II allele) were selected as best antigenic epitope

Table 2
Various antiviral drugs and their mechanism of action.

Virus	Drug	Mechanism of action	Reference
Ebola	mAb114		Rojas et al. (2019)
HIV	Zidovudine	Nucleoside reverse transcriptase Inhibitor	Justice et al. (2004)
	Nevirapine	Nonnucleoside reverse transcriptase Inhibitor	Jiang et al. (2014)
	Ritonavir	Protease inhibitor	Chen et al. (2005)
	Enfuvirtide	Entry (Fusion) inhibitor	Wnuk (2008)
	Raltegravir	Integrase inhibitor	Taramasso et al. (2015)
	Maraviroc	CCR5 receptor inhibitor	Armstrong-James et al. (2010)
SARS-CoVs	Ribavirin	Decrease intracellular guanosine triphosphate which results in inhibition of caps of viral transcripts, suppress cellular and humoral immune response	(Cameron and Castro, 2001; Peiris et al., 2003)
	Lopinavir (LPV) + Ritonavir (R)	R helps in inhibiting CYP3A4 metabolism of LPV and increased LPV serum conc.	Chu et al. (2004)
	Methylprednisolone	Help in decreasing cytokine storm (ILs, and TNF)	Smego and Ahmed (2003)
ZIKA	Chloroquine	Inhibitory effect against early stages of ZIKA Virus in mice	Li et al. (2017) Devaux et al. (2020)

Table 3
List of drugs that have been used to mitigate COVID -19.

S. N.	Drugs	Brand Name	Manufacturer	Dose	Duration of treatment	References
1.	Lopinavir/ ritonavir	Aluvia®	ABBOTT health care Pvt. Ltd.	50 mg/20 0 mg in tablet form	Not more than 10 days	Dong et al. (2020)
2.	Ribavirin	Rebetol, Ribasphere, Copegus and Virazole	Valeant Pharmaceuticals	500 mg thrice a day or given in combination with ritonavir/ Lopinavir and INF-α through Intravenous infusion	Not more than 10 days	Dong et al. (2020)
3.	Chloroquine phosphate	Aralen	Novartis, Mylan and Teva	500 mg, 250 mg twice a day given orally	Not more than 10 days	Dong et al. (2020)
4.	Umifenovir	Arbidol	Pharmastandart	50 mg, 200 mg thrice a day in oral form	Not more than 10 days	Dong et al. (2020)
5.	Oseltamivir	ANTIFLU cap	Cipla	75 mg twice in a day in oral form	3–14 days	(file:///C:/Users/hp/Downloads/Tamiflu_GL-019936.pdf)
6.	Umifenovir	Arbidol	Pharmastandart	0.2 g three times a day	Not more than 14 days	Zhu et al. (2020)
7.	Baricitinib	Olumiant	Eli Lilly	2 mg once daily	Not more than 14 days	(Richardson et al., 2020a, 2020b; Stebbing et al., 2020)
8.	Bromhexine	BROLYT	Alco Pharma Ltd.	4 mg and 8 mg three times a day	–	Rosa and Santos (2020)
9.	Fingolimod	Gilenya	Novartis	0.5 mg once in a day	Not more than 3 days	(https://clinicaltrials.gov/ct2/show/NCT04280588)
10.	Bevacizumab	Avastin	AsparÂ Pharmaceuticals	500 mg	–	(https://clinicaltrials.gov/ct2/show/NCT04275414)
11.	Pirfenidone	Esbriet	Glenmark Pharmaceuticals	267 mg three times a day	–	(https://clinicaltrials.gov/ct2/show/NCT04282902)
12.	Thalidomide	Thalomid	Grunenthal	100 mg	Not more than 14 days	(https://clinicaltrials.gov/ct2/show/NCT04273529)

respectively for vaccine design (Kumar, 2020). Recently, US developed a vaccine and started first human trial (Phase 1 trial) in healthy human volunteers to monitor the desired responses in human immune system along with safety profile. The trial has enrolled 45 healthy volunteers for a period of 6 weeks. The vaccine is based on "messenger RNA vaccine platform technology". The experience on previous MERS vaccine development for targeting the surface protein of virus led to the idea of this vaccine (Roberts, 2020). Out of the two vaccines, REGN 3048 and REGN 3051, manufactured by Regeneron, USA, were able to more keenly bind to viruses resulting in possibility of developing antibodies. Vaccine REGN 3048 was found to be ineffective against COVID-19, however the company is retesting it for the possible effects against COVID-19 (https://clinicaltrials.gov/ct2/show/NCT03301090?term=NCT03301090#wrapper). The traditional immunization technique of using live attenuated or inactivated viruses has been reported with drawback of leaving the recipient sick again. The use of genetic coding technology in the development of new vaccine development can assure safety over the traditional immunization technique.

Bacille Calmette-Guérin (BCG) is a live attenuated strain of mycobacterium bovis used against tuberculosis and leprosy (https://www..int/biologicals/areas/vaccines/bcg/en/who). Vaccine repositioning indicated its potential use against multiple sclerosis, reducing blood sugar levels in type-1 diabetes and also in various types of cancer like non-Hodgkin's lymphoma and bladder cancer. It demonstrates a non-specific effect and thus its use may prove to be favorable against viral pathogens as well (Moorlag et al., 2019). A study reported that oral zinc sulphate being an effective immunomodulator can be combined with BCG vaccine to provide protection against COVID-19 (Sharquie, 2020). The outcomes of the ongoing randomized trials (phase III) of BCG vaccine are eagerly anticipated (https://clinicaltrials.gov/ct2/-show/NCT04328441?term=BCG+vaccine&cond=COVID-19&draw=2&rank=1);(https://clinicaltrials.gov/ct2/show/NCT04327206?term=BCG+vaccine&cond=COVID-19&draw=1&rank=2).

Table 5 compiles the patents on vaccines having therapeutic potential to treat COVID-19 while Table 6 summarizes the trials going on across the globe for the development of drugs and vaccines for the treatment of COVID-19.

5.4. Role of nutraceuticals in RNA virus infection

Certain nutraceuticals have also shown efficacy in combating COVID-19. Their mechanisms are discussed here. Viral toll-like receptor (TLR7) of COVID-19 is responsible to trigger hydrogen peroxide generation within the alveolar macrophages via nicotinamide adenine dinucleotide phosphate hydrogen oxidase 2 (NOX2) activation which oxidizes Cys98 on TLR7. Such oxidation blocks receptor potential to conduct signals for type 1 interferon production. Nutraceuticals having potential to inhibit NOX2, superoxide generation or preventing oxidation of Cys98 in TLR7 have potential to evoke TLR7 mediated type 1 interferon production towards RNA virus infections including COVID-19. RNA virus infections have been shown to induce O-GlcNacylation of mitochondrial antiviral signalling protein (MAVS) at multiple sites which prohibits its susceptibity for K63-linked ubiquitination and further interferon regulatory factor 3 (IRF3) activation. Glucosamine supplementation has been investigated to upregulate MAVS to activate IRF3 in response to viral infections. Currently, vitamin C infusion is under clinical trial for the treatment of severe COVID-19 virus infected pneumonia as it plays important role in reducing inflammatory response and has antioxidant property. Vitamin C has earlier been reported to prevent neutrophil accumulation, alveolar fluid and cytokine surge caused by sepsis (Peng, 2020).

The US-FDA has recently issued certain guidelines pertaining to the ongoing clinical trials for the development of medicinal products. Impact on the conduct of clinical trials of medical products is anticipated since challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product, or other considerations if site personnel or trial subjects become infected with COVID-19 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct--clinical-trials-medical-products-during-covid-19-pandemic).

5.5. Convalescent plasma therapy

Plasma therapy can reduce the mortality rate of COVID-19 (da Silva, 2020). In this therapy, convalescent plasma or immunoglobulins administrated to the patients who are suffering with COVID-19. This therapy can enhance the immunity of the patients (Bloch et al., 2020). In

Table 4
Clinical trials on COVID-19.

Sr. No.	Drug	No. of Patients	Mechanism	Clinical Trials	Outcomes	References
1.	Chloroquine phosphate	100	Increase endosomal pH which is required for fusion of virus and cells, also interfere with the glycosylation of cellular receptors of SARS-CoVs	. ChiCTR2000029939 . ChiCTR2000029760 . C hiCTR2000029609 . C hiCTR2000029761 .ChiCTR2000029837 . C h iCTR2000029 9 . Chi CTR2000029826 . ChiCTR2000029803	*In-vitro* studies reveal that drug block the virus at micro molar concentration with half-cytotoxic concentration (CC50) greater than 100 μM and half-maximal effective concentration (EC50) of 1.13 μM. Drug also improved symptoms of pneumonia in COVID-19 patients	Gao et al. (2020)
2.	Shuanghuanglian oral liquid (SHL)	3	Mast cells stabilization by activation of mitochondrial calcium uniporter	ChiCTR2000029605	Treated patients with COVID-19 but further clinical trials are required to evaluate its efficacy against COVID-19	(Gao et al., 2017; Ni et al., 2020)
3.	Hydroxychloroquine + Azithromycin	36	Hydroxyl chloroquine inhibit toll like receptors and stops dentric cell activation and result in antiinflammatory response while azithromycin inhibits protein synthesis (50S) and inhibits translation process in Mrna	Open-label non-randomized clinical trial	Hydroxychloroquine (600 mg) helped in combating COVID-19 and addition of azithromycin synergesis the effect	Gautret et al. (2020)
4	CamostatMesilate + Hydroxychloroquine	334	CamostatMesilate inhibits serine protease TMPRSS2 while Hydroxychloroquine interrupt the viral entry and replication through glycation of ACE2 receptotors	Randomized	Ongoing trials	(https://clinicaltrials.gov/ct2/show/NCT04338906)
5	Favipiravir	100	inhibits RNA polymerase	Randomized	Ongoing trials	(https://clinicaltrials.gov/ct2/show/NCT04336904?cond=COVID-19&draw=2&rank=2)
6.	Clevudine	60	Inhibiting the replication of viral genetic materials	Randomized	Ongoing trials	(https://clinicaltrials.gov/ct2/show/NCT04347915?cond = COVID-19&draw = 2&rank = 6)
7.	Desferal	50	Inhibits human cytomegalovirus replication	Randomized	Ongoing trials	(Cinatl et al., 1994; Shakiba, 2020)
8.	Losartan	50	decreases activation of nuclear factor kappa B and mitogen-activated protein kinases	Interventional	Ongoing trials	(Fedson et al., 2020; Salathe, 2020)
9.	Ruxolitinib	80	Lower the hyperinflammation caused by the virus	Interventional	Ongoing trials	(https://clinicaltrials.gov/ct2/show/NCT04348071?cond = COVID-19&draw = 2&rank = 31)
10.	Baricitinib	80	Lower the hyperinflammation caused by the virus	Interventional	Ongoing trials	(https://clinicaltrials.gov/ct2/show/NCT04340232?cond=COVID-19&draw=2&rank=32)
11.	Dapagliflozin	900	SGLT-2 Inhibitors	Randomized	Ongoing trials	Kosiboro (2020)
12.	Tocilizumab	400	IL-6 inhibitor	Interventional	Ongoing trials	Perrone (2020)
13.	Ciclesonide	141	blocks coronavirus RNA replication by targeting viral NSP15	Randomized	Ongoing trials	(https://clinicaltrials.gov/ct2/show/NCT04330586?cond=COVID-19&draw=2&rank=42)
Others						
1.	Convalescent Plasma	55	–	Interventional	Ongoing trials	(https://clinicaltrials.gov/ct2/show/NCT04343755?cond=COVID-19&draw=2&rank=19)
2.	BCG Vaccine	700	–	Interventional	Ongoing trials	(https://clinicaltrials.gov/ct2/show/NCT04348370?cond=COVID-19&draw=4&rank=614)

one of the studies in 2014, convalescent plasma therapy was used for the treatment of Ebola virus. It was recommended by WHO (Chen et al., 2020). The Indian Council of Medical Research (ICMR) has approved first clinical trials for convalescent plasma therapy in SVP Hospital, Ahmedabad, India. (theweek.in/news/india/2020/04/19/gujarat-to-start-clinical-trial-with-convalescent-plasma-therapy-for-covid-19.html). FDA is also working on development of convalescent plasma therapy. They provided guidance in mentions about patient eligibility, investigation pathways of convalescent plasma, labelling and records keeping for donated convalescent plasma and regarding treatments (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma).

5.6. Pluristems allogeneic placental expanded cell therapy

Placenta expanded cells are obtained from the placenta and are

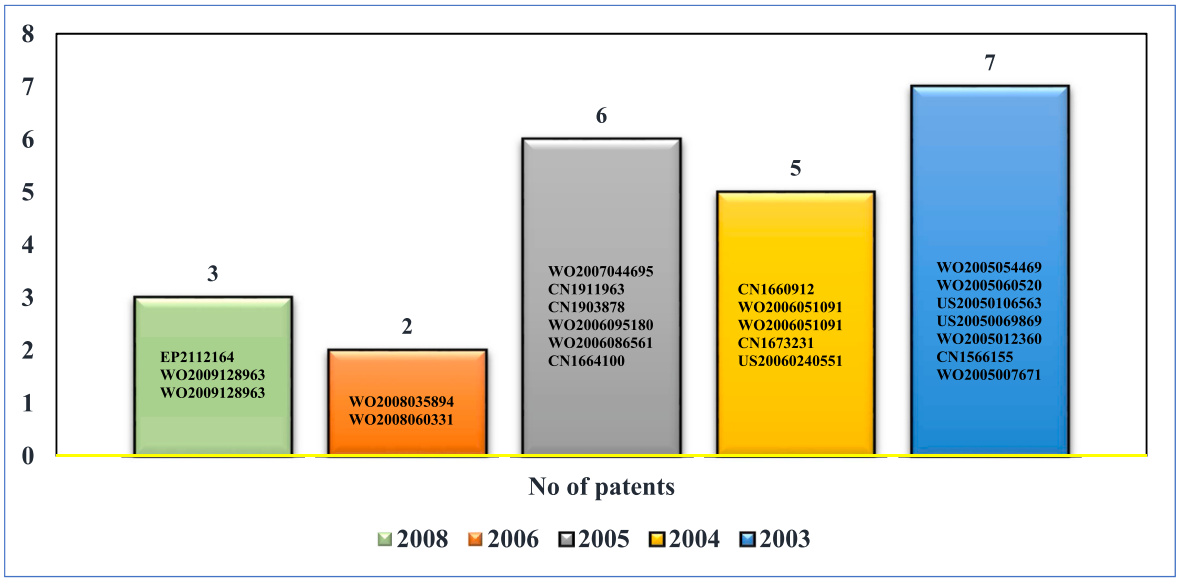

Fig. 4. Number of patents granted to drugs and small molecules having potential to treat COVID-2019.

Table 5
Existing patented vaccines that have been repurposed to treat COVID-19.

Sr. No.	Vaccine	Publication	Patent Number	Patent Date	Targeted site	Observation	Reference
1.	Live attenuated corona virus vaccines	United State Patent Application	US20060039926	Feb 23, 2006	Orf1a/polyprotein (p59/nsp14/ExoN)	MHV virus showed reduction of replication in mice at 5th day with intracerebral inoculation	(https://docs.google.com/viewer?url=patentimages.storage.googleapis.com/pdfs/US20060039926.pdf)
2.	DNA based vaccines	International	WO2005081716	9 Sept 2005	calreticulin−nucleocapsid fusion	Resulted in potent nucleocapsid-specific humoral and T cell-mediated immune responses	(Wu et al., 2005)
3.	Protein-Based Vaccines.	International	WO2010063685	June 10, 2010	S-Trimer subunit, ACE2 Receptor	O/W emulsion helped to treat SARS-CoVs by neutralizing antibody responses in animal models	Baras et al. (2012)
4.	Virus-like Particle Vaccines	International	WO2015042373	19 Sept 2014	S protein	The Sera (SAB-300 or SAB-301) were injected into Ad5-hDPP4 transduced BALB/c mice, which protected mice against MERS-COVs	Smith et al. (2015)
5.	mRNA-Based Vaccines.	International	WO2017070626	April 27, 2017	mRNA-1273	Intradermal administration of a lipid nanoparticle (LNP)-encapsulated mRNA mixture encoding MERS-CoVs S proteins into mice resulted in translation in vivo and induction of humoral immune responses	Ciaramella and Himansu (2017)

designed in such a way that theycan be administered to the patients without tissue or genetic matching. The main function of these cells is to release biomolecules such as growth factors, cytokines and chemokines. These cells act in a endocrine and paracrine manner and help the body to stimulate its defense mechanism and promote healing (https://www.pluristem.com/placental-expanded-plx-products/). The Israel biotech company, Pluristem Therapeutics Inc. reported that the patients who had SARS-CoV-2 and were at a higher risk of death due to respiratory collapse and multiorgan failiure such as kidney and heart failure recovered after receiving this therapy. This happens due to the immunomodulatory effect of the pluripotent plasma cells (PLX). During treatment the 15 mL doses of PLX cells is administered to patients by intramuscular route (https://.com.au/israel-has-found-a-possible-100-cure-for-coronavirus/theindiantelegraph).

5.7. *Miscellaneous treatment strategies*

Melatonin is a N-acetyl-5-methoxytryptamine and having many health benefits such as remission from sleeping disorders, viral infections, delirium, respiratory disease and atherosclerosis (Reiter et al., 2020). Recent studies on COVID-19 revealed that the main cause of COVID-19 pathology is exaggerated immune response, oxidation and inflammation. All these factors lead to cytokine storm and give rise to Acute Respiratory Distress Syndrome (ARDS) and often death. Zhang et al., (2020), described the anti-inflammatory, immunomodulatory and adjuvant effects of melatonin against SARS-CoV-2. Melatonin showed anti-inflammatory action by acting on sirtuin-1 (SIRT1) and nuclear factor kappa-B (NF-κB) pathways. Melatonin resulted in inhibition of high mobility group boxechromosomal protein1 (HMGB1) and led to downregulation of the polarization of macrophages. Melatonin's action

Table 6
Summary of the research projects currently ongoing for the development of drugs and vaccine against COVID-19.

Institute name/ Collaboration	Drug Name	Reference
I-MabBiopharma	TJM2	Jielun Zhu (2020)
Medicago	Virus Like Particle (unnamed)	(https://www.com/en/pipeline/medicago)
Airway Therapeutics	recombinant protein named AT-100	(https://www.co.uk/news-releases/airway-therapeutics-announces-filing-with-nih-to-evaluate-at-100-as-a-therapy-for-novel-coronavirus-821624689.htmlprnewswire)
Tiziana Life Sciences	TZLS-501	(https://www..com/story/uk-biotech-tiziana-life-sciences-says-its-tzls-501-may-be-of-use-in-treating-coronavirus-2020-03-11marketwatch)
OyaGen	OYA1	(https://spectrumlocalnews.com/nys/rochester/coronavirus/2020/03/12/oyagen-lab-discovers-compound-that-they-believe-could-help-with-the-covid-19-)
BeyondSpring	BPI-002	(https://www.com/markets/mergers-and-acquisitions/beyondspring-looks-to-future-after-ipo-pipe-launch-14308176thestreet)
Altimmune	Unnamed intranasal coronavirus vaccine	(https://biobuzz.io/altimmune-becomes-the-second-maryland-based-biotech-advance-potential-coronavirus-covid-19-vaccine/)
Inovio Pharmaceuticals	INO-4700	(https://www.com/investing/2020/03/15/better-coronavirus-stock-inovio-pharmaceuticals-vs.aspxfool)
Inovio Pharmaceuticals and Beijing Advaccine Biotechnology	INO-4800	(https://www.com/investing/2020/03/15/better-coronavirus-stock-inovio-pharmaceuticals-vs.aspxfool)
Algernon Pharmaceuticals	NP-120 (Ifenprodil)	(https://www.-technology.com/news/covid-19-aj-vaccines-algernon-drug/pharmaceutical)
University of British Columbia and APEIRON Biologics	APN01	(https://www.com/news/ubc-apeiron-biologics-covid-19-trial/clinicaltrialsarena)
National Institute of Allergy and Infectious Diseases	mRNA-1273 vaccine	(https://www.com/releases/2020/03/200317150116.htmsciencedaily)
MIGAL Research Institute	Infectious Bronchitis Virus (IBV) vaccine	(http://www.org.il/Migal.covidmigal)
Tonix Pharmaceuticals	TNX-1800	(https://www.-technology.com/news/tonix-pharmaceuticals-covid-19-vaccine/pharmaceutical)
Innovation Pharmaceuticals	Brilacidin	(https://www.com/article/releases/innovation-pharmaceuticals-brilacidin-to-be-researched-as-possible-novel-coronavirus-covid-19-vaccine-brilacidin-now-being-tested-as-drug-and-vaccine-at-different-institutions/biospace)
Clover Biopharmaceuticals	A recombinant subunit vaccine	(http://www.com/news/gsk_recruits_clover_biopharmaceuticals_in_latest_coronavirus_effort_1326917pharmatimes)
Vaxart	Oral recombinant vaccine (unnamed)	(https://pipelinereview.com/index.php/2020020273689/Vaccines/Vaxart-Announces-Initiation-of-Coronavirus-Vaccine-Program.html)
CytoDyn	Leronlimab	(https://www.com/newsroom/press-releases/detail/392/-files-ind-and-protocol-for-phase-2-clinical-trialcytodyncytodyn)
LineaRx and Takis Biotech	Linear DNA Vaccine	(https://adnas.com/coronoavirus-applied-dna-linearx-takis-biotech-vaccine/)
Bioxytran	BXT-25	(https://www.-technology.com/news/bioxytran-coronavirus-patients-treatment/pharmaceutical)
Novavax	MERS CoV vaccine	(https://ir.com/news-releases/news-release-details/-advances-development-novel-covid-19-vaccinenovavaxnovavax)
Gilead Sciences	Remdesivir (GS-5734)	(https://www.com/2020/03/16/remdesivir-surges-ahead-against-coronavirus/statnews)
Roche	Actemra	(https://www.-technology.com/news/roche-actemra-coronavirus-complications/pharmaceutical)
BiocrystPharma	Galidesivir	(https://com/article/4331827-biocryst-pharmaceuticals-multiple-value-drivers-coronavirus-kickerseekingalpha)
Lattice Biologics	AmnioBoost	(https://www.-technology.com/news/can-fite-lattice-biologics-covid-19-treatments/pharmaceutical)
Pfizer	Unnamed	(https://www.aa.com.tr/en/health/pfizer-biontech-jointly-work-on-coronavirus-vaccine/1769465)
ZydusCadila	Unnamed DNA Vaccine	(https://www.com/investing/2020/03/12/biogen-and-vir-biotechnology-to-collaborate-to-fin.aspxfool)
Biogen and Vir Biotechnology	Monoclonal antibodies	(https://www.com/article/india-s-zydus-joins-fight-against-novel-coronavirusthepharmaletter)
Genentech (Roche group)	Actemra® (tocilizumab)	(https://www.com/investing/2020/03/12/biogen-and-vir-biotechnology-to-collaborate-to-fin.aspxfool)

Table 7
List of various treatments currently used against COVID-19.

Sr. No.	Type of Product – Treatment	Developer/ Researcher	Development stage	Anticipated Next Steps Timing	References
Antibodies based treatment against COVID-19					
1.	H-IG	Octapharm and Takeda Pharmaceutical Co.	Pre-clinical	The Phase 1 trials will begin in end of the spring	(https://phrma.org/coronavirus) (https://www..com/articles/drugmaker-takeda-is-working-on-coronavirus-drug-11583301660?mod=article_inlinewsj) (https://pink.pharmaintelligence.informa.com/PS141926/US-FDA-To-Exercise-Maximum-Regulatory-Flexibility-For-COVID19-PlasmaDerived-Therapeutics)
2.	VIR-7831 and VIR-7832	GSK/Vir Biotech/ Samsung	Pre-clinical	The Phase 2 trials will begin in the month of july and september	(https://investors.vir.bio/news-releases /news-release-details/gsk-and-vir-biotechnology-enter-collaboration-find-coronavirus)
3.	Thymosin; PD-1 blocking antibody	Numerous trials with Chinese research sponsors	Clinical	The Phase 2 of clinical trial will end on April 30, 2020	(https://www.com/article/304658biocentury)
4.	Gimsilumab,	Roivant Sciences	Clinical	The phase 2 Study begins from April 2020	(https://roivant.com/roivant-announces-development-of-anti-gm-csf-monoclonal-antibody-to-prevent-and-treat-acute-respiratory-distress-syndrome-ards-in-patients-with-covid-19/)
5.	Siltuximab	EUSA Pharma	Clinical	Interim of April 2020	(https://www.com/news/eusa-pharma-and-the-papa-giovanni-xxiii-hospital/eusapharma)
6.	SAB-185	SAb Biotherapeutics	Pre-clinical	Phase 1 starts early summer 2020	(https://sabbiotherapeutics.com /2020/04/13/hhs-facilitates-development-of-immunotherapies-for-covid-19-patients/)
7.	Soliris	Alexion	Clinical	The phase 2 Study begins from April 2020	(https://ir.alexion.com/news-releases/ news-release-details/alexion-statement-solirisr-eculizumab-and-covid-19)
8.	rCIG	GigaGen	Pre-clinical	–	(https://.com/biotech/gigagen-jumps-into-covid-19-arena-polyclonal-antibodies?mkt_tok=eyJpIjoiT0dFNE16bGhPRFk1WTJNMiIsInQiOiJiUDhYM1ZWdzJLY04zbnc1T3IzVmFUK2NVVzFSeXY3SFhtZnNVWU5wWHFSYUxjcVwva0ZLZUVGRTBVSlBoMFlpY1FHQ0ZGODF0akV6TENzb3pWSmR0bFwvRllHbnQ5amptalwvZTdhN0J5UlJMeXVhSnhYcHNabkNBVXhhZTFSVHNJRHVtVEpqcU02aXN3SWRFSXRuUGNkVlE9PSJ9&mrkid=72869502)
9	Ilaris	Novartis	Clinical	–	(https://www.com/article/health-coronavirus-novartis/novartis-ceo-malaria-drug-is-biggest-hope-against-coronavirus-sonntagszeitung-idUSL8N2BM02Wreuters)
10.	Ultomiris	Alexion Pharmaceuticals	Clinical	The phase 2 will be begin in the month of May 2020	(https://www..com/news/home/20200420005221/en/Alexion-Announces-Plans-Initiate-Phase-3-Studybusinesswire)
11.	COVID-EIG	Emergent BioSolutions	Pre-clinical	The phase 2 will be begin in the month of August 2020	(https://investors.emergentbiosolutions.com/news-releases/news-release-details/emergent-biosolutions-initiates-development-plasma-derived?field_nir_news_date_value%5bmin%5d =)
12.	Octagam	Octapharma	Clinical	–	

(*continued on next page*)

Table 7 (*continued*)

Sr. No.	Type of Product – Treatment	Developer/ Researcher	Development stage	Anticipated Next Steps Timing	References
					(https://www.com/news/home/20200416005144/en/New-COVID-19-Clinical-Trial-Supported-Octapharma-USAbusinesswire)
Cell based therapies used against COVID-19					
1	Mesenchymal stem cells	Numerous trials with global research sponsors	Clinical	–	(https://www..com/article/304658biocentury)
2.	Autologous Adipose-Tissue Derived Mesenchymal Stem Cells (ADMSCs)	Celltex	–	–	(https://www.com/article/releases/celltex-autologous-stem-cell-case-study-published-by-gavin-publishers-demonstrates-potential-cure-for-rheumatoid-arthritis/?keywords=Autologous+Adipose-Tissue+Derived+Mesenchymal+Stem+Cells+(ADMSCsbiospace)
3.	Ryoncil	Mesoblast	Pre-clinical	–	(https://.com/research/melatonin-stem-cells-researchers-step-up-unconventional-approaches-to-covid-19?mkt_tok=eyJpIjoiTlRKak1UZzROV1l5TWpnMSIsInQiOiJ6K0xXSlwvcFZhcmpWenhOS1pxOExUTnlsdzlPM080bVRiQ2phcG1mQmowQWQ2S24yZXZ2alBqVHNJaVUzZGRNQjM5aFQySkg4cEFvdUZrQ0lBWmluTkl1a3NVK3dFUEFRTTUwSkhEMnIwTHR1QUt4VEs4ZGsrc1pZZWF6bWdNTEZ2YXRsc2RlT0haMGV6VWE1bkNVUHB3PT0ifQ%3D%3D&mrkid=72869502)
4.	MultiStem, bone marrow stem cells	Athersys/The University of Texas Health Science Center at Houston	Clinical	Phase 2/3 trial to start 2Q 2020	(https://www.com/article/barda-says-athersys-cell-therapy-highly-relevant-for-covid-19/biospace) (https://www.com/news/home/20200413005160/en/FDA-Authorizes-Athersys-Initiate-Pivotal-Clinical-Trialbusinesswire)
5	Allogeneic T-cell therapies	Baylor College of Medicine/AlloVir	Pre-clinical	–	(https://clinicaltrials.gov/ct2/show/NCT04338347?type=Expn&cond=COVID-19&draw=2)
6	CYNK-001, allogeneic, natural killer cell therapy	Celularity	Clinical	The phase 1/2 will be begin	(https://www.com/news-releases/celularity-announces-fda-clearance-of-ind-application-for-cynk-001-in-coronavirus-first-in-cellular-therapy-301034141.htmlprnewswire)
7	CAP-1002, allogenic cardiosphere-derived cell	Capricor Inc.	–	–	(http://www.irdirect.net/prviewer/release/id/4280782)
8	haNK, natural killer cells	ImmunityBio/ NantKwest	Pre-clinical	–	(https://www.com/news/home/20200414005353/en/NantKwest-ImmunityBio-Announce-Therapeutics-Vaccines-Combatting-COVID-19businesswire)
RNA based treatment for COVID-19					
1.	RNAi - testing 150 RNAis	Sirnaomics	Pre-clinical	–	(https://www..org/sections/health-shots/2020/02/19/807338329/hunt-for-new-coronavirus-treatments-includes-gene-silencing-and-monoclonal-antibnpr)
2.	siRNA candidates	Alnylam Pharmaceuticals/ Vir Biotech	Pre-clinical	–	(https://www.com/news/home/20200402005167/en/Vir-Alnylam-Expand-Collaboration-Advance-Investigational-RNAibusinesswire)
3.	Ampligen; (rintatolimod)	AIM ImmunoTech/ National Institute of Infectious Diseases in Japan	Pre-clinical	–	(https://finance.yahoo.com/news/aim-immunotech-drug-ampligen-tested-103000673.html)
4.	OT-101, a TGF-Beta antisense drug candidate	Mateon Therapeutics	Clinical	–	(https://www.com/analysis/coronavirus-mers-cov-drugs/clinicaltrialsarena)
5.	Inhaled mRNA	Neurimmune/ Ethris	Pre-clinical	Phase 1 to start Q4 2020	(https://www.neurimmune.com/news/neurimmune-and-ethris-sign-collaboration-agreement-to-rapidly-develop-inhaled-mrna-based-antibody-therapy-for-the-treatment-of-covid-19)

on NF-κB resulted in inhibition of pro-oxidative and pro-inflammatory response. The immunomodulatory action of melatonin is due to maturation and proliferation of natural killer cells, B and T lymphocytes, monocytes and granulocytes in bone marrow and other tissues (Miller et al., 2006; Zhang et al., 2020).

Miscellaneous antibodies, cell-based therapies and RNA based therapies which are beingused now a days to mitigate effect of COVID-19 and are under preclinical and clinical trials are depicted in Table 7.

6. Conclusion and future perspective

The worldwide spread of COVID-19 has become a big challenge to control. It has already been declared as pandemic with more than 10 922 324 peoples affected across 195 countries till July 4th 2020. An aggressive approach is required to take care of critically compromised patients in addition to sincere efforts to stop the transmission of disease. Currently many government agencies and pharmaceutical companies are working towards development of effective medicines and vaccines. Also, the available treatment strategies have been adopted to benefit the affected people, however, major step still remains to stop the transmission and alleviate the symptoms of affected people. Use of hydroxychloroquine as well as antiviral drugs are found effective against COVID-19, however, detailed clinical studies are required. Some biotechnology-basedtechniques such as antibodies, cell and RNA based therapies have also been found to be very effective. It is expected that dexamethasone could bring some hope to treat this disease.However, it will be too early to give conclusive remarks on the currently available treatments since more evidence-based data is required to be generated. Government agencies are working on their part; however, a coordinated effort is needed globally to help prepare the healthcare framework cope up with the unprecedented challenge of COVID-19.

Declaration of competing interest

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