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Full length article

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

Ankit Awasthi, Sukriti Vishwas, Leander Corrie, Rajesh Kumar, Rubiya Khursheed, Jaskiran Kaur, Rajan Kumar, K.R. Arya, Monica Gulati, Bimlesh Kumar, Sachin Kumar Singh *, Narendra Kumar Pandey, Sheetu Wadhwa, Pardeep Kumar, Bhupinder Kapoor, Rajneesh Kumar Gupta, Ankita Kumar

School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, 144411, India

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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;
Abbreviations

CoVs  Coronavirus
COVID-19  Coronavirus Disease 2019
E  Envelope protein
hDPP-4  Human Dipeptidyl Pentidase-4
HIV  Human Immunodeficiency Virus
LVF  Lopinavir
M  Membrane protein; MAVS, O-mitochondrial antiviral signalling protein
MERS-CoV  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).

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 cytoplasm 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 5UU 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 (Biebltreu 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 polymerase 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.

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

| Sr. No. | Pathokit Description | Country | Reference |
|---------|----------------------|---------|-----------|
| 1.      | GenMarkDx – Multiplex Diagnostics | Canada | [https://www.startus-insights.com/innovators-guide/5-top-diagnostic-test-kits-to-use-during-the-coronavirus-pandemic/](https://www.startus-insights.com/innovators-guide/5-top-diagnostic-test-kits-to-use-during-the-coronavirus-pandemic/) |
| 2.      | XCR Diagnostics – Quantitative Polymerase Chain Reaction (qPCR) | United states of America | |
| 3.      | Sem Dx – Ultrasensitive Electrodes | Poland | |
| 4.      | Aperionics – 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](https://www.gov.in/team-india-blogs/truenat-beta-test-covid-19-detection-indiainvestindia) |

Fig. 3. Tests used for diagnosis of SARS-CoV-2 infection.
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 studies, it has been found that computed tomography is more sensitive technique for the diagnosis of COVID-19 (Ai et al., 2020). 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 height 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-science-announces-experimental-drug-for-coronavirus-treatments-testing-11580511519wsj). In the meantime, Thai health officials claimed to have successfully handled the infection with cocktail of antiviral drugs that include lopinavir and ritonavir under the name “Kaetr” 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 (Huang 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#ticker).

However, its efficiency to mitigate COVID-19 is yet to be fully established. To analyze antiviral effect of interferon-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 in vivo 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 (Sheshaian 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-event/s/press-announcements/coronavirus-us-covid-19-update-fda-issues-emergency-use-authoriza-tion-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); (Millan-Onate 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 4.2–6.2 days to 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/arbadox/Shufenglieduo 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/32073895c).

In a recent study, Rho kinase (ROCK) inhibitor, Fasudil has been explored to treat COVID-19. In patients with COVID-19, activation of
ACE-2 is widely expressed in alveolar epithelial cells and converts human cells through binding ACE-2 with super-affinity and efficiency. This facilitates 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, TNFs 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 overreaction 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 *Pyrrrosia 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 activity (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. Runtueng 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 cytopathetic 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 also been 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 (IRNITTPSAR and PTDYTTSYVLKFRG) 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 (Busu 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 antigenicity scores, natural inhibitors such as tanshinonel 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

| Virus          | Drug                | Mechanism of action                                      | Reference                      |
|---------------|---------------------|----------------------------------------------------------|--------------------------------|
| Ebola         | mAb114              | Nucleoside reverse transcriptase inhibitor                | Rojas et al. (2019)            |
| HIV           | Zidovudine          | 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 (2006)                    |
|               | Raltegravir         | Integrase inhibitor                                      | Tamasso 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; Petris et al., 2003) |
|               | Lopinavir (LPV) +   | R helps in inhibiting CYP3A4 metabolism of LPV and increased LPV serum conc. | Chu et al. (2004)              |
|               | Ritonavir (R)       |                                                          |                                |
|               | 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)           |
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, Ribosphere, Gopegu 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    | Oselamivir                   | ANTIFLÜ 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          | AsparÀ Pharmaceuticals              | 500 mg                                   | –                     | (https://clinicaltrials.gov/ct2/show/NCT04275414) |
| 11   | Pirfenidone                  | Ebriet           | 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) |

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 susceptibility 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
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-convalescent-plasma).

5.6. Pluristem allogeneic placental expanded cell therapy

Placenta expanded cells are obtained from the placenta and are

Table 4
Clinical trials on COVID-19.

| Sr. No. | Drug No. | 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 | . ChCTR2000029939 . ChCTR2000029760 . C hiCTR2000029609 . C hiCTR2000029761 . ChCTR2000029607 . ChCTR2000029826 | 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 | ChCTR2000029605 | 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 receptor and stops dentic 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 | 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 receptors inhibits RNA polymerase | Randomized | Ongoing trials | (https://clinicaltrials.gov/ct2/show/NCT04338906) |
| 5       | Favipiravir | 100 | Inhibits RNA polymerase | Randomized | Ongoing trials | (https://clinicaltrials.gov/ct2/show/NCT04369047?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 decreases activation of nuclear factor kappa B and mitogen-activated protein kinases | Randomized | Ongoing trials | Cinatl et al., 1994; Shukla, 2020 |
| 8       | Losartan | 50 | | 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      | Dagliprozin | 900 | SGLT-2 Inhibitors | Randomized | Ongoing trials | Kosiboro (2020) |
| 12      | Ticlozumab | 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/NCT04347555?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) |
designed in such a way that they can 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 an 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 failure 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).

### Table 5

| Sr. No. | Vaccine Type | Publication | Patent Number | Patent Date | Targeted site | Observation | Reference |
|---------|--------------|-------------|---------------|-------------|--------------|-------------|-----------|
| 1.      | Live attenuated corona virus vaccines | United State | 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 | 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) |

### 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-kB) pathways. Melatonin resulted in inhibition of high mobility group boxehromosomal 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 | TZ5-501 | (https://www.com/story/uk-biotech-tiziana-life-sciences-says-its-tz5-501-may-be-of-use-in-treating-coronavirus-2020-03-11marketwatch) |
| OyGen | OVA1 | (https://spectrumlocalnews.com/ny/rochester/coronavirus/2020/03/12/oxygen-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 (Iloprost) | (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/clinicaltrialsharena) |
| National Institute of Allergy and Infectious Diseases | mRNA-1273 vaccine | (https://www.com/releases/2020/03/020317150116.htmlsciencedaily) |
| MIGAL Research Institute | Infectious Bronchitis Virus (IBV) vaccine | (http://www.org.il/Migal.covidmigal) |
| Tonix Pharmaceuticals Innovation Pharmaceuticals | TXN-1800 Brilacidin | (https://www..technology.com/news/tonix-pharmaceuticals-covid-19-vaccine/pharmaceutical) |
| Clover Biopharmaceuticals Vaxart | A recombinant subunit vaccine | (http://www.com/news/gsk_recruits_clover_biopharmaceuticals_in_latest_coronavirus_effort_1326917pharmatimes) |
| CytoDyn LineaRx and Takis Biotech | Leronlimab Linear DNA Vaccine | (https://www.com/news/press-releases/detail/392/files-ind-and-protocol-for-phase-2-clinical-trialcytodynamic) |
| Bioxytran Novavax | BXT-25 MERS CoV vaccine | (https://www..technology.com/news/bioxytran-coronavirus-patients-treatment/pharmaceutical) |
| Gilead Sciences | Remdesivir (GS-5734) | (https://www.com/2020/03/16/remdesivir-surges-ahead-against-coronavirus/statnews) |
| Roche BiocrystPharma Lattice Biologies Pfizer | Actemra | (https://www.com/news/roche-actemra-coronavirus-complications/pharmaceutical) |
| | Galidesivir | (https://www.com/article/4331827-biocryst-pharmaceuticals-multiple-value-drivers-coronavirus-kickerseekingalpha) |
| | Anniviboost | (https://www.com/news/can-flte-lattice-biologics-covid-19-treatments/pharmaceutical) |
| | Unnamed DNA Vaccine | (https://www.com/news/roche-actemra-coronavirus-complications/pharmaceutical) |
| | Unnamed DNA Vaccine | (https://www.com/investing/2020/03/12/biogen-and-vir-biotechnology-to-collaborate-to-finnovavax) |
| Biogen and Vir Biotechnology | Monoclonal antibodies | (https://www.com/2020/03/12/biogen-and-vir-biotechnology-to-collaborate-to-finnovavax) |
| Genentech (Roche group) | Actemra® (tocilizumab) | (https://www.com/2020/03/12/biogen-and-vir-biotechnology-to-collaborate-to-finnovavax) |
### Table 7
List of various treatments currently used against COVID-19.

| Sr. No. | Type of Treatment | Developer/Researcher | Development stage | Anticipated Next Steps Timing | References |
|---------|--------------------|----------------------|-------------------|------------------------------|------------|
| 1       | Antibodies based treatment against COVID-19 | 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       |                  | 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       |                  | 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       |                  | 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       |                  | EUSA Pharma | Clinical | Interim of April 2020 | (https://www.com/news/eusa-pharma-and-the-papa-giovanni-xxiii-hospital/eusapharma) |
| 6       |                  | 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       |                  | 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       |                  | GigaGen | Pre-clinical | – | (https://.com/biotech/gigagen-jumps-into-covid-19-arena-polyclonal-antibodies?mkt_tok=eyJpIjoiT0dFNE16bGhPRFk1WTJNMIhsInQOJUDhYm12ZdzJLY04bnc1T3lZrVmFUK2NVzFseYXSFhozWNWWUswHPSYyXcVwvoaZLZ2UVTGRBV5sBuMEy1FHPQGODF0akVGETNZcbgSm0Ri8w8p82j9HHeoQ5amptalwvZTdhN0JU5UxMeXVh5nYcd1NabKNVXbZ7FSVH1NHRHv1VEpqcU02aXN3SWRFSXRuUGNkVIE9PS0k&mrkid=72869502) |
| 9       |                  | Novartis | Clinical | – | (https://www.com/article/health-coronavirus-novartis/novartis-cos-malaria-drug-is-biggest-hope-again-coronavirus-sonnezeitung-idUSL8N2BMOQ?wref) |
| 10      |                  | Alexion Pharmaceuticals | Clinical | The phase 2 will be begin in the month of May 2020 | (https://www.com/news/home/20200402000522/en/Alexion-Announces-Plans-Initiate-Phase-3-Studybusinesswire) |
| 11      |                  | 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-initiades-development-plasma-derived?field_nir_news_date_value%5b5dim%5d=) |
| 12      |                  | Octapharma | Clinical | – | (continued on next page) |
### Table 7 (continued)

| Sr. No. | Type of Product – Treatment | Developer/ Researcher | Development stage | Anticipated Next Steps Timing | References |
|---------|-----------------------------|-----------------------|------------------|------------------------------|------------|
| 1       | Mesenchymal stem cells       | Numerous trials with global research sponsors | Clinical          | –                            | (https://www.com/news/home/20200416005144/en/New-COVID-19-Clinical-Trial-Supported-Octapharma-USAbusinesswire) |
| 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+(ADMSCs)bioindustry) |
| 3       | Ryoncil Mesoblast | Pre-clinical | – | – | (https://clinicaltrials.gov/ct2/show/NCT04338347?type=Expn&cond=COVID-19&draw=2) |
| 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/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, allogeneic killer cell therapy | Celyad | Clinical | The phase 1/2 will be begin | (https://www.com/news-releases/celynCy-001-announces-fda-clearance-of-ind-application-for-cynt-001-in-coronavirus-first-in-cellular-therapy-301034141.htmlprnewswire) |
| 7       | CAP-1002, allogeneic 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) |
| 9       | 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-antibopr) |
| 10      | siRNA candidates | Aplylam Pharmaceuticals/ Vir Biotech | Pre-clinical | – | (https://www.com/news/home/20200420005167/en/Vir-Alnylam-Expand-Collaboration-Advance-Investigational-RNAbusinesswire) |
| 11      | Ampligen; (ritatolimod) | AIM ImmunoTech/ National Institute of Infectious Diseases in Japan | Pre-clinical | – | (https://finance.yahoo.com/news/aim-immunotech-drug-ampligen-tested-10300673.html) |
| 12      | OT-101, a TGF-beta antisense drug candidate | Mateon Therapeutics | Clinical | – | (https://www.com/analysis/coronavirus-mers-cov-drugs/clinicaltrialsarena) |
| 13      | 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).

Micronutrients antibodies, cell-based therapies and RNA based therapies which are being envisaged 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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References

https://www.bluezone.com/en/health/pfizer-biotech-jointly-work-on-coronavirus-vaccin

Acree, W.M., Edwards, B., Black, J.W., 1986. Canine Corona Virus Vaccine.

https://www.aa.com.tr/en/health/pfizer-biontech-jointly-work-on-coronavirus-vaccin

https://www.cytodyn.com/newsroom/press-releases/detail/392/cytodyn-files-ind-and-

https://www.eusapharma.com/news/eusa-pharma-and-the-papagiovanni-xxiii-hospita

https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-

https://www.businesswire.com/news/home/20200410005167/en/Vir-Alllynines-Expan

https://www.businesswire.com/news/home/20200410005160/en/FDA-Authors-Atth

https://www.pfizer.com/news/news-releases/2020/03/coronavirus-vaccine-update-

https://www.businesswire.com/news/home/20200410005353/en/Novartis-Immunbi

https://www.businesswire.com/news/home/20200410005122/en/Alexion-Announces

https://www.clinicaltrialsarena.com/news/ubc-apeiron-biologics-covid-19-trial/ . A

https://www.businesswire.com/news/home/20200410005125/en/Alexion-Plans-Initia

https://www.businesswire.com/news/home/20200410005120/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005123/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005121/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005119/en/Alexion-Announces

https://www.pfizer.com/news/news-releases/2020/03/coronavirus-vaccine-update-

https://www.businesswire.com/news/home/20200410005117/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005116/en/New-Coronavirus-Cli

https://www.businesswire.com/news/home/20200410005114/en/Vir-Alllynines-Expan

https://www.businesswire.com/news/home/20200410005112/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005110/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005108/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005106/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005104/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005102/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005100/en/Alexion-Announces

http://www.360doc.com/content/07/0730/14/63361549_1768465.shtml . Accessed date: 20 May 2020.

Zhang et al., 2020). This review did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Authors declare no conflict of interest.

https://www.europeandrugsearch.com/keywords/ed-by-gavin-publishers-demonstrates-potential-cure-for-rheumatoid-arthritis/

https://www.businesswire.com/news/home/20200410005089/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005087/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005085/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005083/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005081/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005079/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005077/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005075/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005073/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005071/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005069/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005067/en/Alexion-Announces

https://www.businesswire.com/news/home/20200410005065/en/Alexion-Announces

