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Coronavirus Disease 2019 (COVID-19): A Summative Review

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ABSTRACT

At present scenario, severe acute respiratory syndrome, caused by novel coronavirus (2019-nCoV) has created a worldwide pandemic situation. This virus was first identified in bats in Wuhan, Hubei province, China in December 2019 but in humans, this virus was transmitted through unknown intermediary animal. Till date, millions of cases have been reported. Inhalation and contact with infected droplets are the main way of transmission. Fever, cough, sore throat, breathlessness, fatigueless, diarrhea are various symptoms of this infection. In progression, in case of older population pneumonia, Acute Respiratory Distress Syndrome (ARDS), comorbidities, multi organ dysfunction also can be observed and these may be responsible for the death of the effected people. Many people are asymptomatic. Fatality rate ranges from 2 to 4%. The molecular test of saliva and nasal secretion are being used as the diagnostic tool of this disease. Common laboratory findings include normal/low white cell counts with elevated C-reactive protein (CRP). All the treatments available are mainly supportive treatment. Various antiviral agents are being used just as booster of the immunity power of the people. Prevention entails home isolation of suspected cases and those with mild illnesses and strict infection control measures at hospitals that include contact and droplet precautions. Some vaccines are already been formulated by laboratory personnel of different countries. These vaccines are going under human trial to find out whether they are potent to produce antibodies against COVID19 or not. Treatment is essentially supportive; role of antiviral agents is yet to be established. The virus spreads faster than its two ancestors the SARS-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV) but has lower fatality. The global impact of this new epidemic is yet uncertain.

INTRODUCTION:

The whole world is currently fighting against an unseen microscopic enemy, the Novel Coronavirus or COVID-19, which is a new strain of coronavirus that has not been previously identified in humans. The name 'coronavirus' is derived from Latin word 'corona', meaning 'crown' or 'wreath'. The name was first coined by June Almeida and David Tyrrell [1], who first observed and studied the human coronavirus. The scientific name of coronavirus is *Orthocoronavirinae* or *Coronavirinae* [2, 3]. These viruses are divided into alpha and beta which infect mammals and gamma and delta which primarily infect birds [4]. Many human coronaviruses have their origin in bats [5]. In case of COVID-19, the initial case showed direct or indirect contact history with the seafood market [6], and is considered as an original place of outbreak of COVID-19 where people are suffered with pneumonia with unknown etiology in Hubei province of China. On December 2019, the outbreak was traced to a novel strain of coronavirus, which was named as 2019-nCoV by the World Health Organization (WHO). This variety of coronavirus is more similar to the SARS-CoV and thus later renamed SARS-CoV-2 by the International Committee of Taxonomy of viruses. By the middle of March 2020, WHO declared SARS-CoV-2 as a pandemic.

Coronavirus is not an airborne virus. It cannot travel in the air more than 1 meter or 3 feet and generally transmit from one person to another through mucous. As there is no specific medication or vaccine against this virus, so, some healthy habits like maintaining personal hygiene, wearing masks, maintain social distance, sanitization can prevent this virus from transmission. Beside this, the FDA granted permission for some medications which are approved for other diseases, to be used to treat severe cases when no other options are available.

History:

The coronavirus is not new at all for us. Scientists first identified the coronavirus in 1965. It caused the common cold. Later researchers found a group of similar human and animal viruses. Seven coronaviruses can infect humans and they are zoonotic in origin. The most common types of coronaviruses that affect before were SARS and MERS.

SARS Coronavirus (SARS-CoV):

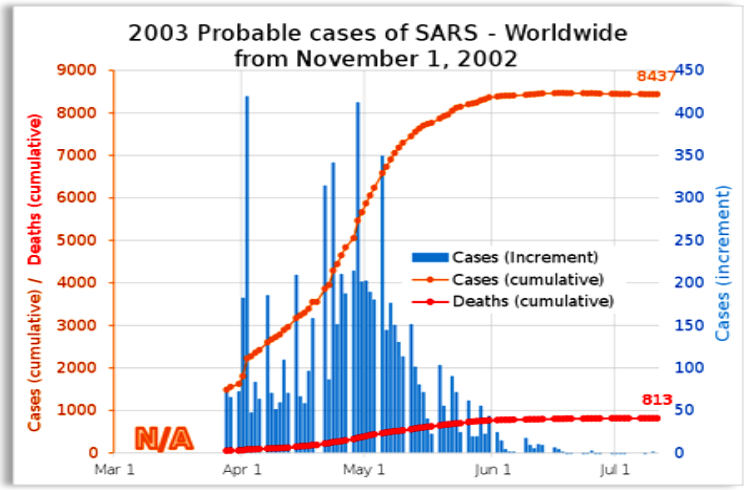
The first identified species of coronavirus is Severe Acute Respiratory Syndrome coronavirus (SARS-CoV). The syndrome caused the 2002-2004 outbreak. SARS was a relatively rare

disease and at the end of the epidemic in June 2003, the incidence was 8422 cases with case fatality rate of 11%[7] (FIG. 1A). People of about 29 countries including China, Hong Kong, Taiwan, Canada, Singapore, USA etc. were affected by this virus with 774 deaths[7]. The ancestors of SARS- CoV first infected leaf-nose bats and then they spread to horseshoe bats, then to Asian palm civets and finally to humans [8, 9]. The symptoms of this syndrome were fever, persistent dry cough, headache, muscle pains etc. The average incubation period is about 4-6 days, although it could be as short as 1 day or as long as 14 days [10].

MERS Coronavirus (MERS-CoV):

Similarly, in 2012, another variety of coronavirus outbreak had been observed in Saudi Arabia [11], which was affected around 2506 people with 862 associated deaths (FIG. 1B), covering 27 countries [12] including South Korea, Jordan, Qatar, United Arab Emirates etc. and this outbreak was named as Middle-East Respiratory Syndrome coronavirus (MERS-CoV). This virus emerged in humans from bats through the intermediate host of camels [5]. Symptoms include fever, cough, and shortness of breath [13]. Some gastrointestinal problems including diarrhea, vomiting, abdominal pain etc. have been observed. It has an incubation period of about 5.5 days (1.9-14.7 days) [14].

A



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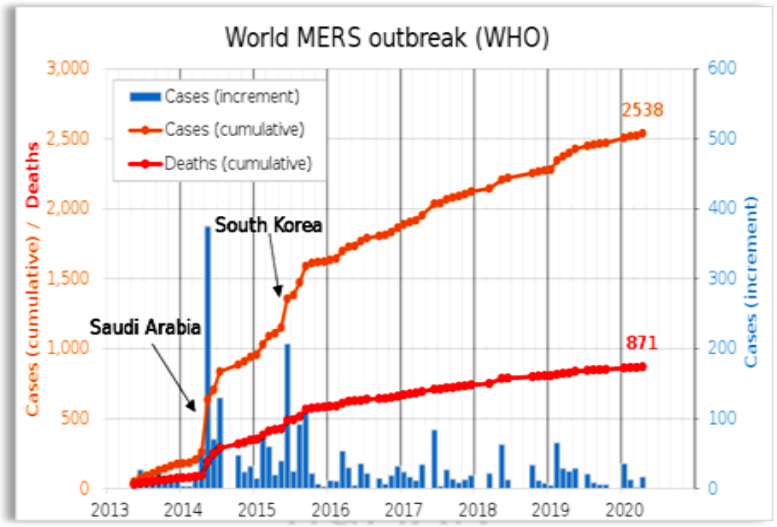

Figure No. 1: (A) Worldwide probable infected cases of SARS. Three sets of data are plotted. On the Y-axis, the number of cumulative cases on daily basis, which are coming from all over the world, is plotted. On the right axis, the incremental number of cases is plotted. On the X-axis, the number of days is plotted, in which it is showed that the infection has been started on the last week of March 2003 [15]. (B) This graph shows the worldwide infected cases of MERS. In this graph also three sets of data are obtained. On the Y-axis, the number of cumulative cases on daily basis, which are coming from all over the world, is plotted. On the right axis, the incremental number of cases is plotted. On the X-axis, number of years has been plotted [16].

STRUCTURE:

Coronaviruses are large group of viruses which is roughly spherical in shape with some projections present on the surface of the virus, called peplomers [17, 18] (FIG. 2A). The average diameter of this virus is around 65-125 nm. They are enveloped virus with positive-sense single-stranded RNA (ssRNA) genome. The RNA is protected by the nucleocapsid proteins. The most prominent feature is the club-shaped spikes, that project from their surface. The diameter of the envelope is 85 nm and the spikes are 20 nm long [19, 20]. The envelope of the virus consists of lipid bilayer in which Membrane (M), Envelope (E) and the Spike (S) structural proteins are anchored [20] (FIG. 2B). On average, a coronavirus particle has 74 surface spikes [21].

S Protein:

The spikes are the homotrimers of the S protein (~150 kDa), which is composed of S1 and S2 subunits. This homotrimeric S glycoprotein is a kind of fusion protein that mediates the receptor binding and membrane fusion between the virus and the host cell. S1 subunit makes up the large Receptor Binding Domain (RBD) of the S protein, while S2 subunit forms the stalk of the spike molecule [22].

M Protein:

The M protein is the most abundant structural protein in the virion. It is a small protein (~25-30 kDa) with three transmembrane domains [22]. It has a small N-terminal glycosylated ectodomain and C-terminal endodomain that extends 6-8 nm into the virus particle [23]. M protein does not contain a signal sequence. It exists as a dimer in the virion and may adopt two different conformations to promote membrane curvature as well as to bind to the nucleocapsid [24].

E Protein:

The E protein (~8-12 kDa) was found in small quantities within the virion. The E protein enables the assembly of the virus and its release from the host cell membrane. It also has ion channel activity which in SARS-CoV-2, is not required for viral replication but is required for pathogenesis [25].

N Protein:

Inside the envelope of the virus, there is the nucleocapsid, formed from multiple copies of the Nucleocapsid (N) protein, which are bound to the single-stranded RNA genome in a continuous beads on astring conformation[19, 26]. N protein is also heavily phosphorylated [27]. These protein interactions help to tie up the viral genome to the Replicase-Transcriptase Complex (RTC), and package the encapsidated genome into viral particles. When the virus is outside the host cell, the lipid bilayer envelope, membrane proteins and the nucleocapsid protect the virus [24].

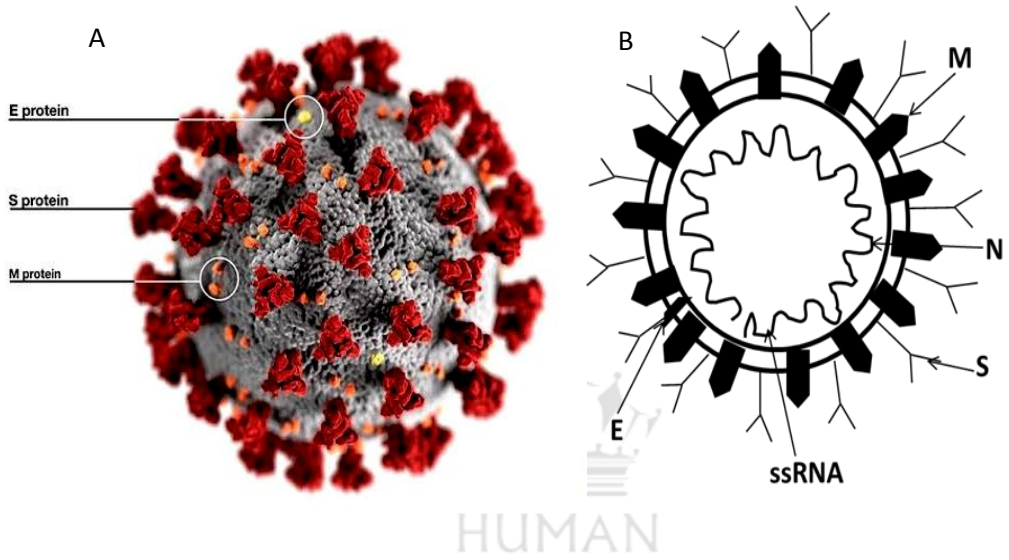

Figure No. 2: (A) Illustrated structure of Coronavirus/SARS-CoV-2, showing three major structural proteins, i.e., envelope (E) protein, spike (S) protein and membrane (M) protein. Spikes are projected from the surface of the virus that can bind with the receptor present on the host cell membrane and can cause infection [28]. (B) This structure shows the major structural proteins as well as nucleocapsid (N) protein, which is present inside the envelope. It also shows single- stranded RNA (ssRNA) which is protected by N protein

GENOMIC ORGANIZATION:

Coronavirus contains a non-segmented, positive-sense RNA genome, the size of which ranges from 26.4 to 31.7 kb [29] (FIG. 3). The genome comprises of ~30000 nucleotides. The genome contains a 5'-methylated cap structure along with a 3'-polyadenylated tail [19] (FIG. 3), which allows it to act as an mRNA for translation of the replicasepolyproteins. The 5' end of the genome contains a leader sequence and UnTranslated Region (UTR) that contains multiple stem loop structures which is required for RNA replication and transcription. The 3'

UTR contains RNA structures which is required for replication and transcription of viral RNA. The genome is organized into six or seven regions, each containing one or more Open Reading Frames (ORFs) which are separated by junction sequences [30]. The single stranded genomes encode two large genes, i.e., ORF1a and ORF1b genes, which encode 16 non-structural proteins (nsp1-nsp16) [19] (FIG. 3). The structural genes encode the structural proteins, i.e., spike, envelope, membrane and nucleocapsid [31]. The organization of coronavirus genome is- 5'-leader-UTR-replicase-S(spike)-E(envelope)-M(membrane)-N(nucleocapsid)-3'UTR poly (A) tail with accessory genes. These accessory genes are interspersed within the structural genes at the 3' end of the genome. The accessory proteins are non-essential for replication; however, some have been shown to have important role in viral pathogenesis [32].

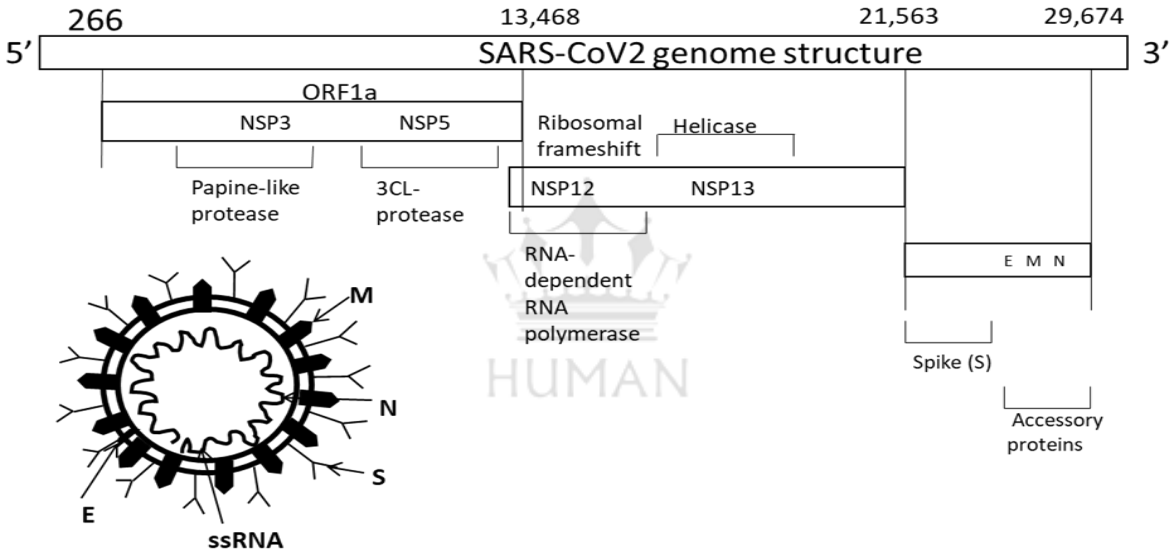

Figure No. 3: Genomic organization of SARS-CoV-2. Genome has 5'-methylated cap region and 3'-poly(A) tail region. Its genome encodes two large genes such as ORF1a and ORF1b and the genome size is about 30 kb. The figure also shows some non-structural proteins (nsp) which are encoded by those genes. Nsp-12 encodes the viral enzyme called RNA dependent RNA polymerase (RdRp) which directly involve in the replication and transcription process of the virus. Beside this, the structural genes encode the four structural proteins (E, S, M and N). Non- essential accessory proteins are also showed in the 3' end of the genome.

REPLICATION CYCLE:

The replication cycle of coronavirus is described by following four sub-headings, i.e.,

Cell Entry:

With the S protein, coronaviruses bind on cell surface molecules to its complementary host cell and then infection begins. After attachment, protease of the host cell cleaves and activates the receptor- attached S protein. This activation allows the virus to enter to the host cell either by endocytosis or by direct fusion of the viral envelope with the host cell membrane [33] (FIG. 4).

Genome Translation:

After entering the host cell, the viral envelope is uncoated and its genome enters into the cytoplasm of the cell. The genome has 5'- methylated cap and 3'- polyadenylated tail [19] which acts as an mRNA and can be directly translated by ribosomes of the cell. The host ribosomes translate the ORF1a and ORF1b of the viral genome into two large overlapping polyproteins, i.e., pp1a and pp1ab [19]. The ribosomal frameshift allows for the continuous translation of ORF1a followed by ORF1b [19]. The polyprotein have their own proteases such as PLpro (nsp3) and 3CLpro (nsp5). The cleavage of polyprotein pp1ab makes the 16 nonstructural proteins (nsp1-nsp16) (FIG. 4).

Replicase-Transcriptase Complex:

A number of non-structural proteins come together and form a multiprotein complex, known as replicase-transcriptase complex. The main protein in this complex is RNA-dependent RNA polymerase (RdRp), which directly involved in the replication and transcription process of the viral RNA. The other proteins in the complex assist in these processes. Another protein named as exoribonuclease provides a proofreading function during the replication [34].

During replication, RdRp directly mediates the synthesis of negative-sense genomic RNA into positive-sense RNA and vice-versa [19]. The other important function of this complex is to transcribe the viral genome. The replication process is followed by the transcription of negative-sense RNA into their respective positive-sense mRNAs[19]. RNA translation occurs inside the endoplasmic reticulum. Beside these functions, this complex is also capable of genetic recombination when at least viral genome is present in the same infected cell [35]. Though the exact mechanism of genetic recombination of coronaviruses is not known properly, but it involves template switching during the process of replication [36] (FIG. 4).

Assembly and Release:

Now, the positive-sense genomic RNA becomes the genome of the progeny viruses. The viral structural proteins (S, E and M) moves into the Golgi mediated compartment. There, an M protein mediates the protein-protein interaction which is required for assembly of viruses and also it's binding to the nucleocapsid. Progeny viruses are then released from the host cell by exocytosis through secretory vesicles. Once they are released, the viruses can infect the other host cells [19] (FIG. 4).

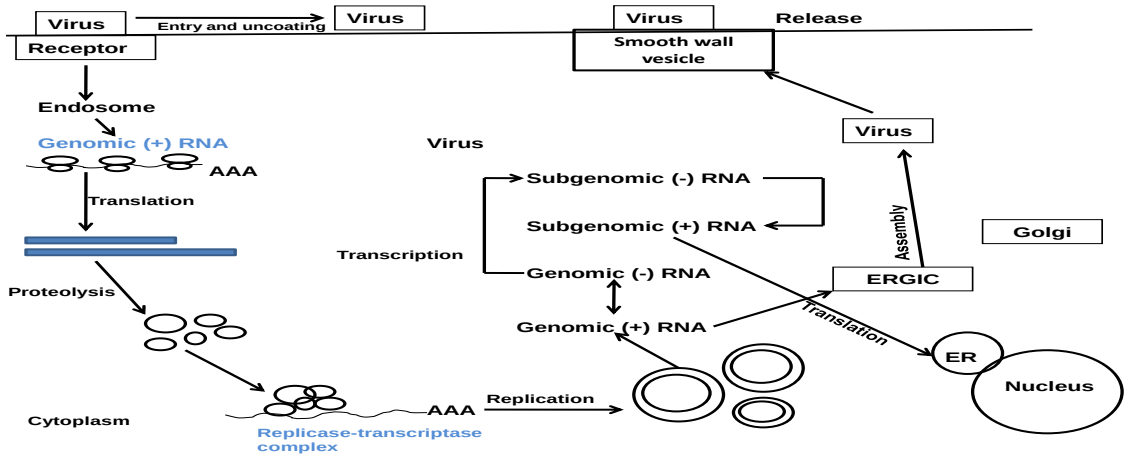

Figure No. 4: Replication cycle of SARS-CoV-2. Replication starts from the binding of the S protein of the virus with the ACE2 receptor present on the surface of the host cell membrane. The virus enters to the cell by endocytosis. S protein changes its conformation. Endosomal membrane is fused and RNA genome id released. Replication and transcription occurs. Structural and nonstructural proteins are obtained. RNA assembles into the virus and the virus is released from the host cell by exocytosis through secretory vesicle and transported to other cell

SYMPTOMS:

Sign and symptoms of this disease may appear 2-14 days after exposure. The time of after exposure and before having symptoms is called incubation period. During this time, a person may undergo to some mild as well as severe symptoms. Depending upon the severity of symptoms persons can be classified into different groups which are as follows.

Asymptomatic:

During the time of incubation period, a person may have the virus, but they do not show any symptoms. This condition is known as asymptomatic. Though, the person can spread the virus to others.

Mild symptomatic:

During the onset of this disease, the infected person may have mild flu-like symptoms in 2-4 days. The symptoms include fever, dry cough, fatigue as well as nasal congestion, sore throat, shortness of breathing, headache, loss of smell or taste[37], nausea, diarrhea etc.[38-41].

Severe symptomatic:

In this case, chest pain, dyspnea, long history of smoking and comorbidities are related with this disease [42, 43]. The virus can lead to pneumonia [44, 45], respiratory failure, septic shock and even death. Strokes have also been reported. Some people, who are hospitalized, have blood clots in their legs, lung and arteries. Leukocyte, lymphocyte or platelet count has been reduced [38-41]. Lymphopenia, eosinopenia and thrombocytopenia has been observed [46, 47]. The failure of multiple organs, such as acute cardiac, renal, hepatic, pulmonary injuries is the main cause of death [39-41]. People over age of 65 years who have weakened immune systems or who have medical conditions like hypertensions, diabetes, heart diseases, Chronic Respiratory Pulmonary Disease (CRPD), cancer, obesity etc. are infected more severely.

MECHANISM OF ACTION:

The virus can enter the host cell by the entry receptor, known as Angiotensin-Converting Enzyme 2 (ACE2) [48, 49]. This virus, which has a significant affinity to the receptor, can directly contact with the ACE2 in humans [50]. After attachment, the S protein is activated by a cellular protease. ACE2 is widely expressed in lungs, myocardial cells, esophagus epithelial cells, enterocytes of ileum and colon, cholangiocytes, proximal tubular cells of kidney, bladder urothelial cells and spermatids or sertoli cell [51-53]. The pathogenic mechanism that produces respiratory trouble and pneumonia shows some clinical presentations. As the virus enter into the respiratory tract, the virus destroys the lung cells known as type II alveolar cells, in which ACE2 receptors are present predominantly [54, 55]. After the viral attack, these calls reduce the surface tension of the lung. As a result, the production of lung surfactant as well as its secretion into the alveolar space has been reduced. This is followed by atelectasis

due to lung surfactant dysfunction and further reduces lung compliance [56] (FIG. 5A). On the other hand, this viral infection is capable of producing some excessive immune reaction in the host which is known as 'cytokine storm' [57] (FIG. 5B). Several cytokines such as TNF-α, IL-1β, IL-8, IL-12 etc. are associated with the pathogenesis of this disease. IL-6 is one of the main factors in this storm which plays a vital role in the pathogenesis of this disease. It acts on large number of cells and can promote the differentiation of B lymphocytes. It is also associated in the pathogenesis of cytokine release syndrome (CRS) which is characterized by fever and dysfunction of multiple organs. The virus binds with the Toll like Receptors (TLRs) and induces the release of pro-IL-1β which is then cleaved into mature IL-1β and mediates lung inflammation until fibrosis occurs [58]. It has also been suggested that patients with heart disease, kidney disease, hypertension, prostrate disease and even cancer should not be exposed to this virus.

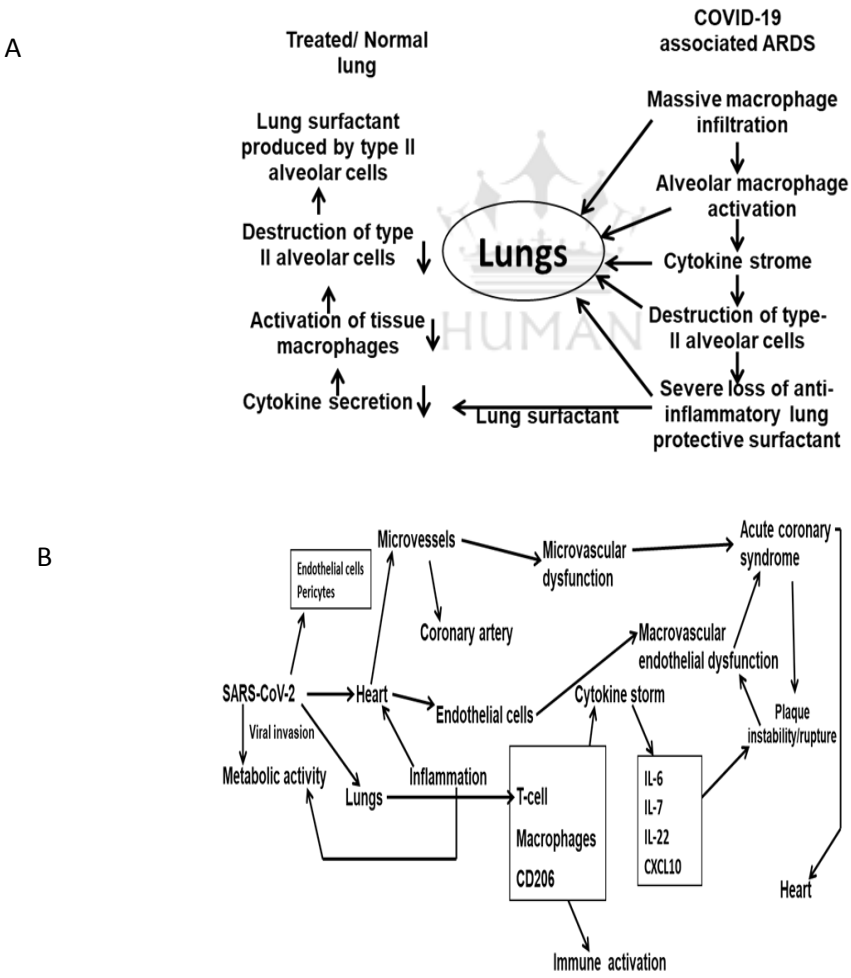

Figure No. 5: (A) Lung surfactant and COVID-19. This figure shows the mechanism of lung surfactant in protection of lung against COVID-19. In this mechanism, at first,

macrophages enter to the lung which causes alveolar macrophages activation. These active macrophages activates 'cytokine storm'. Due to this, type II alveolar cells which produce lung surfactant are destroyed and for that reason, anti-inflammatory lung surfactants are also reduced. If this surfactant is employed from outside to the body, it reduced the cytokine production and decrease the activation of tissue macrophages. Type II alveolar cells destruction decreases and these alveolar cells are further able to produce the lung surfactant. Indicate decreased in amount. (B) Mechanism of action of SARS-CoV-2. After entering to the host cell, it can cause immune reaction known as 'cytokine storm'. It causes increase production of IL-6, IL-7 etc., which involve in the pathogenesis of disease. In lung, the virus can cause inflammation. In heart, it can cause macrovascular endothelial dysfunction and microvascular dysfunction

DIAGNOSIS:

Only symptoms are not enough for the confirmation of the coronavirus disease as all the symptoms very common in day to day life and can be found in common cold. So for the confirmation of the disease, people with mild [37-41] or sever symptoms [44, 45] must undergo clinical test. People who have come across to COVID-19 positive patients are also suggested to undergo clinical test. To avoid the spread of coronavirus through asymptomatic patients which is more dangerous as the person do not know whether he or she is carrying virus, it is suggested to do randomize clinical test.

RT-PCR is the only confirmation test for the coronavirus gene [19]. For this mucous samples are collected from the inner nasal cavity and throat from which the RNA will be isolated through several steps. Then it undergo RT-PCR in search of the viral gene sequence.

TREATMENTS:

There are no specific vaccines or antiviral drugs for the treatment of novel coronavirus. However, FDA has granted permission for some drugs which are basically approved for other diseases, to be used to treat the patients who are suffering from severe COVID-19. Allopathic, homeopathic, ayurvedic medicines are approved by FDA and the Ministry of AYUSH in India for the treatment of COVID-19. Also, immunity boosting food supplements are recommended to make strong one's immune system against this disease. The commonly used drugs and their possible mechanism of actions are described briefly (Table 1).

Allopathic Treatment:

Different kind of allopathic medicines have been trialed to observe their effectiveness against this COVID-19. Among these medicines the commonly used drugs are, i.e. two malaria drugs, named chloroquine and hydroxychloroquine and an antiviral drug, named remdesivir, have been suggested for this purpose [59].

Hydroxychloroquine or HCQ: It is an antiprotozoan drug that is used for the treatment of malaria, is a lipophilic weak base which is readily absorbed by the gastrointestinal tract and eliminated by the kidney easily. The effect of HCQ on the immune system has been established. It interferes with lysosomal acidification and antigen presentation [60], Inhibit toll Like Receptors (TLRs) signal, inhibit T and B cell receptors and decrease cytokine production by macrophages [60, 61]. The inhibition of cytokines such as IL-1, IL-6, TNF-α decreases tissue damage and endothelial inflammation [62]. On the other hand, to be a weak base, it can affect acid vesicles and inhibit several enzymes. This characteristic allows them to inhibit the viral entry to the host cell by endocytosis which is a pH dependent process. An enzyme called lysosomal proteases is important for the viral entry to the host cell. It helps to activate the spike proteins which are present on the surface of the virus. Then these proteins are fused with the host cell membrane and are uncoated. But HCQ increases the pH of the endolysosome and prevents the activity of lysosomal enzymes [63] (FIG. 6).

In France, the combination of HCQ and azithromycin has been used to treat coronavirus[64]. But the efficacy of this combination has become a controversial issue. It is suggested that this combination was successful in clearing the viral replication in small number of sample. But, in large- scale analysis, no clinical benefit is found rather it would produce cardiovascular toxicity among patients in some countries. For that reason, WHO had suspended the trials of hydroxychloroquine on May 25, 2020.

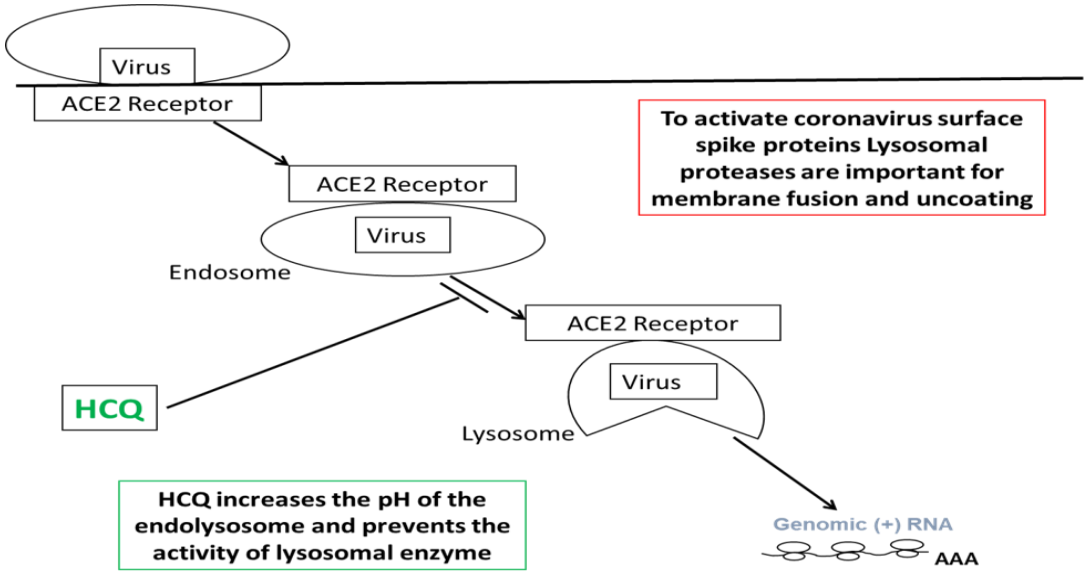

Figure No. 6: Mechanism of Hydroxychloroquine on SARS-CoV-2. This figure shows that HCQ can increase the pH of the endolysosome and prevents the activity of lysosomal enzymes that is important for virus to fuse with the host membrane and uncoating themselves

Remdesivir: This is a broad spectrum antiviral agent [65]. On May 1, 2020, the FDA has been issued the emergency use of this drug for severe COVID-19 patients (adults as well as children) who are hospitalized [66]. Preliminary data showing a faster time to recovery of hospitalized patients with severe disease [67]. After adding remdesivir to the infected host, the polymerase enzyme stops the process of replication of the viral genome. This action is due to remdesivir has the ability to metabolize into an active form of adenosine nucleotide analogue, called GS-441524, which interferes with the action of viral RdRp and decreases the viral RNA production [65] (FIG. 7). But the Union Health Ministry is not satisfied with the effectiveness of this drug as neither the countries which have used this drug did not show any good results nor has the mortality rate due to COVID-19 been reduced.

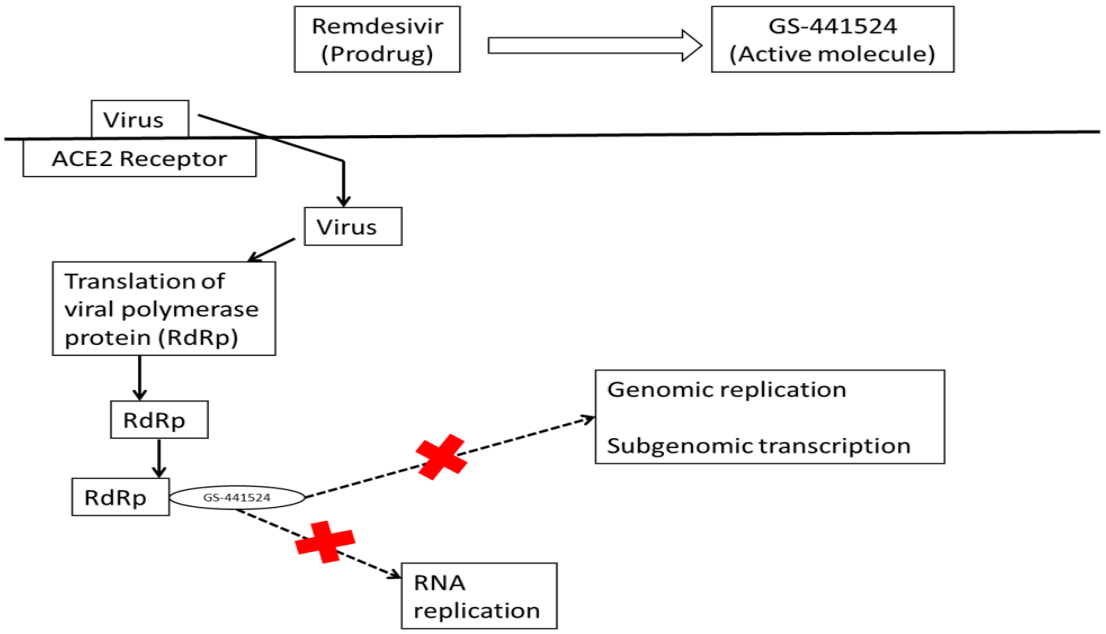

Figure No. 7: Mechanism of Remedisivir on SARS-CoV-2. This figure suggests that after ingestion of Remdesivir, the polymerase enzyme stops the viral genome replication. This drug interferes with the RdRp enzyme and decreases the viral RNA production

Homeopathic Treatment:

For the treatment through homeopathic medicine, the Ministry of AYUSH has been issued proper guidelines [68]. Based on the symptoms of each patient and the presenting signs, the medicines were selected [68-71]. Patients who have mild symptoms can use prescribes medicines such as Arsenicum Album, Bryonia Alb., Rhustox. Also medicines like Iodum, Camphora, VeratrumViride are prescribed depending upon the symptomatic indication [68]. It was known that arsenicum album can cure diarrhea, cough and cold [68]. But its exact mechanism of action against COVID-19 is not known yet. As there is no evidence whether the medicine works or not, so the WHO has no guideline for using of this medicine to treat the coronavirus. But the Ministry of AYUSH has been recommended this medicine because of its existing use in curing of respiratory illness and influenza.

Ayurvedic Treatment:

From the Ayurvedic point of view, COVID-19 is known as 'janapadodhwamsavikara' which means 'epidemic disease'. In India, there is no evidence of the use of Ayurvedic medicine. But in New York, USA, there is a positive report for this kind of medicine [72]. Medicines like

SudarsanaChurna, TalisadiChurna, DhanwantaraGutike, VidaryadiGhritam are used for the treatment [72-74]. The mechanism of action can be assumes that ingestion of ayuevedic medicine can arrest the progression of the disease into a more critical state within a short period [72]. Though the exact mechanism is not known. In addition, Traditional Chinese Medicines (TCM) was used to control this epidemic in China.

Treatment Using Nanoparticles:

Nanoparticles are small which ranges between 1 to 100 nm in size, having a large surface-to-volume ratio. These particles are currently used for drug formulations with faster therapeutic indices for the treatment of COVID-19. But this work is in progress as no such drugs are approved for COVID-19 treatment. Many nanoparticles have antiviral and antibacterial activities [75]. For this reason, these particles should be used to reduce the severity of the disease like COVID-19.

Zinc: Zinc is a nanoparticle that has many important uses against COVID-19 [76]. Zinc can increase host resistance. Though the exact mechanism of zinc is unclear, but it is said that zinc inhibit the binding of virus with the host membrane and prevent the replication of viral genome. Also, zinc can exert its antiviral effect by activating the interferon alpha or gamma and by suppressing the inflammatory reactions [76]. Studies show that zinc can act either by suppressing the viral genome replication or by boosting the immune system.

Polyphenols: Beside zinc, other group of drugs, known as polyphenols, which is a class of bioactive compound present in trees, is also used for treating COVID-19. Polyphenols can be classified into flavonoid, phenolic acids and other polyphenol compounds [77]. The most well known polyphenol is Resveratrol. This drug can cause reduction of cell death, inhibiting the viral genome replication, inhibition of immediate early viral protein expression, inhibition of NFκB signaling pathway, activation of AMPK/ Sirt1 axis in the host cell [78].

Multidrug Nanoparticles: Recent studies suggested that multidrug nanoparticles can be used to treat COVID-19 which can control and reduce the effect of uncontrolled inflammation. Nanoparticles, made by conjugating the Squalene (endogenous lipid), adenosine (endogenous immunomodulator) and α-tocopherol (natural antioxidant) are used for the treatment of COVID-19 [79].

Immunity Boosting Food Supplements:

The virus attacks most to the person who have weaker immunity. So to get rid of the virus, one should boost their immunity system by taking healthy foods and balanced diet. Proper nutrition and hydration are very much important. WHO has recommended a guideline of nutrition for adults in COVID-19 outbreak [80]. According to the guideline, fresh and unprocessed foods, which are cooked in home like vegetables, whole grains, eggs, fish, brown rice etc. and fresh fruits, nuts has been suggested to eat. 8 to 10 cups of water has been recommended to drink every day. Moderate amount of fats and oils and less amount of salt and sugar are also been suggested to intake during this pandemic situation.

Plasma Therapy:

The most promising treatment against this infection is convalescent plasma therapy [81]. As no drug has been proved to be safe and effective for the treatment of COVID-19 yet, so, doctors have done this experimental treatment to the patients who are suffered with severe COVID-19. The therapy aims at transfusing plasma containing antibodies donated by the patients who were recovered from COVID-19 to the actively infected person. The patients, who are recovered after 21 to 28 days of their illness, are selected as the donor of the plasma. For plasma donation many procedures have been followed as the recovered patients are repeatedly tested and when they are found to be negative, are selected as a suitable donor. Antibody detection tests are also done to observe whether the protective antibodies are formed or not in the recovered patients. After that the plasma is ready for donation and then the plasma is infused into blood group of matched recipients who are suffering from active COVID-19 infection. The patients are given dose of 200 ml of plasma on two consecutive days. This treatment can improve the ability to recover from the disease. In preliminary treatment, several studies have shown a shorter hospital stay and a lower mortality rate in patients who are treated with convalescent plasma. Though there is some risk factors of using this plasma which is differ from patient to patient. The transfusion of plasma can create some allergic reaction, lung damage, transmission of other blood borne diseases like HIV, Hepatitis B etc. But the chance of these risk factors is very low because the donated bloods are handled properly to test its safety [82]. Many countries throughout the world have already started to use plasma therapy for the treatment of COVID-19.

TABLE No. 1: DIFFERENT TREATMENT MODE, DIFFERENT MOLECULE ALONG WITH THEIR MECHANISM OF ACTION

Mode	Molecule/ Drugs	Action	Mechanism	Remarks
Allopathic Treatment	Hydroxychloroquine	This drug has a direct action on COVID-19.	• Inhibits cytokine [60] [61] • Decreases tissue damage and endothelial inflammation[62] • Increases the pH of endolysosome • Prevents the activity of lysosomal enzyme[63]	WHO has banned the use of it as this drug may produce cardiovascular toxicity
	Remdesivir	This drug has a direct action on COVID-19.	• Interferes with the RdRp enzyme • Decreases viral replication and transcription[65]	Government is not satisfied the use of this drug as • This drug does not show any good results. • Mortality rate is not reduced.
Homeopathic Treatment	Arsenicum album	It has not any direct action on COVID-19	This drug can treat the symptoms only such as fever, diarrhea, cough and cold[69]	This drug has been recommended because of its use in curing respiratory illness but excessive use can cause arsenic poisoning.
Ayurvedic Treatment	Sudarsana Churna, Talisadi Churna, Dhanwantara Gutike, Vidaryadi Ghritam	This drug has a direct action on COVID-19.	These medicines can arrest the progression of disease into a more critical state[73]. Though the exact mechanism is unknown.	China and USA have used these medicines and had a positive result. But in India, there is no evidence of the use of it.
Treatment	Zinc	This	• Increases the host resistance	This method of

Using Nanoparticle		drug is supposed to has a direct action on COVID-19.	• Inhibits the binding of virus with the host membrane • Prevents the replication of viral genome • Activates the interferon alpha or gamma and by suppressing the inflammatory reactions[77]	treatment is under clinical trial.
	Polyphenols (Resveratrol)	This drug is supposed to has a direct action on COVID-19.	• Reduces cell death • Inhibits the NFκB signaling pathway • Activates of AMPK/ Sirt1 axis in the host cell[79]	
	Multidrug nanoparticle (Squalene, adenosine, α-tocopherol)	This drug is supposed to has a direct action on COVID-19.	• Reduces the effect of uncontrolled inflammation[80]	
Immunity Boosting Food Supplements	Fresh, unprocessed foods, fruits, eggs, fish, meat etc. and sufficient amount of water	It has not any direct action on COVID-19	These can boost the persons immunity	WHO has recommended these food supplements for immunity boosting
Convalescent Plasma Therapy	Plasma of infected person	This therapy has a	Transfuses the plasma containing antibodies donated by the patients who were recovered	As several studies have shown a shorter hospital stay and a

		direct action on COVID-19.	from COVID-19 into the actively infected person. The infected person now has protective antibodies to fight against this virus.	lower mortality rate in patients, this therapy nowadays has been started in many countries throughout the world.

CONCLUSION:

Coronaviruses are large family of viruses that circulate mainly among mammals and birds. These viruses rarely transmitted to humans. But this zoonotic virus that has arisen in recent times such as COVID- 19, SARS, MERS, can affect the human also. The infection is spread through transmission of viral droplet from the infected person to the healthy individual. USA, Brazil, India along with 212 countries and territories around the world has been affected by this disease. Due to its alarming levels of spread among people and severity of affecting this infection, WHO has declared this outbreak as pandemic as this virus is spread through person-to-person in multiple countries around the world at the same time. To protect from this infection, one should follow some simple precautions such as washing hands regularly and thoroughly, maintaining at least 1 meter distance from one another, avoiding going to the crowded place, wearing masks, avoiding touching eyes, nose etc. If mild symptoms have been observed then self-isolation is recommended in home to avoid contact with others. For washing hands, soaps or any alcohol based hand sanitizer has been suggested for use. To break the worldwide transmission chain, any kind of national and international travel has been stopped and the governments of the respective countries have announced a lockdown period so that every person can stay at home to avoid regular contact with each other. Persons who have a critical condition are treated with some FDA approved medicines, though some of them are under clinical trial. Researchers from all over the world are also trying to formulate the vaccine against COVID-19. Some vaccines are already been formulated by laboratory personnels of different countries. These vaccines are going under human trial to observe whether they are potent to produce antibodies against COVID-19 or not.

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CONFLICT OF INTEREST:

There is no conflict of interest.

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