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A Pharmacological Review on Covid-19

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Review Article

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ABSTRACT

Coronaviruses are a group of related RNA viruses that cause diseases in mammals and birds. In humans and birds, they cause respiratory tract infections that can range from mild to lethal. Mild illnesses in humans 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. In cows and pigs they cause diarrhea, while in mice they cause hepatitis and encephalomyelitis. Coronaviruses constitute the subfamily *Orthocoronavirinae*, in the family *Coronaviridae*, order *Nidovirales* and real Riboviria. They are enveloped viruses with a positive-sense single-stranded RNA genome and a nucleocapsid of helical symmetry. The genome size of coronaviruses ranges from approximately 26 to 32 kilobases, one of the largest among RNA viruses. They have characteristic club-shaped spikes that project from their surface, which in electron micrographs create an image reminiscent of the solar corona, from which their name derives.

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INTRODUCTION

The coronavirus particles are organized with long RNA polymers tightly packed into the center of the particle, and surrounded by a protective capsid, which is a lattice of repeated protein molecules referred to as coat or capsid proteins. In coronavirus, these proteins are called Nucleocapsid. Coronaviruses are a large family of viruses which may cause disease in animals or humans. Seven coronaviruses can produce infection in people around the world but commonly people get infected with these four human coronaviruses: 229E, NL63, OC43, and HKU1. They usually cause a respiratory infection ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) and the most recently discovered coronavirus (COVID-19) cause's infectious disease[1]. This zoonotic disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The WHO originally called this infectious disease Novel Coronavirus-Infected Pneumonia (NCIP) and the virus had been named 2019 Novel Coronavirus (2019-nCoV). The virus is typically rapidly spread from one person to another *via* respiratory droplets produced and sneezing. It is considered most contagious when people are symptomatic, although transmission may be possible before symptoms show in patients. Time from exposure and symptom onset is generally between two and 14 days, with an average of five days. Common symptoms include fever, cough, sneezing and shortness of breath. Complications may include pneumonia, throat pain and acute respiratory distress syndrome. Recommended preventive measures include washing your hands with soap, covering the mouth when coughing, maintaining 1-meter distance from other people and monitoring and self-isolation for fourteen days for people who suspect they are infected. The standard tool of diagnosis is by Reverse Transcription Polymerase Chain Reaction (rRT-PCR) from a throat swab or nasopharyngeal swab. The infection can also be diagnosed from a combination of symptoms, risk factors and a chest CT scan showing features of pneumonia[2].

LITERATURE REVIEW

According to WHO, in December 2019, several pneumonia cases of unknown aetiology were identified in the city of Wuhan in central China. Towards the end of December 2019, patients presenting with viral pneumonia because of an unknown microbial agent were reported in Wuhan, China. A novel coronavirus was subsequently identified as the causative pathogen, provisionally named 2019 Novel Coronavirus (2019-nCoV). On February 11th 2020, WHO announced the rapidly spreading coronavirus disease as COVID-19? As of 26th January 2020, more than 2000 cases of COVID-19 infection have been confirmed; most of which involved people living in or visiting Wuhan and human-to-human transmission was confirmed [3]. The initial infected individuals mostly were linked to exposures to a seafood market in Wuhan. In 2020, the Chinese authorities reported 2835 confirmed cases in mainland China, including 81 deaths. Additionally, 19 confirmed cases were identified in Hong Kong, Macao, Taiwan and 39 imported cases were identified in Thailand, Japan, South Korea, United States, Vietnam, Singapore, Nepal, France, Australia and Canada. The pathogen was soon identified as COVID-19, which is closely related to Severe Acute Respiratory Syndrome CoV (SARS-CoV). The Chinese authorities officially announced a novel *coronavirus*, 2019-n CoV, as the causative agent. Coronaviruses (CoV) are a family of viruses called *Coronaviridae*. The subfamily

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Coronavirinae has three genera, alpha coronavirus, beta coronavirus and *gammacoronavirus*. The subfamily *Torovirinae* has two genera, *torovirus* and *bafinivirus*. CoV can lead to a range of conditions as mild as the common cold, fever and cough and as severe as pneumonia, respiratory distress kidney failure or even death[4-6]. These viruses are zoonotic, that is, they are transmitted between animals and humans. A couple of coronaviruses were previously identified: MERS-CoV, which causes Middle East Respiratory Syndrome and was transmitted from dromedary camels to humans, and SARS-CoV, which causes severe acute respiratory syndrome and was transmitted from civet cats to humans. COVID-19 is believed to have been transmitted zoonotically, in a wet market in Wuhan where game animals and meat were sold.

Origin

The Most Recent Common Ancestor (MRCA) of all coronaviruses is estimated to have existed as recently as 8000 BCE, although some models place the common ancestor as far back as 55 million years or more implying long term coevolution with bat and avian species. The most recent common ancestor of the alpha coronavirus line has been placed at about 2400 BCE of the beta coronavirus line at 3300 BCE of the gamma coronavirus line at 2800 BCE and the delta coronavirus line at about 3000 BCE. Bats and birds, as warm-blooded flying vertebrates, are an ideal natural reservoir for the coronavirus gene pool (with bats the reservoir for alpha coronaviruses and beta coronavirus and birds the reservoir for gamma coronaviruses and delta coronaviruses). The large number and global range of bat and avian species that host viruses have enabled extensive evolution and dissemination of coronaviruses.

Many human coronaviruses have their origin in bats. The human coronavirus NL63 shared a common Ancestor with a bat Coronavirus (ARCoV.2) between 1190 and 1449 CE, The ancestors of SARS-CoV first infected leaf-nose bats of the genus *Hipposideridae*; subsequently, they spread to horseshoe bats in the species *Rhinolophidae*, then to Asian palm civets, and finally to humans. Unlike other *beta* coronaviruses, *bovine coronavirus* of the species Beta *coronavirus* 1 and subgenus *Embecovirus* is thought to have originated in rodents and not in bats. In the 1790s, equine coronavirus diverged from the bovine coronavirus after a cross-species jump. Later in the 1890s, human coronavirus OC43 *diverged* from bovine coronavirus after another cross-species spillover event. It is speculated that the flu pandemic of 1890 may have been caused by this spillover event, and not by the influenza virus, because of the related timing, neurological symptoms, and unknown causative agent of the pandemic[7]. Besides causing respiratory infections, human coronavirus OC43 is also suspected of playing a role in neurological diseases. In the 1950s, the human coronavirus OC43 began to diverge into its present genotypes. Phylogenetically, mouse hepatitis virus (Murine coronavirus), which infects the mouse's liver and central nervous system, is related to human coronavirus OC43 and bovine coronavirus. Human coronavirus HKU1, like the aforementioned viruses, also has its origins in rodents.

Structure

Coronaviruses are large, roughly spherical particles with unique surface projections. Their size is highly variable with average diameters of 80 to 120 nm. Extreme sizes are known from 50 to 200 nm in diameter. The total molecular mass is on average 40,000 kDa. They are enclosed in an envelope embedded with a number of protein molecules. The lipid bilayer envelope, membrane proteins and nucleocapsid protect the virus when it is outside the host cell. The viral envelope is made up of a lipid bilayer in which the membrane, envelope and spike structural proteins are

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anchored. Different species can have either N or O-linked glycans in their protein amino-terminal domain[8]. The M protein is crucial during the assembly, budding, envelope formation, and pathogenesis stages of the virus lifecycle. The spikes are the most distinguishing feature of coronaviruses and are responsible for the corona or halo-like surface. On average a coronavirus particle has 74 surface spikes. Each spike is about 20 nm long and is composed of a trimer of the S protein. The two subunits remain noncovalently linked as they are exposed on the viral surface until they attach to the host cell membrane. The HE proteins occur as homodimers composed of about 400 amino acid residues and are 40 to 50 kDa in size. They appear as tiny surface projections of 5 to 7 nm long embedded in between the spikes[9,10].

Figure 1. Coronaviruses internal structure.

Inside the envelope, there is the nucleocapsid, which is formed from multiple copies of the Nucleocapsid (N) protein, which are bound to the positive-sense single-stranded RNA genome in a continuous beads-on-a-string type conformation. N protein is a phosphoprotein of 43 to 50 kDa in size, and is divided into three conserved domains. The majority of the protein is made up of domains 1 and 2, which are typically rich in arginines and lysines (Figure 1). Domain 3 has a short carboxy terminal end and has a net negative charge due to excess of acidic over basic amino acid residues [11].

DISCUSSION

Coronaviruses form the subfamily *Orthocoronavirinae*, which is one of two sub-families in the family *Coronaviridae*, order *Nidovirales* and realm Riboviria. They are divided into the four genera: *Alphacoronavirus*, *Beta coronavirus*, *Gamma coronavirus* and *Delta coronavirus*. *Alpha coronaviruses* and *beta* coronaviruses infect mammals, while *gamma coronaviruses* and *delta coronaviruses* primarily infect birds.

Genus: *Alpha coronavirus*

Species: *Alphacoronavirus 1 (TGEV, Feline* coronavirus*, Canine coronavirus),* Human coronavirus *229E,* Human coronavirus *NL63, Miniopterus bat coronavirus 1, Miniopterus bat* coronavirus *HKU8, Porcine epidemic diarrhea virus, Rhinolophus bat coronavirus HKU2, Scotophil us bat* coronavirus *512.*

Genus: Beta coronavirus

Species: *Betacoronavirus 1 (Bovine* Coronavirus*, Human coronavirus OC43), Hedgehog* coronavirus *1,* Human coronavirus *HKU1, Middle East respiratory syndrome-related* coronavirus*, Murine* coronavirus*, Pipistrellus bat*

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coronavirus *HKU5, Rousettus bat* coronavirus *HKU9, Severe Acute Respiratory Syndrome-Related* Coronavirus *(SARS-CoV, SARS-CoV-2), Tylonycteris bat* coronavirus *HKU4.*

Genus: Gamma coronavirus

Species: Avian coronavirus, Beluga whale coronavirus SW1.

Genus: Delta coronavirus

Species: Bulbul coronavirus HKU11, Porcine coronavirus HKU15.

Symptoms

Maximum of the patients infected with the virus will experience common cold and flu, while few of them remain asymptomatic. 80% of patient will show mild symptoms of the disease. Adults have the best immunity to fight against the infection but the demerit is that they are more likely to spread the infection a recent study of nearly 140 patients at the Zhongnan Hospital of Wuhan University identified different types of symptom, which lead to a disease known as COVID-19. 99% of the patients developed a fever with extremely high temperature, while more than half experienced fatigue and a dry cough. One-third of the patient developed a dry cough and difficulty in breathing.

Day 1: In the starting day of the symptom, the patient suffers from fever along with fatigue, muscle pain and a dry cough. Few of them may experience nausea and diarrhea a few days before the arousal of symptoms.

Day 5: Patients may suffer from breathing problem especially if they are elderly or have some pre-existing health condition.

Day 7: According to the Wuhan University study, these are the symptoms of the patient that lead the patient to be admitted in the hospital.

Day 8: On the 8th day, patients (15%, according to the Chinese CDC) develop acute respiratory distress syndrome (ARDS), a condition where the fluid fills up in the lungs and this is mostly fatal. This usually happens in severe cases.

Day 10: The progression of the disease leads to worsening of the symptom and at this point the patient is shifted to ICU. Patients with milder symptoms probably have more abdominal pain and loss of appetite. Only a small fraction dies. The current mortality rate is around 2%.

Day 17: On average, after two-and-a-half weeks patients who recover are discharged from the hospital. However, it's difficult to find out the symptoms in the earlier days of the infection. This is usually seen after 5-6 days. Reported symptoms have ranged from mild to severe illness and death for confirmed coronavirus disease 2019 cases. Emergency warning signs of COVID-19 needs medical attention immediately, continuous pain or pressure in the chest, include trouble in breathing, confusion and bluish lips or face. The progressed condition leads to Pneumonia and the incubation period is yet to be determined as the virus is recently identified. As per the new

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information, symptoms could appear as soon as three days after exposure to as long as 13 days later. Recently published research found that on average, the incubation period is about five days.

Infection in humans

Coronaviruses vary significantly in risk factor. Some can kill more than 30% of those infected, such as MERS-CoV and some are relatively harmless, such as the common cold. Coronaviruses can cause colds with major symptoms, such as fever, and a sore throat from swollen adenoids. Coronaviruses can cause pneumonia and bronchitis. Six species of human coronaviruses are known, with one species subdivided into two different strains, making seven strains of human coronaviruses altogether.

Four human coronaviruses produce symptoms that are generally mild, even though it is contended they might have been more aggressive in the past:

1. *Human Coronavirus OC43 (HCoV-OC43), β-CoV*
2. *Human Coronavirus HKU1 (HCoV-HKU1), β-CoV*
3. *Human Coronavirus 229E (HCoV-229E), α-CoV*
4. *Human Coronavirus NL63 (HCoV-NL63), α-CoV*

Three human coronaviruses produce potentially severe symptoms:

1. Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), β-CoV (identified in 2003)
2. Middle East Respiratory Syndrome-Related Coronavirus (MERS-CoV), β-CoV (identified in 2012)
3. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), β-CoV (identified in 2019)

These cause the diseases commonly called SARS, MERS, and COVID-19 respectively.

Infection in animals

Coronaviruses have been recognized as causing pathological conditions in veterinary medicine since the 1930s. They infect a range of animals including swine, cattle, horses, camels, cats, dogs, rodents, birds and bats. The majorities of animal related coronaviruses infect the intestinal tract and are transmitted by a fecal-oral route.

Farm animals: Coronaviruses infect domesticated birds. *Infectious Bronchitis Virus* (IBV), a type of coronavirus, causes avian infectious bronchitis. The virus is of concern to the poultry industry because of the high mortality from infection, its rapid spread, and its effect on production. The virus affects both meat production and egg production and causes substantial economic loss. In chickens, infectious bronchitis virus targets not only the respiratory tract but also the urogenital tract. Coronaviruses also affect other branches of animal husbandry such as pig farming and the cattle rising.

Domestic pets: Coronaviruses infect domestic pets such as cats, dogs, and ferrets. There are two forms of feline coronavirus which are both members of the species *Alphacoronavirus* 1. Feline enteric coronavirus is a pathogen of

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minor clinical significance, but spontaneous mutation of this virus can result in Feline Infectious Peritonitis (FIP), a disease with high mortality.

Laboratory animals: Coronaviruses infect laboratory animals. Mouse Hepatitis Virus (MHV), which is a member of the species *Murine coronavirus*, causes an epidemic murine illness with high mortality, especially among colonies of laboratory mice. *Sialodacryoadenitis Virus* (SDAV), which is a strain of the species Murine coronavirus, is highly infectious coronavirus of laboratory rats, which can be transmitted between individuals by direct contact and indirectly by aerosol. Rabbit enteric coronavirus causes acute gastrointestinal disease and diarrhea in young European rabbits. Mortality rates are high.

CONCLUSION AND RECOMMENDATION

People should stay aware of the latest information on the COVID-19 outbreak provided by WHO and follow the directions of your local health authority and prevent secondary infections, interrupt human-to-human transmission to your close contacts, health care workers and prevent further international spread. Most of the people who infected, experience mild illness and recover it, but its infection can be more severe for other individuals.

To take care of your health and protect others take the subsequent steps:

- Wash your hands regularly and thoroughly with soap and water for at least 20 seconds or with an alcohol-based hand rub (hand sanitizer that contains at least 60% alcohol) completely cover your hands and rub them together until they do not dry especially after you have been visited a public place, or after blowing your nose, sneezing or coughing.
- Maintain social distancing (maintain at least 1 meter or 3 feet distance between yourself and anyone) and avoid close contact with people who are sick (who is coughing or sneezing).
- Avoid large events and mass gatherings.

A number of vaccines using different methods have been developed against human coronavirus SARS-CoV-2. Antiviral targets against human coronaviruses have also been identified such as viral proteases, polymerases, and entry proteins. Drugs are in development which targets these proteins and the different steps of viral replication. Vaccines are available for animal coronaviruses IBV, TGEV, and Canine CoV, although their effectiveness is limited. In the case of outbreaks of highly contagious animal coronaviruses, such as PEDV, measures such as destruction of entire herds of pigs may be used to prevent transmission to other herds.

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