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Review Article

A REVIEW ON COVID-19 PANDEMIC A GLOBAL THREAT-CURRENT STATUS AND CHALLENGES AND PREVENTIVE STRATEGIES

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ABSTRACT

Covid19 (Coronavirus) is a life-threatening virus that mainly affects our respiratory system, kidney, and GIT tract. People with a low immune system in their body fall prey to it. This virus (2019-nCoV) spreads easily from one person to another. As there is no treatment to kill the virus, the only way to stop this pandemic is through precautions and reduce the viral load in the body. This review reveals the main types of coronaviruses, history, pathophysiology, current treatment, drawbacks of current treatment, targets for drug development against Covid-19, vaccines discovered for covid-19, side effects of the currently available vaccines, and current status of this situation. The main mechanism of action of the virus easily enters to bind with the Angiotensin-Converting Enzyme 2 (ACE2) in the human body cells. Management of the virus several approaches will be taken mainly isolation of the patients and contacts the contacts, oxygen therapy for respiratory failure patients based on the severity Remdesivir, Lopinavir/ritonavir, Chloroquine, and Hydroxychloroquine, Alpha-interferon and plasma therapy can be used to control the infections. In India, AYUSH is also recommended to enhance the immune system through herbal-based products, Vaccination is also recommended by most of the countries, but many side effects and drug-drug interactions were reported for the above treatments. So that in future a new way of approach should be developed by our health organization as soon as possible.

Keywords: Corona Virus, Treatment, Vaccines, Mutant strain virus

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INTRODUCTION

Viruses are infectious agents that replicate only inside the body. There are different kinds of viruses such as chickenpox virus, herpes virus, adenovirus, etc [1]. In many ways, a virus can spread. The main ways are transmission from plant to plant through insects, transmission by coughing and sneezing, fecal-oral route transmission, and transmission by sexual contact [2]. Among these, coronavirus, which belongs to the *Coronoviridae* family and Orthocoronavirinae subfamily, is the most likely to get infected in mammals and birds which have a single-stranded RNA genome [3]. In the 1930s the first coronavirus was identified. It was noticed when the domesticated chicken was affected by the acute respiratory infection that is caused by the contagious bronchitis virus (IBV). In the 1960s, the human coronavirus was discovered. The main symptoms were common cold, fever, and breathing difficulty. Later this was named human coronavirus OC43 and human coronavirus 229E [4]. The word corona came from the Latin word, *corona which* means *crown.* It has the structure of large spherical pleomorphic particles with bulbous surface projections. 120 nm is the average diameter of a coronavirus. The main mechanism of entry of virus to the host cell is the attachment of (s) glycoprotein of the virus-cell to the host cell receptor. After attaching to the receptor, the protease of the host cell cleaves and activates the receptor attached glycoprotein. The main portion for the host cell attachment is the 5-methylated cap and 3polyadenylated tail, which helps for translation. There are a total of six coronaviruses are available. In that, one is divided into two. So a total of seven are available. Those are Human coronavirus OC43, HKU1, 229E, NL63, MERS-related coronavirus, severe acute respiratory syndrome coronavirus, SARS CoV 2 [5]. In the Wuhan city of china, the Coronavirus disease 2019 was first reported and named as SARS-CoV-2. The world health organization has to develop updates on the current status of this infection and its health measures [6].

Search criteria

The information was gathered using a methodical strategy that began with studying pathophysiology and targets identified for the SARS CoV 2 from high-quality publications. More than 200 articles were searched and identified, and 61 important types of literature were chosen from the huge corpus of COVID-19 publications. This review included the article from 1995 to 2021 and the data related to the review topic was collected from the various databases PubMed, Science Direct, and Google Scholar by using the search words: SARS Cov2, pathophysiology, Current treatment strategy, Vaccines, herbal studies in Covid and new strains of Corona Viruses.

History

In 2003 in Hong Kong, fifty patients were affected by severe acute respiratory syndrome (SARS) in the age group of 23 to 74 with the symptoms of fever, myalgia, and cough. The liver dysfunction patients with older age groups were found to be more severe compared to other people. In Saudi Arabia, in the year 2014 had MERS-CoV a high mortality rate in the age group of 65 and greater than 65. They did not show any symptoms in the early stage [7].

Epidemiology and pathophysiology

A high mortality rate was found in these coronavirus diseases. From that 34.4% death rate was found in MERS-CoV and other percentages of disease death were unknown [8, 9]. As per the latest report of WHO published in April 2021, globally confirmed cases of Covid-19 were 147,539,302. 3,116,444 deaths were confirmed by the World Health Organization (WHO). Infection begins with membrane fusion attachment and the RNA genome is used as a template after un-coating to utilize the synthesize of genomes of the progeny and a nested collection of RNA sub genomics [10]. The replication transcription centers are closely associated with DMVs which are proposed to be adopted from the modified ER, probably through the combined activities of nsp3, nsp4, and nsp6 non-structural proteins [11]. The proteins E, M, and S are prepared and anchored on the ER, while the protein N is translated into the cytosol. Assembly takes place in the ERGIC, and exocytosis releases mature virions through smooth-walled vesicles. The three stages that presumably induce ER stress are illuminated with numbered star signs, namely: (1) DMV formation, (2) major structural protein development and alteration, and (3) depletion of ER membrane during budding [12, 13]. The virus that lives in the host cell is picturized in fig. 1.

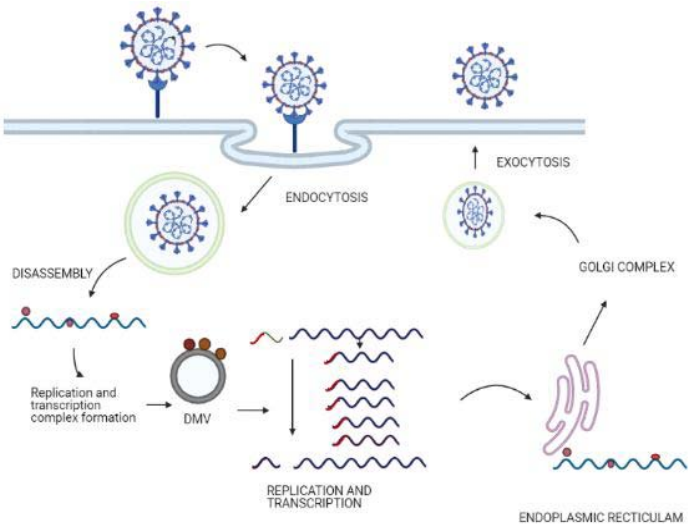

Fig. 1: Virus life cycle in the host cell

Treatment for covid-19

Several antiviral agents are available for many viral infections. During the corona outbreak there was no treatment available; later Chloroquine Phosphate by oral administration was recommended for this disease [14, 15]. For older patients whose body weight is more than 50 kg, Chloroquine phosphate 500 mg is given orally. For those with a bodyweight of 50 kg or less, it is recommended to bid 500 mg on the 1st and 2nd days, and 500 mg, four times in a day (q. i. d) on the 3rd to 7th days, with a 7-day course of treatment. The only FDA-approved drug for treating Covid-19 is Remdesivir. It is an anti-viral agent belonging to the non-nucleoside analogues class, used to prevent viral RNA synthesis. It is administered at a dose of 100 mg vial. Later, patients with severe pneumonia conditions were administered with Dexamethasone, belonging to the corticosteroid class. The drug is administered orally or intravenously at a dose of 6 mg once daily for 10 d but less benefited to non-severe pneumonia patients. It modulates immune-mediated lung injury and cuts the risk of death in patients on ventilators. But Dexamethasone is not approved in India. Adult patients hospitalized with confirmed SARS-COV-2 infection were provided with Lopinavir/ritonavir combination drug at a dose of 400 mg and 100 mg, respectively, twice a day for 14 d. It is an HIV protease inhibitor used to prevent polyprotein proteolysis. The dosage of the drug mainly depends on the patients' medical condition and for children, the approach of the drug is through the patient's body weight and height. The combination lowers the mortality or SARS-COV-2 RNA level but a standard cure from the treatment is not found. Patients with elevated IL-6 levels are recommended for Tocilizumab of repeated-dose, which is an IL-6 inhibitor used to treat cytokine release syndrome. It is given intravenously at a single dose of 400 mg, which reduced inflammation, mortality, oxygen requirement, and vasopressor support. The drug is an alternative treatment for COVID-19 patients with a risk of cytokine storms recently. Dapagliflozin, SGLT-inhibitor, is used in COVID-19 patients, which reduces the adults with metabolic or renal risk factors, cardiovascular complications. The goal of the trial, called DARE-19 (Dapagliflozin in Respiratory Failure in patients with COVID-19). Patients with onset of symptoms treated less than 7 d delivered a triple combination therapy of 14 d of oral lopinavir-ritonavir, every 12 h, ribavirin 400 mg every 12 h, and s/c injection of one to three doses of Interferon-beta-1 b 1 ml (8 million IU) on alternative days, people with symptom onset of day 1-2 are received all doses of Interferon-beta-1b; if start off on day 3-4; received 2 doses; if commenced on day 5-6 are received 1 dose. The patients having membrane attack complex were provided with the drug Eculizumab, the dose of 10 mg/ml, which modulates the activity of distal complement [16-19].

Convalescent plasma therapy is found to be an experimental treatment and researchers are in the hope that this therapy could help patients with severe COVID-19 complications. This remedy helps the patients to boost up their ability to fight the virus and also to avoid patients being more ill and experiencing the symptoms from their moderate condition. The blood from people who've recovered is called convalescent plasma. This mechanism mainly works has the patient's Antibodies-proteins the body uses to fight off infections-to the disease in their blood. This therapy is useful to the patients with COVID-19 where other drugs haven't helped them during the treatment. The latest news for COVID-19 treatment is that a first new biologic therapy-Itolizumab which is administered at a dose of 25 mg/5 ml injection solution to treat cytokine release syndrome (CRS) in moderate to Severe Acute Respiratory Distress Syndrome (ARDS) patients with COVID-19 [20].

Drawbacks of current treatment

Many adverse effects and drug interactions were reported for Chloroquine Phosphate. Patients having a cardiovascular problem can affect the drug controversy. Neuromuscular pain, granulocytopenia, irreversible visual impairment, itching, dermatitis, rashes also reported the remaining adverse effects. Many drug interactions were also reported by the continuous use of chloroquine phosphate. Combined use of Chlorpromazine and chloroquine phosphate leads to increased liver dysfunction. Administration of this drug after the use of digitalis causes cardiac block. The combined use of antibiotics and this drug causes an inhibitory effect of neuromuscular junction [21]. Hydroxychloroquine/chloroquine doesn't help hospitalized COVID-19 patients and when used as a prophylactic drug, it failed to prevent infection. Combined use of Azithromycin and Hydroxychloroquine has not shown any clinical benefit or any known and no evidence of strong antiviral activity. Recently, WHO announced that the Solidarity trial for HCQ has stopped where the drug doesn't show any reduction in the mortality of hospitalized COVID-19 patients. In the case of, Ribavirin and Remdesivir trial studies showed that these drugs have only limited benefits. The combinational drug Lopinavir-ritonavir has shown no therapeutic effect for the treatment of severe illness caused by SARS-COV-2. The slightly affected patients weren't benefited with Tocilizumab has this drug only helped patients with a critical illness. In the case of convalescent plasma therapy, the risk of infection was low but another carrier risk was also found in the trials like allergic reactions, breathing difficulty, lung damage, and transmission of infection during the transfusion. The drugs under the Solidarity trial are mainly off-label agents for the treatment of COVID-19, such as Eculizumab drug are pending the confirmation for the remedy [22].

Target identified in covid-19

For the development of a potent therapeutic agent against covid-19, the preferred targets are mainly based on host-based targets and virus-based targets. The virus-based targets are divided into

structural proteins and non-structural proteins; structural proteins are considered as the potential targets against covid-19, they are spike protein, Nucleocapsid protein, envelope protein, and membrane protein. There are 16 non-structural proteins such as RNA-dependent RNA polymerase, helicase, and Proteases 3CLpro. RNA-dependent RNA polymerase is a conserved protein that plays a crucial role in the virus lifecycle [23].

Another promising drug target is host-based like ACE2 host receptor in which virus entry occurs through binding to this receptor. The spike protein present in the infectious coronavirus is stimulated by the Transmembrane Serine Protease 2, a host-based receptor. Other targets based on the host are Adaptor-Associated Kinase 1 (AAK1) and Cyclin G-Associated Kinase, Phosphatidylinositol 3-Phosphate 5-Kinase, and Cathepsin L.

In silico studies are done to identify the potential candidates targeting both human and viral gene/receptor/enzyme taking part in the pathogenesis of the disease. Nowadays *in silico* studies involving both host and viral-based targets, the main targets selecting for studies are spike protein, main protease, transmembrane protein serine, and RNA-dependent RNA polymerase [24, 25]. Many targets have been identified and some of them have undergone drug repurposing studies and are listed in table 1.

Table 1: Targets chosen for the covid-19

Gene/Receptor/Enzyme	PDB ID	Organism	Reference
Papain-like protease (PLP/PLpro)	3E9S	SARSCoV2	[26]
	5Y3E		[27]
3C-like protease (3CLpro/Mpro)	1Z1I	SARSCoV2	[28]
	5R82		[29]
	2Z9J		[30]
	6Y2G		[31]
RNA-dependent RNA polymerase (RdRp)	6NUR	SARSCoV2	[32]
	7BV2		[33]
	6NUS		[34]
Helicase	6JYT	SARSCoV2	[35]
Guanine-N7 methyl transferase	5C8S	SARSCoV2	[36]
Uridylate-specific endoribonuclease (Nsp15)	6VWW	SARSCoV2	[37]
2'-O-Methyltransferase	3R24	SARSCoV2	[38]
ORF7a protein	1YO4	SARSCoV2	[39]
Spike protein (S protein)	3SCI	SARSCoV2	[40]
	6VYB		
Envelope protein	5X29	SARSCoV2	[41]
Nucleocapsid phosphoprotein (N protein)	1SSK	SARSCoV2	[42]
	2CJR		
Angiotensin converting enzyme 2 (ACE 2)	1R42	HUMAN	[43]
	6VW1		
Transmembrane protease serine 2 (TMPRSS2)	5CE1	HUMAN	[44]
AP2-associated protein kinase 1 (AAK1)	5L4Q	HUMAN	[45]
human furin (hFUR) protease	5JXH	HUMAN	[46]
Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM 1)	5YIQ	HUMAN	[47]
	2QSQ		

Herbal based studies in covid-19

For primary health care, many countries still depend on herbal medicines, although traditional medicines are used as antiviral agents. Alkaloids, steroids, di-terpenoid lactones, and glycosides are the phytochemicals derived from the plants which have shown antiviral effects in human. Currently, many+herbal-based studies are undergoing in coronavirus disease. The herbal plant Tinospora cordifolia is used in many Ayurveda preparations for treating urinary disorders, allergic conditions, diabetes, inflammation, rheumatism, enhance the body's immune system, anemia, and skin diseases [48]. Papia Chowdhury reported that berberine, the phytoconstituent present in Tinospora cordifolia has established its strong candidature to serve as potential inhibitors in regulating the 3CLpro [49]. Mansi Pandit and N. Latha stated that the compound Silybin from Silybum marianum, Catechin, and Quercetin from Aloe Barbadensis, Withaferin A in the Withania somnifera and Cordioside from the Tinospora cordifolia showed greater energy of binding [50]. Glycyrrhizin which is present in the root of licorice neutralizes the SARS-CoV 2 *in vitro* through targeting the main protease Mpro. The chemical constituent present in turmerics such as curcumin and cyclocurcumin also dihydroxy dimethoxy flavone and andrographolide from the plant Andrographis paniculata is inhibiting SARS CoV-2 main protease enzyme also many of the phytochemicals are understudies to identify the effectiveness against covid-19.

Covid-19 vaccination

During the pandemic situation, it is a challenging process to develop and scale up the process of a vaccine. Around the world, dozens of vaccines have been authorized and still many vaccines are under development. Covishield, covaxin by India are the authorized vaccines and many vaccines are in the clinical trials. For the safe and effective development of the vaccine, the design of the vaccine is mainly based on the mRNA, Adenovirus vaccine, live attenuated vaccine, etc [51, 52]. The authorized vaccines are tabulated in table 2.

Table 2: Few authorized vaccines for COVID-19

Name	Primary developer	Country of origin	Mechanism	Reference
Covishield	Oxford University and AstraZeneca,	UK	Adenovirus vaccine	[53]
Comirnaty	Pfizer, BioNTech	Multinational	mRNA based vaccine	[53]
Covaxin	Bharat Biotech, ICMR	India	Inactivated vaccine	[54]
CoronaVac	Sinovac Biotech	China	Inactivated vaccine (formalin with alum adjuvant)	[54]
Sputnik V	The gamaleya research institute, acellena contract drug research and development	Russia	Recombinant adenovirus vaccine (rAd26 and rAd5)	[53]

ZyCoV-D is a vaccine candidate in the development stage sponsored by the Zydus Cadila. ZyCoV-D is a DNA vaccine and it is in phase 3 clinical trial. CVnCoV is an mRNA-based vaccine developed by curevac: GSK, which is in the 2b/3 phase trial. Abdala (CIGB66) a protein subunit vaccine developed by the Center for genetic engineering and biotechnology and it's in phase 3 clinical trial. Bacillus Calmette-Guerin (BCG) vaccine, INO-4800, VIR-7831, and UB-612 are the vaccines in the phase 2b/3 stage.

Preventive strategies

"Prevention is better than cure" so that Preventive measures should be following the Government norms and World health Organization advise to overcome the medical emergency such as break the chain through social distancing, make awareness to wear masks like N95, Double Masking (one surgical Mask and one triple-layer Cloth Mask), maintenance of hygiene, gargling with hot water, Inhalation of a stream (with or without herbs), isolation, and movement restrictions can help in the control of COVID-19 spread. Proper sanitization and cleaning of hands can be effective in inhibiting the spread of the virus.

Safety of covid-19 vaccines

In this pandemic situation, there is an essentiality for the Covid vaccine. Many of the countries started to provide vaccines to health care workers and common people, but the side effects are reporting after receiving the vaccines. Pfizer-BioNTech vaccines urgent approval from US-FDA. E 1-shitanyNA *et al.* conducted a retrospective study and researched the mild to moderate effects of Pfizer BioNTech vaccines in Saudi residents. As per the European Medicines Agency (EMA) information, thromboembolic events have been reported among the recipients who received Oxford–AstraZeneca COVID-19 vaccine. Moderna, the mRNA vaccine reported side effects are fatigue, joint pain, fever, and muscle pain. Still, studies are going on to find out the mild to moderate side effects and effectiveness of Covid vaccines [55, 56].

Current status

World Health Organization reported the current case comparison of COVID 19 at a global level. There is no cure for corona virus-infected patients. A medical electronics research unit in De Scalene Organization revealed a device that can help to neutralize the spread of coronavirus disease and it will be tested by the University of Maryland in the U. S. Dr. Rajah Vijay Kumar, Chairman of this Organization said that the device cannot have the capability to cure the patients who have already infected it can keep in houses, schools, auditorium and public places for the prevention of spreading of virus from one person to other. The mechanism he was explaining the neutralization of electrons. The virus consists of cells containing a large amount of S-proteins. These S-proteins having a highly positive charge and our body has highly negatively charged DNA [57, 58]. So, when the virus once gets into the body, it sticks into the negatively charged cells and starts replicating. The device helps to resist this replication by neutralizing the positively charged particles. This device produces a large number of electrons and the virus attaches these electrons and neutralizes the charges because the virus doesn't know the difference between electrons in our body and the device. In such a way they are developing a large device for more resistance. The current situation of this pandemic is that, reporting mutant strains and developed unusual public health events. There are three clinically recognized mutant variants of the virus. The London variant with 23 mutations will spread rapidly and have an increased risk of death. The London variant is known as B.1.1.7 and in 2021 January the South African variant knows as B.1.351 was reported. Indian variants, London variant viruses are reporting around the world, and the Indian variant is found to be more infectious, as the vaccination campaigns are still going on in every country. The primary studies of covaxin and Covishield show that they are effective against an Indian strain of Covid-19 [59-61].

CONCLUSION

This review reveals the main types of coronavirus, history, pathophysiology, current treatment, drawbacks of current treatment, covid-19 studies based on the herbal plants which have already reported antiviral, anti-inflammatory, and immunomodulatory activities, vaccines developed for covid-19, and the side effects of vaccines, and current updates of coronavirus disease 2019. COVID 19 is a life-threatening problem, the main problem of this situation is the lack of immunity and lack of precautions. By avoiding the contact and proper progress of our immune system can overcome the virus infection. World health departments are developing new techniques day by day. Effective vaccination will fight against the covid-19 but the mutation of the coronavirus is reporting in every country, which will be a new crisis and threaten the public health care system worldwide.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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