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COVID-19: CAUSES, MECHANISMS AND POSSIBLE TREATMENTS

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ABSTRACT

At the end of 2019 in December, a bunch of deadly pneumonia cases were found in Huanan sea food market in city of Wuhan in Hubei province, china. They were caused by a previously unknown corona virus. All patients had been associated with the Wuhan Whole food market, where seafood and live animals are sold. The virus spread at an alarming speed and lead authorities in China to initiate effort and investigation. However, by that time, the great row of travelers had carried the virus to many countries, sparking memories of the previous corona virus epidemics, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), and causing widespread media attention and panic. Based on clinical criteria and available serological and molecular information, the new disease was called corona virus disease of 2019 (COVID-19), and the novel corona virus was called SARS Corona virus -2 (SARS-CoV-2), emphasizing its close relationship to the 2002 SARS virus (SARS-CoV). The scientific community raced to uncover the origin of the virus, understand the pathogenesis of the disease, develop treatment options, define the risk factors, and work on vaccine development. In this manuscript we portray the causes, mechanisms and possible treatments for corona virus.

Keywords: Wuhan, Pandemic, Corona virus; COVID-19, Mechanism, Treatments

INTRODUCTION

Epidemics in Human History

An epidemic is the rapid spread of infectious disease to a large number of people. Throughout human history, some epidemics claimed millions of lives. Let's discuss few of the in brief. The Black Death, which is thought to have originated around the Black Sea region. It spread rapidly through Europe and parts of Asia among rats nestling in the bowels of grain ships. The pandemics most devastating moment was between 1347 and 1351. It is estimated that it killed two-third of Europe's population. The plague would reappear in subsequent decades and is believed to have killed roughly 100 million people worldwide in the space of some 200 years. The plague of Justinian, which is a disease borne by rats in Egypt around 540^{AD}. It spread to the Byzantine capital at Constantinople. It claimed 5000 lives a day and killed nearly half of the ancient cities population. The plague became antiquity's most lethal known pandemic. In half a century, it killed between 25 million and 100 million in Europe and Asia. The 1918-19 influenza pandemic also known as Spanish Flu and killed tens of millions of people which is more than the number of those who died in all of world war I. It infected an estimated one-third of the global population and hit young adults especially hard. Those who contracted the disease died quickly and painfully. The last great plague pandemic begin in 1850, China's Yunnan province. The infectious fever killed tens of thousands of Chinese citizens. By the late 19^{th} century it reached Hong Kong and Guangzhou. These both cities were major coastal shipping hubs and this allowed the disease to spread throughout the world. This plague killed some 12 million people. It occurred at a time when scientific research was developing giving scientists a perfect empirical test case for germ theory. This has been a large part of why we have not seen a fourth pandemic till current Covid-19.

COVID-19 Background

In December at the close of 2019 there was a cluster of pneumonia cases found in some individuals operating dealers and vendors in the Huanan seafood market in city of Wuhan in Hubei province (WHO, 2014), china. Investigations found that it was caused by a previously unknown virus now named the 2019 novel Corona virus. On 11 Feb. 2020 WHO announced a name for the new corona virus disease as Covid-19 (WHO, 2020). Corona virus is a large group of viruses that consists of a core of genetic material surrounded by an envelope with protein spikes. This gives the appearance of a "crown" and the crown in Latin is called "corona" and that is what these viruses get their name. There are different types of corona-viruses that cause respiratory and sometimes gastrointestinal symptoms. Respiratory disease can range from common cold to pneumonia and in most people the symptoms tend to be mild, however, there are some types of

corona-viruses that can cause severe diseases which include severe acute respiratory syndrome (SARS-CoV) first identified in china in 2003 (WHO, 2020 and 2019) and Middle East Respiratory Syndrome (MERS-CoV) first identified in Saudi Arabia in 2012. The disease has since spread from those who were sick to others including family members and health care professionals. There are many cases present and the disease has spread within china and also to number of other countries. On 13 Jan. 2020 a first case of novel corona virus outside of China in Thailand and reinforces WHO for active monitoring and preparedness in other countries (WHO, 2020b). On 30 Jan. 2020 the outbreak was declared as public health emergency of international concern. Subsequently on 11 March 2020 by the alarming levels of spread and severity the WHO by assessing Covid-19 outbreak around the clock made the assessment that Covid-19 can be characterized as a pandemic.

Corona virus Overview

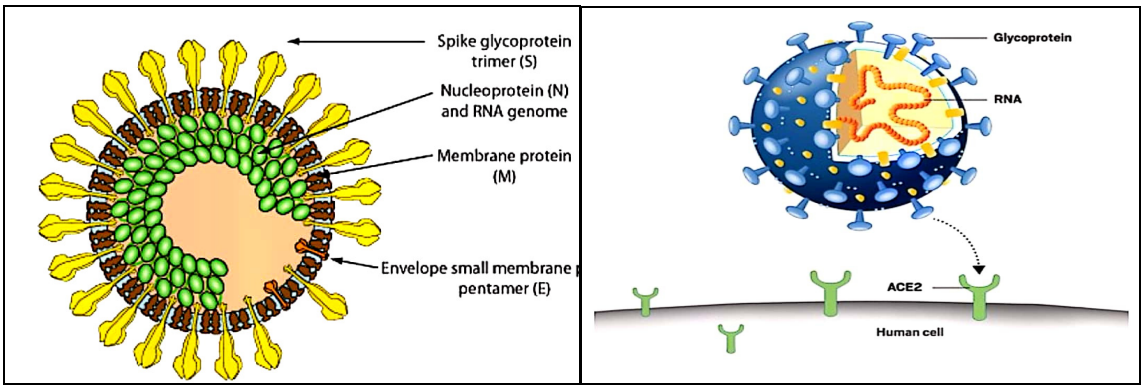
Corona viruses are enveloped positive sense RNA viruses that belong to the Orthrocoronvirinae subfamily, in the Coronaviridae family of the Nidovirales order (WHO, 2020) and is categorized into four genra of CoVs: Alpha corona virus (alphaCoV), Beta corona virus (betaCoV), Delta corona virus (deltaCoV) and Gamma corona virus (gammaCoV) (WHO, 2019) that are distributed broadly among humans, other mammals, and birds and that cause respiratory, enteric, hepatic, and neurologic diseases. Although there are six known species of this virus that are known to infect humans, however, only four are prevalent and usually cause cold-like symptoms source. These include 229E, OC43, NL63 and HKU1. The other two species of viruses, severe acute respiratory syndrome corona virus (SARS-CoV) and Middle East respiratory syndrome corona virus (MERS-CoV) are zoonotic viruses and have previously caused major pandemic incidents in 2002-2003 and 2012.

SARS-CoV-2 Origin

All corona viruses that have caused diseases to humans have had animal origins generally either in bats or rodents. Previous outbreaks of beta corona viruses in humans involved direct exposure to animals other than bats. In the case of SARS-CoV and MERS-CoV, they were transmitted directly to humans from civet cats and dromedary camels respectively (WHO, 2020 and 2019). Genetic analysis conveyed that SARS-CoV-2 is closely related to SARS-CoV, the virus that caused a pandemic in 2002-2003 and is a part of the genus Beta corona virus. It is an enveloped positive-sense RNA virus, and contains four major structural proteins which include the spike (S), membrane (M), envelope (E) and nucleocapsid (N). A recent study confirmed that angiotensin converting enzyme 2 (ACE 2), a membrane exopeptidase, found mainly in the capillaries of the lungs, is the receptor used by SARS-CoV-2 for entry into the human cells. The virus has been revealed to enter cells via endocytosis and membrane fusion. The spike proteins contain a variable receptor-binding domain (RBD) which binds to angiotensin-converting enzyme-2 (ACE-2) receptor found in the heart, lungs, kidneys, and gastrointestinal tract thus facilitating viral entry into target cells. Based on genomic sequencing, the RBD of SARS-CoV-2 appears to be a mutated version of its most closely related virus, RaTG13, sampled from bats (*Rhinolophus affinis*). It is, therefore, believed that the SARS-CoV-2 also originated from bats and, after mutating, was able to infect other animals. The mutation increased the RBD affinity to ACE-2 in humans, but also other animals such as ferrets and Malayan pangolins (*Manis javanica*; a long-snouted, ant-eating mammal sold illegally for use in traditional Chinese medicine), but also decreased the RBD affinity to ACE-2 found in rodents and civets. The pangolin is believed to be the intermediate host of SARS-CoV-2 (Chan JF *et al* 2013). There was some early speculation that SARS-CoV-2 emerged from a manmade manipulation of an existing corona virus, but there is no evidence to support such a theory. In fact, Anderson *et al.* suggest that the particular mutation that was found in the RBD of SARS-CoV-2 is different to what would have been predicted based on previously used genetic systems.

Mechanism of action of Covid-19

All corona-viruses contain specific genes in ORFI downstream regions that encode proteins for viral replication, nucleocapsid and spikes formation (Fan *et al.,* 2019). The glycoprotein spikes on the outer surface of corona virus are responsible for the attachment and entry of the virus to the host cells (Figure 1a). The receptor binding domain (RBD) is loosely attached among virus, therefore, the virus may infect multiple hosts (Cyranoski *et al.,* 2020 and Ksiazek *et al.,* 2003). Other corona virus mostly recognizes amino-peptidases or carbohydrates as a key receptor for entry to human cells while SARS-CoV and MERS-CoV recognize exo-peptidases (Chan *et al.,* 2013). The entry mechanism of a corona-virus depends upon cellular proteases which include human airways trypsin-like protease (HAT), cathepsins and transmembrane protease serine 2 (TMPRSS2) that split the spike protein and establish further penetration changes (Andersen K, *et al* 2020 and Van S, *et al* 2012). MERS-CoV employs dipeptidylpeptidase 4 (DPP4) while HCoV-NL63 and SARS-CoV recognize angeotensin converting enzyme 2 (ACE2) as as key receptor [7,13] SARS-CoV2 possesses the typical corona-virus structure with spike proteins and also expressed other polyproteins, nucleoproteins and membrane proteins such as RNA polymerase, 3-chemotrypsin-like protease, papain-like protease, helicase, glycoprotein and accessory proteins (Perlman *et al.,* 2009). The life cycle of SARS-CoV2 in host cells, begins its life cycle when S glycoprotein binds to the cellular receptor ACE2 (Figure 1b). After receptor binding, the conformation change in the S protein facilitates viral envelope fusion with the cell membrane through the endosomal pathway. Then SARS-Co2 releases RNA into the host cells. Genome RNA is translated into viral replicase polyproteins which are in turn cleaved into even small products by viral proteases. The polymerase produces a series of sub-genomic mRNAs by discontinuous transcription and finally translated into relevant viral proteins. Viral proteins and genome RNA are subsequently assembled into virus in the Endoplasmic reticulum and Golgi complex and then transported via vesicles and released out of the cell.



(A) **(B)**

Fig. 1a, 1b: Structure of Coronavirus and its attachment to ACE2 receptor

Modes of Transmission

Respiratory infections can be transmitted through droplets of different sizes. When the droplet particles are >5-10µm in diameter they are referred to as respiratory droplets and when they are <5 µm in diameter they are called as droplet nuclei (Glowacka *et al.,* 2011). According to current evidence, Covid-19 virus is primarily transmitted between people through respiratory droplets and contact routes (Bertram *et al.,* 2011 and Chan *et al.,* 2020). In an analysis of 75,465 Covid-19 cases in China, airborne transmission was not reported (Li *et al* 2020). Droplet transmission occurs when a person is in close contact with someone who has respiratory symptoms (Coughing or Sneezing) and is therefore at high risk of having his/her mucosa (Mouth and Nose) or conjunctiva (Eyes) exposed to potentially infective respiratory droplets. Transmission may also occur through fomites in the immediate environment around the infected person (Li *et al.,* 2020). Therefore, transmission of the Covid-19 virus can occur by direct contact with infected people and indirect contact with surfaces in the immediate environment or with objects used on the infected person (e.g. Stethoscope or Thermometer). Some evidence showed that Covid-19 infections may lead to intestinal infection and be present in feces. However, to date only one study has cultured the Covid-19 virus from a single stool specimen (Li *et al.,* 2020). There have been no reports of fecal-oral transmission of the Covid-19 virus to date.

Signs and Symptoms

Common signs of Covid-19 infection include respiratory symptoms, fever, cough, shortness of breath and breathing difficulties. In more severe cases infection can cause pneumonia, severe acute respiratory syndrome, kidney failure and even death. Standard recommendations to prevent infection spread include regular hand washing, covering mouth and nose when coughing and sneezing. Thoroughly cooking meat and eggs and avoid contact with anyone showing symptoms of respiratory illness such as coughing and sneezing.

COVID-19 - the global challenges

COVID-19 has emerged as the most dangerous pandemic threat throughout the globe since its outbreak during December 2019. It has become a big challenge for the researchers and virologist to find a solution for this deadly disease. This is attributed to the fact that COVID-19 is a viral infection that has been known to have the fastest frequency of recombination or replication in its positive strand resulting in the quick formation of new progeny viral cells inside the host cells. It has also been reported that SARS-CoV-2 has a high rate of mutagenesis and changes in structure, which has created a barrier for both investigations of the disease and therapeutic regimens [22]. Recently, few researchers have identified that the SARS-CoV-2 has mainly two types of strains, which are the L and S strains. Among these strains the L strain is more common and may have evolved from the S strain; additionally, this L strain has a higher rate of replication inside the human host cell, which has resulted in the escalation of the infection in limited time. Hence, it has become a big challenge to analyze the condition and offer therapy at the short time available. Due to the high mutation rate, it has been harder to understand the genomic organization and host interaction of the virus. The genomic structure of the virus is not the only factor that presents a great challenge to research, its ability to adapt and survive in different environmental conditions make it nearly impossible to identify its mode of survival. It has been earlier reported that the SARS virus can survive at 4^0C with a humidity rate of 20%. The first outbreak of the SARS-CoV-2 was during the peak of winter, where the environmental temperature was around 2^0C to 10^0C. But since then the virus has infected people and survived in countries of completely different climatic conditions, making its demographic association hard to predict. The health care professionals and equipment are limited and are unable to handle the vast number of patients who are infected. Moreover, some of the individuals who are infectious are asymptomatic and continue to travel or gather in social surroundings infecting more people. These factors pose a challenge for scientists, health-care professional and government officials to handle and contain the condition. Government officials in all countries continue to make efforts to minimize human contact by facilitating country wide shutdowns of public places as well as various steps have been initiated to ensure the safety of the people, like social distancing and self-quarantine which limits our social interactions. This will reduce the risk of spreading the COVID-19 to people by breaking the transmission chain and the influx of new COVID-19 cases in a given time period (Ong *et al.,* 2020).

Possible Treatments to Defeat Corona virus

The first one involves developing a potent vaccine against the virus. The vaccine would induce the bodies' immune system to fight against the virus and produce antibodies that can stay in the blood stream for life, but developing vaccines under normal circumstances can take several years. As researchers must study the virus bit by bit in detailed manner then they choose a small harmless

fragment of the virus to serve as a vaccine. In other cases they choose any fragment of the virus and deactivate it with chemicals. The second method involves designing a drug that targets either the virus or the host cell. After the virus makes entry into human cellist begins making copies of it and destroys the cell and releases new copies to infect adjacent cells. The drug could block the virus from replicating inside human cells. But this means the virus would remain dormant without any activity inside human cells during which it could mutate and come up with even greater aggressive version of itself. The drug could also force the infected cells to undergo apoptosis and form apoptotic vesicles. The Phagocytes which are wandering cell of immune system then come in and ingest the vesicles. Developing such a drug normally takes years of research, development and testing which makes this an unlikely solution to the ongoing global outbreak. The third method involves testing existing drugs to see which one could work against the virus. Viruses in general share similarities in their genetic makeup, some of them can be as high as 90%, which means existing drugs for other viruses such as influenza virus or HIV could solve the problem and help contain the spread of corona virus. Such drugs would target the same sites or block same processes in viral replication. Current reports show that many drugs including HIV etc are being repurposed to fight current virus. The two drugs have been around for about 10-15 years and are off patient. The fourth method involves genetically engineering human T-cell using CRISPR and then injecting the genetically engineered cells into the human body. The T-cells are engineered to become more potent in recognizing and killing the infected cells. Genetically engineering human T-cells must be done separately and differently for each person as our genome are slightly different; the engineered T-cells won't work on every one which means every one infected must have his/her own genetically engineered T-cells. Given how fast the current outbreak is spreading and how slow genetically engineering can be, this won't likely be an ideal solution for the ongoing outbreak. The fifth possible method is the development of immunotoxins which have proven against most cancers. Immunotoxins composed of pathogen specific monoclonal antibodies coupled to lethal toxins are potentially valuable therapeutic reagents. The toxins used in preparing immune-toxins include ricin, shegilla toxin, diphtheria toxin, all of which inhibit protein synthesis in different possible ways. These toxins are so potent that a single molecule has been shown to kill a cell. Each of these toxins consists of two types of functionally distinct polypeptide components and inhibitory (toxin) chain and one or more binding chains, which interact with receptors on cell surface, without the binding polypeptides the toxins cannot go into cells and therefore is harmless. An immune-toxin is prepared by replacing the binding the polypeptides with monoclonal antibody that is specific for a particular virus. In theory the attached monoclonal antibody will deliver the toxin chain specifically to virus infected cells where it will cause death of cells by inhibiting protein synthesis and may likely target to reduce the disease burden. The sixth method involves use of plasma therapy or by passive immunization. Immunoglobulins are glycoprotein's secreted by B-cells and fight off against infectious pathogens. In theory the immune-globulins are prepared from the pooled plasma of thousand of recovered patients. Passively administrated antibody exerts its protective action in a number of ways without producing memory cells. One of the most important is the recruitment of the complement pathway to the destruction or removal of pathogens. The virus can be bound and neutralized by antibody even as the antibody marks the virus for removal from the body by phagocytes and by organs such as liver and kidneys. By the initiation of antibody dependent cell mediated cytotoxicity (ADCC) antibodies can also mediate the killing of target cells by cytotoxic cell populations such as Natural Killer cells. One more strategy is to create an ACE-2-like molecule that would bind to the S protein of the corona virus itself. Again, research in to the 2002 SARS virus demonstrated that soluble ACE-2 proteins blocked the SARS virus from infecting cells in vitro [25,28]. The additional benefit to using this strategy lies in the possible prevention of S protein-mediated ACE-2 shedding that has been shown to induce the pulmonary edema characteristic of SARS (LI *et al.,* 2003 and Elshabrawy *et al.,* 2012). A phase II clinical trial of recombinant ACE-2 in ARDS reported significant modulation of inflammatory proteins, but no significant differences in respiratory parameters (Arbabi-Ghahroudi *et al.,* 2017). Further research is necessary to assess if the animal studies will translate to clinical benefit. Above all possible treatments, for the moment one only hope are that vaccine is developed fast enough to contain the disease or an existing drug be repurposed to block the virus from spreading further.

Ongoing Promises in Pipeline to treat COVID-19

Researchers are also testing older medications (that are typically used to treat other conditions) to see if they are also effective in treating COVID-19 as there are no approved corona virus treatments at this time. Below we highlight a few medications and treatments that have been making a buzz in the science community.

1) Remdesivir

Remdesivir is an experimental antiviral drug originally meant to treat Ebola, but is currently being explored as potential therapeutic treatment for COVID-19. This drug is administrated into the body via daily infusion for about 10 days. It works by inhibiting the activity of a key enzyme called as RNA-dependent RNA polymerase in the corona virus. This enzyme allows the virus to make more copies of it inside the host cells. By inhibiting the activity of this particular enzyme, the virus cannot replicate inside the host cell. The drug gained attention after showing efficacy against MERS-CoV in monkeys. As per studies MERS-CoV shows genetic similarities with SARS-CoV-2 which depicts that if remdesivir worked against MERS-CoV it could also work against SARS-CoV-2. Doctors across the U.S. are enrolling patients with severe COVID-19 into clinical trials to see if remdesivir is an effective treatment.

2) Hydroxychloroquine and chloroquine

Hydroxychloroquine and chloroquine are two medications that have been used for many decades to treat malaria and autoimmune conditions like rheumatoid arthritis and lupus. A few small studies suggest that they may also be helpful for treating hospitalized patients with mild cases of COVID-19, while other studies showed that hydroxychloroquine did not make a difference rather make the situation worse. More robust studies are needed to confirm whether these medications actually work.

3) Azithromycin

Azithromycin is an antibiotic commonly used to treat bacterial infections such as bronchitis and pneumonia. It has been shown to have some in vitro activity against viruses like influenza A and Zika, but did not work against the corona virus that causes MERS. One research group looked at azithromycin in combination with hydroxychloroquine for COVID-19 but there are concerns about potentially serious side effects when using azithromycin and hydroxychloroquine together.

4) Convalescent plasma

On March 24, 2020, the FDA issued an Emergency Investigational New Drug (eIND) application for the use of convalescent plasma to treat people with COVID-19. Plasma is the liquid part of blood that carries blood cells. Convalescent plasma is collected from people who have recovered from COVID-19. It is then transfused into someone with an active corona virus infection. It is thought that antibodies found in the convalescent plasma can help fight the corona virus infection.

5) Actemra (tocilizumab)

Actemra is a disease-modifying anti-rheumatic drug (DMARD) approved for rheumatoid arthritis and juvenile idiopathic arthritis. (Both are inflammatory diseases.) It works by blocking interleukin-6 (IL-6), a protein involved in our natural immune responses. IL-6 normally signals other cells to activate the immune system, but too much activation can cause issues. One possible serious issue with an overactive immune system is a cytokine storm, a potentially fatal problem in which the immune system goes haywire and inflammation gets out of control. With COVID-19, people can be at risk of cytokine storms as their bodies continue to ramp up their immune system to fight off the infection. By blocking IL-6, Actemra helps to calm down the immune system and is believed to also help with managing cytokine storms. Other medications that affect the body's immune response are also being tested for COVID-19. These include:

Calquence (acalabrutinib)

Xeljanz (tofacitinib)

Jakafi (ruxolitinib)

Olumiant (baricitinib)

Kineret (anakinra)

Mavrilimumab

6) Kaletra (lopinavir/ritonavir)

Kaletra is an HIV medication containing a combination of two antiviral called lopinavir and ritonavir. In vitro and clinical studies looking at patients who had previously received these antiviral agents suggest that they may have some activity against SARS and MERS (infections caused by other corona virus es).

7) Tamiflu (oseltamivir)

Tamiflu is an antiviral medication used for influenza (flu). Results from a hospital in Wuhan, China were not promising. Nonetheless, several clinical trials are currently looking at Tamiflu in combination with other medications for corona virus .

8) Avigan (favipiravir) and other antiviral medications

Favipiravir (also known as Avigan) is an antiviral medication approved in Japan and China for the flu. In vitro studies have shown that high doses of favipiravir were able to prevent human cells from being infected with SARS-CoV-2. Other antivirals being tested for COVID-19 include umifenovir and galidesivir: Umifenovir (Arbidol) is a flu medication that is used outside the U.S. As mentioned above, it was not as good as favipiravir in helping patients recover in a study from China. However, it seems to be better than Kaletra at helping patients with COVID-19. Galidesivir is a new drug that is currently being developed for a variety of viral infections; it has not yet been approved for human use, though Clinical trials for galidesivir are in action.

9) Colcrys (colchicine)

Colchicine is a medication used for gout. It works in many different ways, including activating anti-inflammatory processes and interfering with cells involved in inflammation. Researchers think that colchicine could work similarly to Actemra in COVID-19 patients in that it might be helpful if the immune system becomes too activated and a cytokine storm occurs. A large clinical trial is currently seeing if colchicine, when given soon after a COVID-19 diagnosis, can lower the chances of hospitalization and death.

10) Ivermectin

Ivermectin is an oral medication used to treat infections caused by parasites. It is also available as a lotion or cream to treat lice and rosacea. A recent in vitro study found that ivermectin can stop SARS-CoV-2 from replicating. A lot more research is needed to see if the doses studied would be safe and effective against the virus in humans.

11) Auranofin

Auranofin is a drug used to treat rheumatoid arthritis could help in the fight against COVID-19. Researchers confirmed that this drug is effective at inhibiting the nove corona virus known as SARS-CoV-2. Auranofin was approved in 1985 by US FDA to treat rheumatoid arthritis. As researchers tested the drug while screening FDA-approved medications for their potential use in the fight against SARS-CoV-2 and mentioned that drug repurposing is the fastest route to treat COVID-19 mainly because these medicines are proven to be safe to use in humans. SARS-CoV-2 cannot reproduce on its own and needs host cell proteins to manufacture additional copies of it and the drug interferes with this copying process. The current study depicted that treating COVID-19 infected patients with auranofin reduce the amount of virus within the cell by 95% in less than 48 hours of treatment. The treatment also showed a significant reduction of inflammation induced by the virus. Many patients died due the "cytokine storm" that kills healthy tissue and organ failure. The drug also drastically reduced the expression of cytokines which refers to proteins that draw immune cells to the site of infection.

Hurdles to jump for effective and successful treatment:

Genome analysis suggests two viruses may have combined. In February, scientists discovered a virus with 99% of genomic concordance to SARS-CoV-2 in pangolins. Scientists have been trying to understand the origin of

COVID-19 and the virus that causes it, SARS-CoV-2. Originally, scientists believed the virus may have developed in bats, and later pangolins. However, genomic comparisons suggest that the SARS-Cov-2 virus is the result of a recombination between two different viruses, meaning the exact origin of the virus is still unclear.

Genomic data

The SARS-CoV-2 genome was rapidly sequenced by Chinese researchers. It is an RNA molecule of about 30,000 bases containing 15 genes, including the S gene which codes for a protein located on the surface of the viral envelope (for comparison, our genome is in the form of a double helix of DNA about 3 billion bases in size and contains about 30,000 genes).

Comparative genomic analyses have shown that SARS-CoV-2 belongs to the group of β-corona virus es and that it is very close to SARS-CoV, responsible for an epidemic of acute pneumonia which appeared in November 2002 in the Chinese province of Guangdong and then spread to 29 countries in 2003. A total of 8,098 cases were recorded, including 774 deaths. It is known that bats of the genus *Rhinolophus* (potentially several cave species) were the reservoir of this virus and that a small carnivore, the palm civet (*Paguma larvata*), may have served as an intermediate host between bats and the first human cases. [33,34] Since then, many β-corona viruses have been discovered, mainly in bats, but also in humans. For example, RaTG13, isolated from a bat of the species *Rhinolophus affinis* collected in China's Yunan Province, has recently been described as very similar to SARS-CoV-2, with genome sequences identical to 96%. These results indicate that bats, and in particular species of the genus *Rhinolophus*, constitute the reservoir of the SARS-CoV and SARS-CoV-2 viruses.

Recombination mechanism

On February 7, 2020, Scientists learned that a virus even closer to SARS-CoV-2 had been discovered in pangolin. With 99% of genomic concordance reported, this suggested a more likely reservoir than bats. However, a recent study under review shows that the genome of the corona virus isolated from the Malaysian pangolin (*Manis javanica*) is less similar to SARS-Cov-2, with only 90% of genomic concordance. This would indicate that the virus isolated in the pangolin is not responsible for the COVID-19 epidemic currently raging. However, the corona virus isolated from pangolin is similar at 99% in a specific region of the S protein, which corresponds to the 74 amino acids involved in the ACE2 (Angiotensin Converting Enzyme 2) receptor binding domain, the one that allows the virus to enter human cells to infect them [35]. By contrast, the virus RaTG13 isolated from bat *R. affinis* is highly divergent in this specific region (only 77 % of similarity). This means that the corona virus isolated from pangolin is capable of entering human cells whereas the one isolated from bat *R. affinis* is not. In addition, these genomic comparisons suggest that the SARS-Cov-2 virus is the result of a recombination between two different viruses, one close to RaTG13 and the other closer to the pangolin virus. In other words, it is a chimera between two pre-existing viruses. It is important to know that recombination results in a new virus potentially capable of infecting a new host species. For recombination to occur the two divergent viruses must have infected the same organism simultaneously but still it remain enigma that in which organism did this recombination occur (a bat, a pangolin or another species) and above all, under what conditions did this recombination take place, the questions yet to remain answered.

Queries and Apprehensions

What are FDA-approved treatments for corona virus (COVID-19)?

There are currently no FDA-approved treatments for corona virus. The FDA recently created a new emergency program, Corona virus Treatment Acceleration Program (CTAP), aimed at speeding up research for the development of COVID-19 treatments.

Is there a cure or vaccine for COVID-19?

There is no cure or vaccine for COVID-19 at this time. More studies are needed to confirm if any of the potential treatments listed above will work for COVID-19. Research on COVID-19 is rapidly evolving. For more on COVID-19 vaccines being studied, follow live updates on our vaccine tracker here.

Why is corona virus so contagious?

The main reason that the novel corona virus SARS-CoV-2 is so contagious is that it is new to humans. This means that humans don't have any immunity against it. As a result, the virus easily and freely infects human cells. Another reason it's so contagious is because of how it spreads. When an infected person sneezes or coughs, droplets of liquid from their mouth or nose go into the air around the person. Those drops of snot and saliva are heavy with viral particles. If someone else is close (within 6 feet) and inhales those droplets, the virus enters the lungs and finds a new place to call home. The virus can also find its way into your lungs if infected droplets land on your hands and you then touch your mouth, nose, or eyes. It's possible that you can get the virus from a surface or an object that has the virus on it if you touch your mouth, nose, or eyes with infected hands. A third reason why the SARS-CoV-2 virus is so contagious is that an infected person becomes contagious before their symptoms begin. They are then most contagious very soon after symptoms start, when their symptoms are still pretty mild and maybe not even noticeable.

Why is corona virus so deadly?

The corona virus SARS-CoV-2 is so deadly because of how contagious it is and its potential to cause a severe and very unusual type of pneumonia. Its contagiousness comes in part from the fact that humans have no immunity to it. The virus infects cells in the upper airway (nose and throat) meaning it can spread into the air every time an infected person sneezes, coughs, or even speaks. In some people, the virus travels down and infects the cells deep in the lung. Here, the virus is less contagious, but can cause real trouble. Double lung infections, or bilateral pneumonias, can drastically lower the amount of oxygen in the person's blood. This can make them very sick, very fast. Between 20% and 40% of people hospitalized with COVID-19 in China developed a severe lung failure, similar to something called acute respiratory distress syndrome, or ARDS. This makes it very difficult for the lungs to get enough oxygen into the bloodstream, and it's the main reason why people with severe

COVID-19 need help breathing with an artificial ventilator. The particular type of lung failure seen with COVID-19 is unlike anything any doctors have ever seen before and is very difficult to treat.

How sick will the corona virus make you rely on your genetic makeup.

COVID-19, caused by the new pandemic corona virus, is strangely and tragically selective. Only some infected people get sick, and although most of the critically ill are elderly or have complicating problems such as heart disease, some killed by the disease are previously healthy and even relatively young. Researchers are now gearing up to scour the patients' genomes for DNA variations that explain this mystery. The findings could be used to identify those most at risk of serious illness and those who might be protected, and they might also guide the search for new treatments. The projects range from ongoing studies with DNA for many thousands of participants, some now getting infected with the corona virus , to new efforts that are collecting DNA from COVID-19 patients in hard-hit places such as Italy and USA. The goal is to compare the DNA of people who have serious cases of COVID-19 (which stands for corona virus disease 2019) but no underlying disease like diabetes, heart or lung disease with those with mild or no disease. In addition to genetic variants of the ACE2 receptor, scientists want to see whether differences in the human leukocyte antigen genes, which influence the immune system's response to viruses and bacteria, affect disease severity.

Concluding Remarks

Over the past few decades, there was an urge to discover the root cause of corona virus infections not only in animals but in humans as well. Currently, COVID-19 has emerged as the most intense and petrifying viral infection to be handled by the human race. According to WHO (Rothe *et al* 2020), major concern among public health throughout the world and many countries have taken precautionary measures against the virus, and Government officials in all countries continue to make efforts to minimize human contact by facilitating countrywide shutdowns of public places as well as various steps have been initiated to ensure the safety of the people, like social distancing and self-quarantine which limits our social interactions (Wang *et al.,* 2020). This will reduce the risk of spreading the COVID-19 to people by breaking the transmission chain and the influx of new COVID-19 cases in a given time period. Total confirmed cases throughout the world are 4,16,686 and total number of confirmed deaths are 18,589 (WHO, 2020) as on 26th

March 26, 2020 and in India 581 cases (ICMR, 2020) have been identified to be positive for this COVID-19 and 11 death cases in India as on 25th March 2020. More cases are likely to be identified in the coming days in India. This increase in infection was mainly due to the ability of this virus to recombine, mutate, block the immune system of the host cells and infect multiple species as well as cell types. Moreover, discovering the gene pool of SARS-CoV-2 may help accelerate the production of drugs and vaccines. Further, analyzing and understanding the role of non-structure and accessory proteins encrypted in this virus will aid us in understanding its mechanism of action. Also, acquiring an in-depth framework of its unique RNA replication process will enable us to find a breakthrough point to understand the host immunological response (Guan WJ, *et al* 2020). The review reveals the overall scenario of the current COVID-19 pandemic, its challenge across the globe, current and future approaches and high hope for the successful treatment.

RECOMMENDATIONS

The cases reported in many parts of China and the outbreaks involve large numbers in Italy, USA, Spain and Germany; hence travel restrictions and quarantine measures have been placed in severely affected areas. The spectrum of symptoms associated with COVID-19 ranges from difficulties in breathing and other respiratory conditions to critical conditions including SARS, kidney failure and sometimes even death (Chen *et al.,* 2020). Individuals are likely to be infected by others who have been inflicted with the virus. The disease can spread from person to person via small droplets from nose or mouth when a person with COVID-19 coughs or exhales. These particles in the air, settle on surfaces in the environment further infecting people who breathe these particles or touch these places and then touch their body parts. Hence, it is important to stay N1 m (3 ft) away from a person who is sick (Cui *et al.,* 2019). The WHO and other organizations have issued the following general recommendations:

- Avoid close contact with subjects suffering from acute respiratory infections.
- Wash your hands frequently, especially after contact with infected people or their environment.
- Avoid unprotected contact with farm or wild animals.
- People with symptoms of acute airway infection should keep their distance, cover coughs or sneezes with disposable tissues or clothes and wash their hands.
- Strengthen, in particular, in emergency medicine departments, the application of strict hygiene measures for the prevention and control of infections.
- Individuals that are immunocompromised should avoid public gatherings.

The most important strategy for the populous to undertake is to frequently wash their hands and use portable hand sanitizer and avoid contact with their face and mouth after interacting with a possibly contaminated environment. Slowing the spread of the COVID-19 cases will significantly reduce the strain on the healthcare system of the country by limiting the number of people who are severely sick by COVID-19 and need hospital care. It will also give researchers more time to develop the vaccine against COVID-19. So, it's time for all the citizens to join hands together to fight against corona virus by practicing self-hygiene and social distancing.

Table 1: Symptomatic Comparisons of COVID-19, SARS and MERS

Disease	Symptoms	Incubation Period	Transmission/ Causes	Complications, If Any
Novel Corona virus (COVID-19)	Fever, Cough, Shortness of Breath, Fatigue	2-14 days after exposure	Human to Human	Acute pneumonia, Respiratory failure in adverse conditions
Severe Acute Respiratory Syndrome (SARS)	Fever, Dry cough, Headache, Difficulty in breathing, Muscle ache, Loss of appetite, Diarrhea	2-7 days after exposure	Human to Human Civet Cats	Heart, Liver and Respiratory failure in adverse conditions
Middle East Respiratory Syndrome (MERS)	Fever, Chills, Diarrhea, Nausea, Vomiting, Congestion, Sneezing, Sore throat	5-6 days after exposure	Human to Human Dromedary Camels	Acute pneumonia, Kidney failure in adverse conditions

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