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Review Article

An Overview of Novel Coronavirus Disease 2019 (nCOVID19) outbreak: History, Treatment option and Vaccines

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Abstract

Humankind surviving is a continuous battle with the new emerging and existing pathogens like Spanish flu, HIV, Ebola, and COVID-19. A new way of fast-tracking drug development strategies, and unique way of possible treatment options are therefore necessary to win the fight against these pathogens. In the past few decades practicing personal safety measures like self-sanitization, wearing masks and consumption of the antiviral agents were the essential measures that are being practiced globally to prevent from the spreading of the disease and themself isolated from the society for life saving. In this review, we focused on the new potential drug molecules that have been studied *in vitro* through drug re-purposing strategy was included. In addition to this, different treatment options like plasma therapy, stem cell therapy, vitamin c therapy, and the important role played by the traditional medicine of China during the disease outbreak were comprised in this review.

Introduction

Coronavirus is an RNA genetic material containing virus and belongs to the family coronides. The name corona is coined because of its morphological appearance like a crown-shaped due to the surface-expressed spike-like proteins when observed under the electronic microscope. Through its spike proteins, the virus invades into the lung tissue majorly through the ACH-2 receptors. There are seven types of coronaviruses that cause severe to mild pneumonia-like symptoms to humans. They are 229E (alphacoronavirus), NL63 (alphacoronavirus), OC43 (beta coronavirus), HKU1 (beta coronavirus), MERS-CoV (beta coronavirus that responsible for Middle East Respiratory Syndrome, or MERS), SARS-CoV (beta coronavirus that causes a severe acute respiratory syndrome, SARS), SARS-CoV-2 (the novel coronavirus that causes coronavirus disease in other words COVID-19) [1]. In addition to severe pneumonia the viruses like HKU1, HCoV-229E, HCoV- OC43, HCoV- NL63 have been associated with the enteric and neurological diseases as well [2]. The first global pandemic was caused by the SARS-CoV in the year 2003 and spread nearly 32 countries with a mortality rate of 10-15% [3]. After ten years down the line in the year (2013) another MERS-CoVID pandemic attack have been witnessed in the Middle East countries.

In addition to this, in 2015, a major outbreak happened in the Republic of Korea in 2015 with a reported mortality rate 39% [4]. Adding to this, again in the year 2019 mid-December patients with symptoms like severe pneumonia were found in the Wuhan city in China. Later the causative virus was named as the nCOVID-19 (n-novel, coronavirus 2019) which spread in 219 countries as on April 7, 2021 [5]. To win the battle against this pathogen, a new way of fast-tracking drug development strategies was

taken charge by the scientists worldwide and discovered many vaccines like astrazeneca, biontech, covishield, covaxin, johnson and johnson, moderna, novavax, sinovac, sinopharm, sputnik v, etc., Even after the invention of vaccine and administered to the public, spreading of nCOVID-19 still exist as a challenging problem to the researchers. To overcome the major issue, a unique way of possible treatment options and a drug to treat nCOVID-19 are necessary. In this review, we have addressed the novel vaccines and possible drug molecules against the different strains of the coronaviruses selected by drug repurposing strategies were included. In addition to this, the novel way of treatment options like plasma therapy, Mesenchymal stem cell therapy, and vitamin C therapy was reviewed, in addition to this, the role played by the traditional chines medicine during the disease outbreak in China have also been comprised.

Cellular receptor and natural host of the different classes of corona virus

Coronaviruses invades the host cells through the interaction of the viral surface spike proteins with host cell-expressed membrane receptors (Figure 1). Viruses and their respective receptors for the entry of cells have been explained in detail in (Table 1) [6-9]. Apart from these receptors, some viruses enter the host cells with the help of proteases, for example, cathepsin L. Cathepsin L has been linked with the SARS and MERS-coVs entry; the other transmembrane proteases include serine 2 (TMPRSS2) and airway trypsin-like proteases TMPRSSIID could activate the spike proteins in the virus and facilitate the virus entry during the Hcov-229E and SARC-COV infection.

History of the coronavirus outbreaks

The history of the human coronavirus can be traced back to 1965, with the discovery of a virus named B814 from the embryonic tracheal organ culture obtained from the respiratory tract of adults having a common cold [10]. The first corona outbreak was recorded in the year 2003 in China, and the mortality rate was 10%. In Saudi Arabia first outbreak of MERS-CoV lasted for one year, while the second attack was recorded in 2012 with a mortality rate of 35.6%. This epidemic lasted for seven years, and the third spell was observed in 2019 in China with a mortality rate of 2 to 3% [11]. The detailed outbreaks of the coronavirus and associated information were listed in (Table 2).

Disease Treatment strategies

Coronavirus is an RNA containing virus, and no specific drug has yet been approved permanently by FDA for the disease treatment. In practices globally, the broad-spectrum antiviral drugs and combination therapies were under recommendation for disease management. Herein we focused on the different available treatment strategies for the disease treatment that can broadly divide into synthetic drug molecules, novel cell-based and plasma therapy, vitamin c therapy and traditional Chinese medicines.

Table 1: Viruses and their respective receptors for entry inside the cells.

S. No.	Corona Viruses	Cellular Receptor	Natural Host.
1	HcoV-229E	Human aminopeptidase N	Bats
2	HCOV-NL63	ACE-2	Palm civets, bats
3	HCOV-OC43	9-0 –Acetylated sialic acid	Cattle
4	HCOV-HKU1	9-0 –Acetylated sialic acid	Mice
5	SARS-CoV	ACE2	Palm civets
6	MERS-CoV	DPP4	Bats, camels.

Table 2: History of the corona viral reported pandemics.

HEADING	SARS-CoV	MERS-CoV	COVID-19
Origin	China	Saudi-Arabia	China
Year of Outbreak	2002-03	2012	2019
Target	Epithelial cells of the respiratory tract (ACE-2 receptor)	Epithelial cells of the respiratory tract and kidney (DPP-4 receptor)	Epithelial cells of the respiratory tract (ACE-2 receptor)
Genetic Material	RNA	RNA	RNA (Minimum 10 open reading frame)
Mortality Rate	10%	35.6%	2%-3%
Infection Rate According to Age	Young age	Age above 50 years	Middle age and above
Associated Health Issues	Cardiovascular complications less frequent, acute kidney failure	Cardiovascular complication more often, acute kidney failure	Cardiovascular complications, acute kidney failure less often
Epidemic Period	Ended in less than 1 year	Last for near about 7 years	In question (Pandemic continues till today)

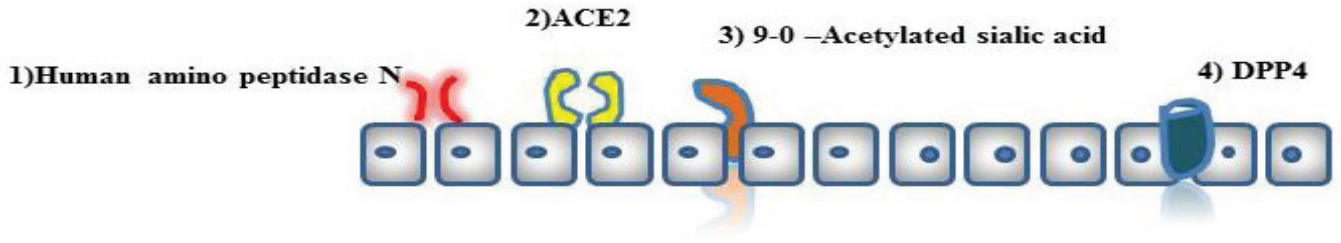

Figure 1: Diagrammatic representation of types of host receptors facilitates virus entry.

Synthetic drug molecules

The threat of the coronavirus infection was known to the scientific community from the early beginning of the 20 centuries. The endemic effect of MERS in 2003 and by SARC in 2012 were the few examples. Since then, the search for the novel targeted corona viral drug molecules were more focused on the MERS and SARS because of their severe illness and mortality rate. The broad-spectrum antiviral drug molecules like the ritonavir, lopinavir, and in combination with corticosteroids and interferons collectively reduce the illness and the death rates of the infected persons. To speed up the current treatment options for the pandemic nCOVID19 infection, we here listed the potent and possible drug molecules that have been studied in vitro through drug repurposing strategy.

The main advantage of this strategy is the availability of the already know pharmacokinetic and pharmacodynamics parameters of the drug molecules. By using this approach, shen et al., and group reported the drug molecules that potentially inhibited the coronaviruses. His list of drug molecules includes that are generally used for the other type of disease options like the Analgesics, antiprotozoal, antibacterial, etc. [12]. The IC_{50} and CC_{50} values and the general mode of action were represented in (Table 3). In another effort by the same group systematically screened the FDA approved library of drug molecules that contain 2334 approved drugs and pharmaceutically active compounds [13]. This yielded a series of hit compounds and their in vitro EC_{50}, and CC_{50} values, besides, their primary mode of action was depicted in (Table 4). In search of the potential antiviral drug molecules, wild and group identified the drug molecules like the chloroquine, chlorpromazine, loperamide, and lopinavir from screening; the FDA approved the drug library. The drug molecules chloroquine previously reported as active antiviral molecules against the viruses like the flaviviruses, influenza virus, HIV, and

Table 3: Repurposed drug molecules and their EC_{50} and CC_{50} values against different classes of corona viruses.

S. No.	Compound name	Activity	HcoV-OC43 $EC_{50}(CC_{50})$ µM	HcoV-NL63 EC_{50} (CC_{50}) µM	MERS-Cov EC_{50} (CC_{50}) µM	MHV-A59 $EC_{50}(CC_{50})$ µM
1	Lycorine	Antiviral, antineoplastic	0.15 (4.37)	0.47(3.81)	1.63(3.14)	0.31(3.51)
2	Emetine	Inhibit transcription and translation levels	0.30 (2.69)	1.43(3.63)	0.34(3.08)	0.12(3.51)
3	Mycophenolate	Immune suppressant antiviral.	1.58(3.43)	0.23(3.01)	1.54(3.17)	0.27(3.33)
4	Phenazopyridine	Analgesic	1.90(20)	2.02(20)	1.93(20)	0.77(20)
5	Mycophenolic acid	Immune suppressant, antiviral	1.95(3.55)	0.18(3.44)	1.95(3.21)	0.17(4.18)
6	Pyrvinium pamoate	Anthelmintic	3.21(20)	3.35(20)	1.84(19.91)	4.12(19.98)
7	Monensin sodium.	Antibacterial.	3.81(20)	1.54(20)	3.27(20)	0.18(20)

Table 4: Repurposed drug molecules and their EC_{50} and CC_{50} values against MERS and SARS.

S. No.	Drugs	Class	MERS-Cov EC_{50}(µM)	SARS-Cov EC_{50}(µM)
1	Emetin dihydrochloride hydrate	Antibacteriaal agent	0.014	0.051
2	Mefloquine	Antiparasite agent	7.41	15.55
3	Amodiaquine	Antiparasite agent	6.21	1.27
4	Loperamide	Antidiarrheal agent	4.8	5.90
5	Lopinavir	Anti-viral	8.0	24.4
6	E-64-D	Cathepsin inhibitor	1.27	0.76
7	Gemcitabine hydrochloride	DNA metabolism inhibitor	1.21	4.95
8	Tamoxifen citrate	Estrogen receptor antagonist	10.11	92.88
9	Toremifene citrate	Estrogen receptor antagonist	12.91	11.96
10	Terconazole	Sterol metabolism inhibitor.	12.20	15.32
11	Fluspirilene	Neurotransmitter inhibitor	7.47	5.96
12	Thiothixene	Neurotransmitter inhibitor	9.29	5.31
13	Fluphenazine hydrochloride	Neurotransmitter inhibitor	5.86	21.43
14	Promethazine hydrochloride	Neurotransmitter inhibitor	11.80	7.54
15	Astemizole	Neurotransmitter inhibitor	4.88	5.59
16	Chlorophenoxamine hydrochloride	Neurotransmitter inhibitor	12.64	20.03
17	Triflupromazine hydrochloride	Neurotransmitter inhibitor	5.75	6.39
18	Clomipramine	Neurotransmitter inhibitor	9.33	13.23
19	Imatinibmesylaate	Kinase signalling inhibitor	17.68	9.82
20	Dasatinib	Kinase signalling inhibitor	5.46	2.10

Ebola virus [14] Nipha –Hendra virus [15] has shown a dose-dependent inhibition activity with a EC_{50} of 3.0µM.

Cell-based therapy

Cells are the fundamental unit part of the living species, and all the essential biochemical reactions occur in it. In cell-based therapy, stem cell-based therapy approaches are emerging as a promising therapeutic field that has the potential to cure incurable diseases. Even though it appears as a promising therapeutic field, factors like the ethical issues, immunogenicity, and limited cell were the few limiting factors that hinders the potential of this field [16] Alternatively, here comes the Mesenchymal stem cells (MSC) that have attracted attention due to a high proliferation rate, free of ethical issues, and a minimally invasive procedure. In addition to this, these MSC can be easily obtained from the Bone marrow, adipose tissues, dental pulp, buccal fat pad, and menstrual blood, etc. [17]. The logic in the use of MSC therapy in the nCOVID infected patients mainly because of the immunomodulatory and regenerative functions of the MSC. Preliminary studies show that, after the systemic administration of the MSC cells in the nCOVID patients, these cells recruit at the microenvironment of the lung tissue and protect the lung tissue from the cytokine Strome and promoted the repair of the damaged lung cells [18].

Passive immunization or convalescent plasma therapy

In the human body, antibodies perform a crucial role to restrict and inhibit the growth of the pathogens. The antibodies act by binding the pathogen thereby inhibiting its entry into the cells or by activating the immune system to degrade the pathogen by macrophages [19]. Unfortunately, the antibody production starts only after the entry of the pathogens in the body, and thus by the time body shows immune response to novel pathogen infection, it might affect the vital organs. To overcome this issue, researchers have used the passive immunization approach where antibodies from the immunized animal were transferred to the diseased animal for treatment purpose [20]. Like this, the human antibodies have also been found to work as an active immunizing agent against the multiple infections. Numerous studies have shown the treatment of the bacterial (Staphylococcal, Diphtheria, and Tetanus) and viral (Hepatitis, RSV, and Ebola) infections [21].

In the next step, convalescent plasma injected to another patient results in the neutralization of the virus resulting the recovery from symptoms.

Continuous emergence of the new viral infections, including SARS, MERS, Ebola, and COVID-19 is a great challenge to develop the antiviral therapy. Due to the pandemic spread of the viruses and unavailability of the specific antiviral agents, passive immunization, or the convalescent plasma therapy (CPT) has again attracted the researchers for its therapeutic potential. Foreign pathogens infections can be treated with the whole blood or plasma isolated from the immunized or convalescent patient (**Figure 2**). The convalescent plasma therapy ultimately involves the use of the antibodies, or the humoral immunity developed against the pathogen. In last two decades, world has witnessed the pandemics of SARS, MERS, Ebola and H1N1, and because of this, the importance of the CPT has been reiterated. Studies carried out on SARS patient exhibited a statistically significant reduction in the mortality following the treatment with CPT [22, 23].

The effectiveness of CPT was also studied during the outbreak of Ebola in African countries. In the view of earlier studies in 1995 (in Democratic Republic of the Congo) and recent developments, WHO approved the convalescent serum to treat patients with Ebola [24, 25]. Since the beginning of the SARS-Cov-2 infection spread in China, no specific treatment has been approved and patients are recovering by supportive care and oxygen supply. Following this, CPT trials on patients have been successful in stabilizing the patient's conditions. The study carried out in Shenzhen Third People's Hospital at Shenzhen reported that 5 critically ill patients (severe pneumonia) with earlier treatments of antiviral and prednisolone were given CPT. The results of the study showed that after treatment for 12 days, patients were relieved of acute respiratory distress syndrome and tested negative for viral load [26] Another study of CPT carried out on 10 severe COVID-19 patients in China showed that the level of the neutralizing antibodies were increased rapidly after transfusion. After the 3rd day of the transfusion, patients started to recover

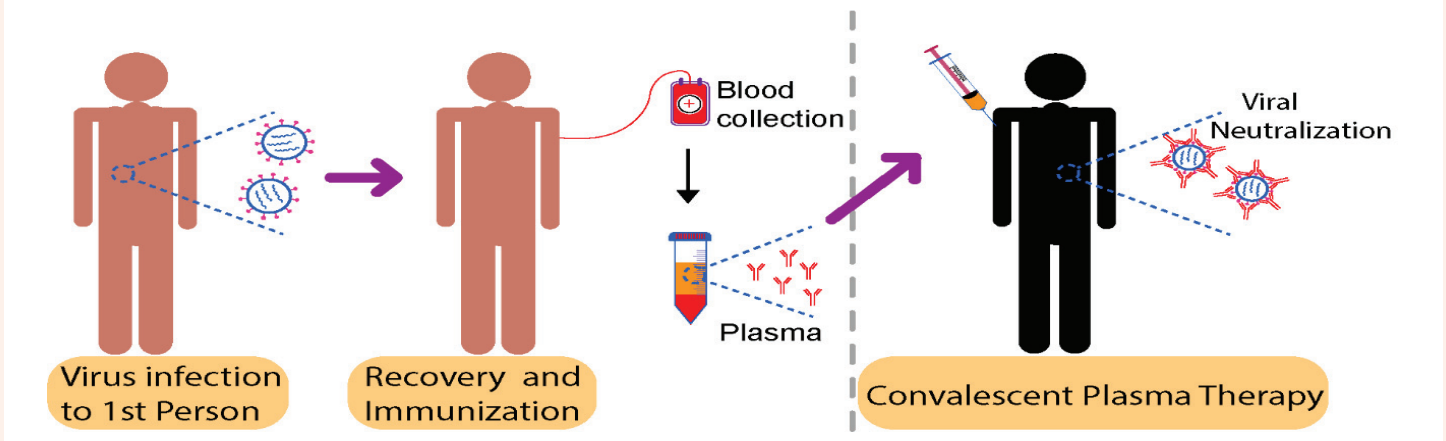

Figure 2: Illustration of the Convalescent plasma therapy. Virus infection to the patient generates antibody against virus, and after recovery blood is collected for plasma preparation. In the next step, convalescent plasma injected to another patient results in the neutralization of the virus resulting the recovery from symptoms.

from the symptoms and lymphocyte counts were increased significantly [27]. These reports suggests that with optimal dose and time point, CPT holds a great potential to treat the novel COVID-19 as well as possible future outbreaks.

Vitamin C therapy

In this current pandemic situation development of the vaccines and the new drug molecules for the disease, treatment is the time-consuming process. To overcome this situation new approach towards the treatment options are necessary, in this prospect, we here reviewed the milestones achieved by the vitamin c antioxidant molecule in the treatment of the covid patients. Hemila and colleagues reported the various high dose intravenous IVC infusion (200mg/kg body weight/day) shortened the intensive care stay by 7.8% and decreased the mortality rate [28]. The previous studies reported the oral vitamin C (6g/day) was able to reduce the risk of viral infection [29]. In recent times a study from China reported the high intravenous vitamin C had been successfully used in the treatment of 50 moderate to severe nCOVID patients, and all were cured and discharged. The probable mechanism of the vitamin C would be the free radical scavenging action, that are generated during the viral infection and the disease mediated stress.

Traditional Chinese medicine

China is the first country in the world that experienced a challenging condition with the nCOVID infection early at the beginning of the year 2020. Till the date, end of the March 2020, China reported a total of 85,000 and more active cases with a death rate of 3%. In recent times the report of the new cases and the death rates was fall over meaningfully. Herein, in this section, we review a few of the medically important chines traditional medicines that played a significant role in controlling the disease. Along with the synthetic drug molecules for the disease treatment, the active prescription of the traditional Chinese medication (TCM) was under practice during the high of the disease infection period. The prescription generally includes the decoction like Quingfeipaidu (QPD) Gancaoganjiang, Sheganmahuan, Qingfeitouxiefuzheng recipe. In a case study of 701 cases treated by the QPD, 130 cases were cured and discharged, clinical symptoms of 51 cases disappeared, 268 cases of symptoms improved, and 212 cases of stable symptoms without aggravation. The effective cure rate of the QPD decoction against the COVID-19 is 90% [30]. The mechanism of the action was not known, but the decoction of the (QPD) contains the composition of the 23 herbs that are primarily used for the treatment of the lungs related disfunction in the traditional Chinese practice.

nCOVID-19 vaccines

During the early 2020, moment the world witnessed this pandemic, virologist and industrialist globally started in search of the drug and vaccines against nCOVID-19. From late 2020 to till date several countries have come up with different vaccines using virus like particles, inactivated virus, viral vectors, and encapsulated mRNA vaccine. India discovered a vaccine using chemically inactivated SARS-CoV2 with beta-propiolactone in a such a way that it cannot replicate but the proteins remain intact. Further, the vaccine named it as “Bharat Biotech” and reported with 81% efficacy. Similarly China discovered an inactivated virus vaccine “SinoVac” and “Sinopharm” using beta-propiolactone with the efficacy rate of 50% and 79% respectively. America discovered “Novavax” a virus like particle vaccine nanoparticles coated with synthetic spike proteins and adjuvant in order the boost the immune reaction.

They developed against original as well as virus nCOVID-19, United Kingdom and South African strains with the efficacy of 95%, 85% and 60% respectively. Pfizer’s BioNTech introduced an encapsulated mRNA vaccine in which mRNA encoding for the spike protein was protected in a lipid nanoparticle. They claim that the efficacy rate against the original strain was 95%. Similarly another American encapsulated mRNA vaccine “Moderna” reported with 94% efficacy against the original strain. Russia discovered “Sputnik V” a viral vector vaccine where dsDNA encoding for the spike protein is protected in a safe virus. Further the infected cell expresses the spike protein which leads to an immune response, and they claim 91% of efficacy rate against original strain. England’s Oxford University discovered a “AstraZeneca” viral vector vaccine with the efficacy of 82% against the original strain [31-39]. Still the world researchers are focusing more to develop a vaccine with 100% efficacy.

Conclusion

Since the report of the first pandemic affects the research community around the globe, have been focusing on the development of the novel antiviral drug molecules and the treatment options for disease management. In their journey, few of them reported the use of the repurposing approach to bring the existing drug molecules for the treatment of nCOVID infection. The drug molecules like the broad-spectrum antiviral drug like the Ritonavir and the antimalarial drug chloroquine were found to be the promising molecules for the disease treatment. In addition to this novel plasma therapy looks promising; the underlying issues like anaphylactic reactions during the transfusion should be addressed. Besides, stem cell-based treatment mesenchymal therapy found promising extensive research that needs to be done to establish the safety parameters. Vitamin C and traditional chines medicine reported the successful treatment options; comprehensive clinical trials should be done to develop solid proof for the treatment options. Under these circumstances, the development of the vaccines and the viral-specific drug molecules is time consuming process we all should follow the basic measures like sanitization, social distancing, and the diet that generally boost the immune system would the possible and straight forward options to protect our self from the disease.

Highlights

- Dangerous new emerging and existing pathogens like Spanish flu, HIV, Ebola, and COVID-19
- Unique way of possible treatment options
- New potential drug molecules that have been studied *in vitro* through drug re-purposing strategy
- Plasma therapy, stem cell therapy, vitamin C
- Vaccines with improved percentage of efficacy

Author Contributions

Dr. S. B. Santhosh, Dr. Veera Vijaya Basamshetty, Dr. Anil Bidkar and Mr. Nimma Ramesh conceptualized and developed the idea for the review. Mr. Vijay Kumar along with Mr. Sarvan Kumar collected the data for the work. All the authors were involved in the interpretation of the data and in critical revision of the manuscript preparation. The final approval and accountability rests with Dr. S. B. Santhosh.

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