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AN OUTLOOK OF PANDEMIC DISEASE: COVID 19

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ABSTRACT

Human corona virus (HCoV) infection causes respiratory diseases with mild to severe outcomes. Recently we have witnessed the emergence of highly pathogenic human corona virus causing severe acute respiratory syndrome corona virus (SARS-CoV2). Recent studies have begun to reveal some fundamental aspects of the HCoV detail. In this review, we summarize the current knowledge of human corona virus origin, development and mechanism of HCoV infection, next, we elaborated with genome and proteome organization. Further, the diagnosis and available remedies are also discussed. In the current, scientists are using multiple strategies to handle the current outbreak to control the spread as well as the rapid development of a new treatment. Deeper studies are required for the further development study.

***Keywords*:** Pandemic; Corona Virus; Genome; Proteome; Virus

INTRODUCTION

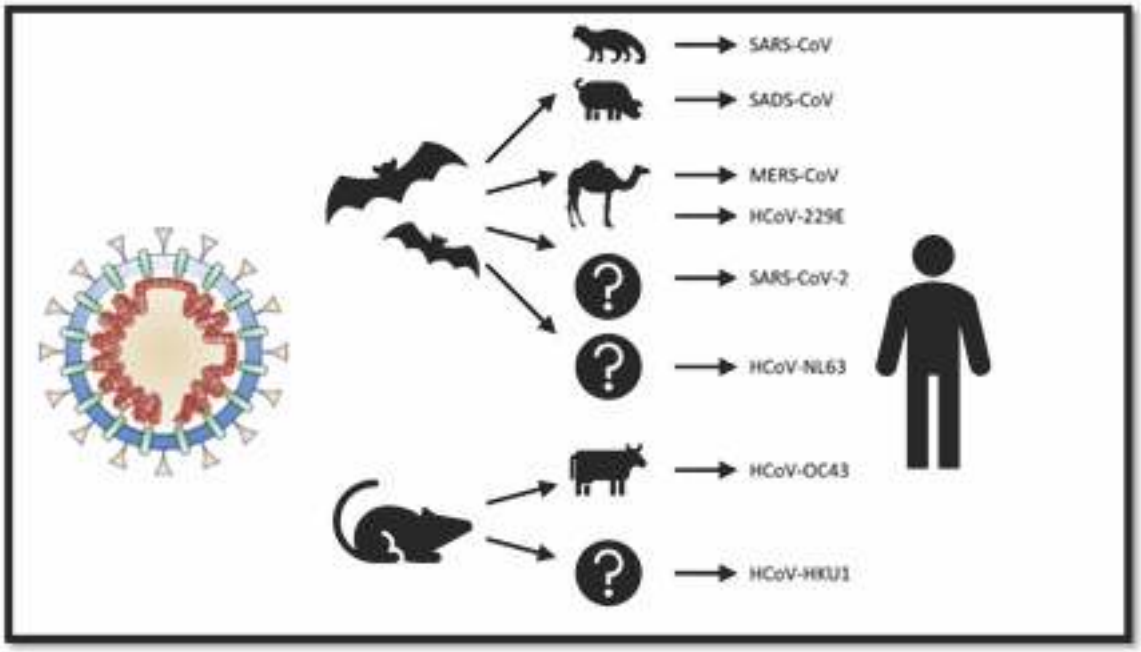
The name corona virus is derived from the Latin corona and the Greek meaning crown or halo. The name refers to the characteristic appearance of virions (the infective form of the virus) by electron microscopy, which has a fringe of large, bulbous surface projections creating an image of a crown or of a solar corona. This morphology is created by the viral spike peplomers, which are proteins on the surface of the virus that determine host tropism. During epidemics, common cold corona viruses are the cause of up to one-third of community-acquired upper respiratory tract infections in adults and probably also play a role in severe respiratory infections in both children and adults. In addition, it is possible that certain common cold corona viruses cause diarrhea in infants and children. Their role in central nervous system diseases, except for a single case report of encephalitis in a severely immune compromised infant, has been suggested but not proven.[1] Corona viruses are a family of viruses that cause illness such as respiratory diseases or gastrointestinal diseases. Respiratory diseases can range from the common cold to more severe diseases like Middle East Respiratory Syndrome (MERS-CoV) , Severe Acute Respiratory Syndrome (SARS-CoV) . [1] A novel coronavirus (nCoV) is a new strain that has not been identified in humans previously. Once scientists determine exactly what corona virus it is, they give it a name (as in the case of COVID-19, the virus causing it is SARS-CoV-2). Corona virus genomes encode a protein called a replicase which allows the viral genome to be transcribed into new RNA copies using the host cells machinery. The replicase is the first protein to be made; once the gene encoding the replicase is translated, translation is stopped by a stop codon.

ORIGIN AND DEVELOPMENT OF CORONA VIRUS

Corona viruses were first identified by a group of virologists, who relayed their findings as a brief annotation. [2] In 1937, corona viruses were first identified as an infectious bronchitis virus with which birds suffered that could devastate poultry stocks. Today, the viruses are the cause of the common cold in 15% to 30% of all cases. In the past 70 years, researchers have found camels, cattle, cats, dogs, horses, mice, pigs, rats and turkeys that were infected with corona viruses (Fig. 1). The 2019 novel corona virus has the potential to be a global pandemic. Health officials say it originated in a market in Wuhan, China that sold live and dead wild animlas that people ate and dead wild animals

that people ate for food, improved health and vitality and a number of other purposes. The virus has now been detected in Australia, Canada, Finland, France, India, Italy, Japan, Nepal, Russia, Singapore, Span, Taiwan, Thiland, Vietnam, the United States and over a dozen other countries.

Figure 1: Indicate Corona viruses infected with the animals camels, cattle, cats, dogs, horses, mice, pigs, rats and turkeys. [3]



Corona viruses are single-stranded RNA viruses, about 120-140 nanometers in diameter. They are susceptible to mutation and recombination and are therefore highly diverse. There are about 40 different varieties and they mainly infect human and non-human mammals and birds. They reside in bats and wild birds, and can spread to other animals and hence to humans. The virus that causes COVID-19 is thought to have originated in bats and then spread to snakes and pangolins and hence to humans, perhaps by contamination of meat from wild animals, as sold in China's meat markets. The corona-like appearance of corona viruses is caused by so-called spike glycoproteins, or peplomers, which are necessary for the viruses to enter host cells. The spike has two subunits; one subunit, S1, binds to a receptor on the surface of the host's cell; the other subunit, S2, fuses with the cell membrane. The cell membrane receptor for both SARS-CoV-1 and SARS-CoV-2 is a form of angiotensin converting enzyme, ACE-2, from the enzyme that is inhibited by conventional ACE-1 inhibitors, such as enalapril and ramipril. The S1 subunit of the spike binds to the ACE-2 enzyme on the cell membrane surface. A host transmembrane serine protease, TMPRSS2, then activates the spike and cleaves ACE-2. TMPRSS2 also acts on the S2 subunit, facilitating fusion of the virus to the cell membrane. The virus then enters the cell. Inside the cell the virus is released from endosomes by acidification or the action of an intracellular cystine protease, cathepsin. [4,5]

PROPOSED MODELAND MECHANISM

The corona virus approaches the cell membrane. An S1 subunit at the distal end of a glycoprotein spike of the virus binds to a membrane-bound molecule of ACE-2. As more S1 subunits of the glycoprotein spikes bind to membrane-bound molecules of ACE-2, the membrane starts to form an envelope around the virus (an endosome). The process continues until the endosome is complete. The virus can enter the cell in two ways (a) A cell membrane-bound serine protease, TMPRSS2, cleaves the virus's S1 subunits from its S2 subunits

and also cleaves the ACE-2 enzymes; the endosome enters the cell (endocytosis), where the virus is released by acidification or the action of another protease, cathepsin.(b) The same serine protease, TMPRSS2, causes irreversible conformational changes in the virus's S2 subunits, activating them, after which the virus fuses to the cell membrane and can be internalized by the cell. [5]

NOVEL CORONA VIRUS

Corona viruses are a large family of viruses that can cause illness ranging from the common cold to more severe diseases. A novel corona virus (nCoV) is a new strain that has not been previously identified in humans. **Novel corona virus** (**nCoV**) is a provisional name given to corona viruses of medical significance before a permanent name is decided upon. Although corona viruses are endemic in humans and infections normally mild, such as the common cold (caused by human corona viruses in 15% of cases), cross-species transmission has produced some unusually virulent strains which can cause viral pneumonia and in serious cases even acute respiratory distress syndrome and death. The word novel indicates a new pathogen of a previously known type (*i.e.* known family) of virus. Use of the word conforms to best practices for naming new infectious diseases published by the World Health Organization (WHO) in 2015. Historically, pathogens have sometimes been named after locations, individuals, or specific species. However, this practice is now explicitly discouraged by the WHO. A study published in 2020 suggested that referring to the novel corona virus (COVID-19) as the "Chinese virus" was stigmatizing and could hinder public health efforts. [6]

MECHANISM OF CORONA ACTION IN HUMAN AND OTHER ANIMALS

Corona viruses are a group of related familythat cause diseases in mammals and birds. In humans, these viruses cause respiratory tract infections that can range from mild to lethal. Mild illnesses include some cases of the common cold (which is also caused by other viruses, predominantly rhinoviruses), while more lethal varieties can cause SARS, MERS, and COVID-19. Symptoms in other species vary: in chickens, they cause an upper respiratory tract disease, while in cows and pigs they cause diarrhea. There are as yet no vaccines or antiviral drugs to prevent or treat human corona virus infections. [6]

HUMAN CORONA VIRUS

Prior to the SARS-CoV outbreak, corona viruses were only thought to cause mild, self-limiting respiratory infections in humans. Two of these human corona viruses are **α-corona viruses, HCoV-229E** and **HCoV-NL63**, while the other two are **β-corona viruses, HCoV-OC43** and **HCoV-HKU1**. HCoV-229E and HCoV-OC43 were isolated nearly 50 years ago[7, 8], while HCoV-NL63 and HCoV-HKU1 have only recently been identified following the SARS-CoV outbreak. [9-10] They cause more severe disease in neonates, the elderly, and in individuals with underlying illnesses, with a greater incidence of lower respiratory tract infection in these populations. HCoV-NL63 is also associated with acute laryngotracheitis (croup). One interesting aspect of these viruses is their differences in tolerance to genetic variability. HCoV-229E isolates from around the world have only minimal sequence divergence, while HCoV-OC43 isolates from the same location but isolated in different years show significant genetic variability. **SARS-CoV** primarily infects epithelial cells within the lung. The virus is capable of entering macrophages and dendritic cells but only leads to an abortive infection. In fact, many cytokines and chemokines are produced by these cell types and are elevated in the serum of SARS-CoV infected patients. The exact mechanism of lung injury and cause of severe disease in humans remains undetermined. [10]

ANIMAL CORONA VIRUS

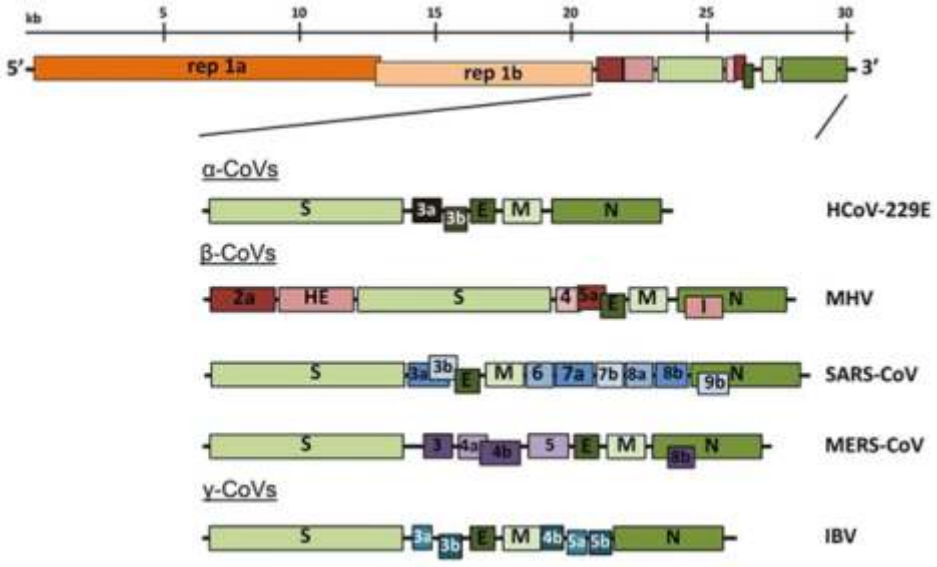
Corona viruses cause a large variety of diseases in animals, and their ability to cause severe disease in livestock and companion animals such as pigs, cows, chickens, dogs, and cats led to significant research on these viruses in the last half of the twentieth century. **Transmissible Gastroenteritis Virus** (TGEV) and **Porcine Epidemic Diarrhea Virus** (PEDV) cause severe gastroenteritis in young piglets, leading to significant morbidity, mortality, and ultimately economic losses. Animals infected with rodent-adapted SARS-CoV strains show similar clinical features to the human disease, including an age-dependent increase in disease severity. These animals also show increased levels

of proinflammatory cytokines and reduced T-cell responses, suggesting a possible immune pathological mechanism of disease. **Feline enteric corona virus** (FCoV) causes a mild or asymptomatic infection in domestic cats, but during persistent infection, mutation transforms the virus into a highly virulent strain of FCoV, **Feline Infectious Peritonitis Virus** (FIPV), that leads to development of a lethal disease called feline infectious peritonitis (FIP). **FIPV** is macrophage tropic and it is believed that it causes aberrant cytokine and/or chemokine expression and lymphocyte depletion, resulting in lethal disease .[11] Some strains of **IBV**, a **γ-corona virus**, also affect the urogenital tract of chickens causing renal disease. A novel coronavirus named **SW1** has been identified in a deceased Beluga whale .[12] Large numbers of virus particles were identified in the liver of the deceased whale with respiratory disease and acute liver failure. MERS-CoV and hundreds of novel bat corona viruses have been identified over the past decade.[6] Finally, another novel family of **nido viruses, *Mesoniviridae***, has been recently identified as the first nido viruses to exclusively infect insect hosts.[13-14] These viruses are highly divergent from other nido viruses but are most closely related to the roni viruses. In size, they are ~20 kb, falling in between large and small nido viruses. Interestingly, these viruses do not encode for an endoribonuclease, which is present in all other nido viruses.

GENOME ORGANIZATION

Corona viruses contain a non-segmented, positive-sense RNA genome of ~30 kb. Genome contains a 5′ cap structure along with a 3′ poly (A) tail, allowing it to act as an mRNA for translation of the replicase polyproteins (Fig. 2). The replicase gene encoding the non-structural protein (nsps) occupies two-thirds of the genome, about 20 kb, as opposed to the structural and accessory proteins, which make up only about 10 kb of the viral genome. The 5′ end of the genome contains a leader sequence and untranslated region (UTR) that contains multiple stem loop structures required for RNA replication and transcription. Additionally, at the beginning each structural or accessory gene are transcriptional regulatory sequences (TRSs) that are required for expression of each of these genes. The 3′ UTR also contains RNA structures required for replication and synthesis of viral RNA. The organization of the corona virus genome is 5′-leader-UTR-replicase-S (Spike)-E (Envelope)-M (Membrane)-N (Nucleocapsid)-3′ UTR-poly (A) tail with accessory genes interspersed within the structural genes at the 3′ end of the genome. The accessory proteins are almost exclusively nonessential for replication in tissue culture; however, some have been shown to have important roles in viral pathogenesis .[15]

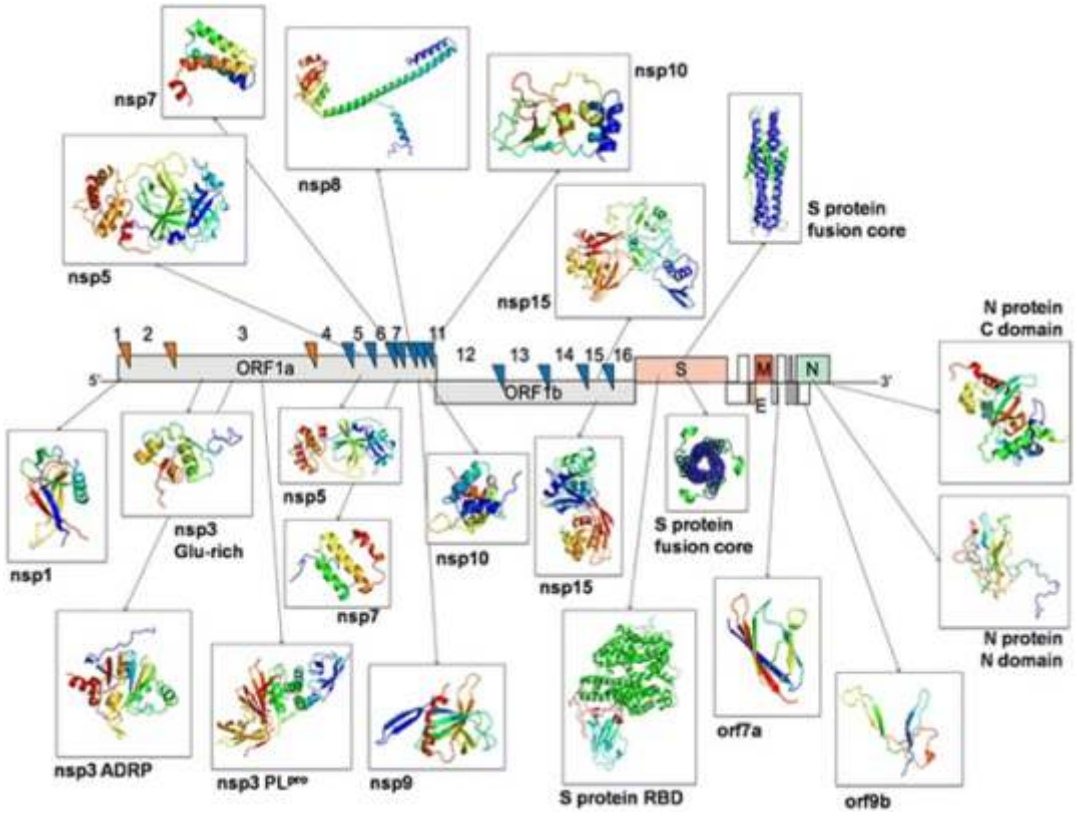
Figure 2: Genome organization of corona virus [15]



PROTEOME ORGANISATION

As NSP12 protein in conjugation with NSP7 and NSP8 initiates the replication and transcription of corona virus COVID-19. So it is the primary target of majority of drugs in order to halt replication and transcription. Recently the first FDA approved drug remdesivir has been shown to exhibit promising effect over combating COVID-19 infection. Similarly, SARS-NSP13 has been identified as an ideal target for development of anti-viral drugs due to its sequence conservation and indispensability across all CoV species .[16] The study of COVID-19 proteome is of special significance as it could help in the identification of critically mutated proteins responsible for its pathogenesis and virulence as compared to its non virulent corona viral strain. Spike proteins (Spike S, Spike E, Spike M and Spike N) of COVID-19 are critical for the invasion of human cell as these binds to the ACE2 receptors on the pharynx cell, have been targeted as a vaccine candidate. Another vaccine mRNA-1273, coding for the "spike protein" is under human clinical trials, while Pfizer vaccine BNT162 is also exploring similar mRNA technology to combat COVID-19. Oxford University research project on the vaccine CHAdOx1 nCOV-19 is based upon the use of genetic engineering to ligate segments of the COVID-19 genome into a non pathogenic modified viral host, hoping to provoke an immune response in humans .[17] The corona virus genome ends with a snippet of RNA that stops the cell's protein-making machinery. The comparative analysis of the COVID-19 protein can help us to identify key important viral proteins which could serve as the targets for vaccine development in combating COVID-19 infection. The SARS-CoV replicase gene encodes 16 non-structural proteins (nsps) with multiple enzymatic functions .[18] These are known or are predicted to include types of enzymes that are common components of the replication machinery of plus-strand RNA viruses: an RNA-dependent RNA polymerase activity (RdRp, nsp12), a 3C-like serine protease activity (M^{pro} or $3CL^{pro}$, nsp5), a papain-like protease activity ($PL2^{pro}$, nsp3), and a super family 1-like helicase activity (HEL1, nsp13).

Figure 3 : Proteomic organization of COVID 19 [17, 18]



DIAGNOSIS

In general, these lab tests fall into two categories: Molecular tests, which look for evidence of active infection; and Serology tests, which look for previous infection by detecting antibodies to MERS-CoV. Serology tests are for surveillance or investigational purposes and not for diagnostic purposes. **Molecular test:** Molecular tests are used to diagnose **active infection** (presence of MERS-CoV) in people who are thought to be infected with MERS-CoV based on their clinical symptoms. Real-time reverse-transcription polymerase chain reaction (rRT-PCR) assays are molecular tests that can be used to detect viral RNA in clinical samples. CDC's current case definition for laboratory confirmation of MERS-CoV infection requires either a positive rRT-PCR result for at least two specific genomic targets, or a single positive target with sequencing of a second target.CDC considers a person under investigation to be negative for active MERS-CoV infection following one negative rRT-PCR test on the recommended specimens. Since a single negative result does not completely rule out MERS-CoV infection, in some circumstances additional specimens may be tested.CDC considers a known MERS patient to be negative for active MERS-CoV infection following two consecutive negative rRT-PCR tests on all specimens. [19] **Serology Tests:** Serology testing is used to detect **previous infection** (antibodies to MERS-CoV) in people who may have been exposed to the virus. Antibodies are proteins produced by the body's immune system to attack and kill viruses, bacteria, and other microbes during infection. The presence of antibodies to MERS-CoV indicates that a person had been previously infected with the virus and developed an immune response. [20] CDC has a two-phase approach for serology testing, using two screening tests and one confirmatory test to detect antibodies to MERS-CoV. ELISA, or enzyme-linked immunosorbent assay, is a screening test used to detect the presence and concentration of specific antibodies that bind to a viral protein. CDC tests by ELISAS for antibodies against two different MERS-CoV proteins, the nucleocapsid (N) and spike (S). If a clinical sample is determined to be antibody-positive by either ELISA, CDC then uses the micro neutralization test to confirm the positive result. Corona virus Disease-2019 tracking and diagnostic testing are critical and also critical to understanding epidemiology, informing case management, and to suppressing transmission. The Corona virus disease outbreak is additionally typical to prevent virus community transmission, including how testing might be rationalized when lack of reagents/ testing kit or testing capacity necessitates prioritization of certain populations group or individuals for testing." To test for COVID-19, doctor or health practitioner may take samples, including a sample of saliva (sputum), a nasal swab and a throat swab, to send to a lab for testing or follow the directions of your local health authority.

GENERAL TREATMENT

A confirmed patient of COVID 19 needs complete bed rest and supportive treatment, ensuring adequate calorie and water intake to reduce the risk of dehydration. Water electrolyte balance and homeostasis need to maintain along with the monitoring of vital signs and oxygen saturation; keeping respiratory tract unobstructed and inhaling oxygen in more severe cases; measuring blood count, C-reactive protein, urine test, and other blood biochemical indexes including liver and kidney function, myocardial enzyme spectrum, and coagulation function according to patient's conditions. Chest imaging should be continuously re-examined and blood gas analysis should be performed when required . [21]

SYMPTOMATIC TREATMENT

Control measures are needed for patients with a high fever. Antipyretic drug treatment should be performed in case the temperature exceeds 38.5 °C. Warm water bath and antipyretic patches are preferred as a preventive measure to lower the temperature. Common drugs include ibuprofen orally, 5–10 mg/kg every time; acetaminophen orally, 10– 15 mg/kg every time . [21]

OXYGEN THERAPY

The chances of hypoxia are increased as the virus targets the lungs. Nasal catheter, mask oxygen should be immediately provided to the patient. In emergency conditions, Non-invasive or invasive mechanical ventilation should be provided to the patient . [22]

HERBAL THERAPY

HIOWNA-Herbal Neutraceutical of Indian pharmaceutical company had lack of potential to increase the immunity of the body.

MAJOR DRUGS AVAILABLE

Remdisivir

This is an intravenous antiviral drug that was developed to block infection with related corona viruses and even Ebola, and is one of the drugs the WHO is helping to investigate. Remdisivir has already been shown to work against SARS-CoV-2 in cells in a dish in a lab as well as in mice infected with the virus. Remdesivir specifically targets key viral proteins involved in making new copies of the virus and prevent them from working. Remdesivir has already been used in some COVID-19 patients in the US and appears safe, but large trials are needed to really know if this is the case . [23]

Lopinavir/ritonavir

This is a drug combination used against viruses like HIV. It works in a similar way to remdesivir by blocking key viral proteins called proteases. Lopinavir/ritonavir has also been shown to be effective against SARS-CoV-2 in lab cells as well as in mice and is being tested alongside an antiviral drug called interferon beta. This is currently used to treat Multiple sclerosis and can enhance the natural defenses of the body's cells against COVID-19 . [24]

Chloroquine and hydroxychloroquine

Both of these drugs are currently used to treat malaria and the autoimmune disease lupus. Chloroquine has been tested against lots of different infections because in the lab it can block viruses including SARS-CoV-2 from getting inside cells placed in a dish and so prevent infection . [25]

Favilavir

Extensive trials propagating the use of Favipiravir have been going on in Japan and another trial is set to begin in India. Researchers say that Favipiravir works by preventing the virus from replicating inside the organs and were also used in fighting the deadly Influenza virus in the past . [26]

PLASMA THERAPY

There are a lot of hopes sailing on the effectiveness of this therapy and trials are underway in several Delhi hospitals as well. Convalescent Plasma Therapy (CPT) involves the process of transfusing healthy antibodies from a recovered COVID patient to a sick person, thereby, strengthening their immunity in fight against corona virus. Very few side-effects have been reported so far but more medical research is needed before the therapy gets vetoed as a proper treatment plan . [27]

FUTURE PERSPECTIVE

The COVID-19 outbreak is proving to be an unprecedented disaster, especially in the most afflicted countries including China, Italy, Iran and USA in all aspects, especially health, social and economic. It is too early to forecast any realistic scenario, but it will have a strong impact worldwide. Therefore deeper study is required first to develop vaccine and to control the mechanism replication.

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