A review on the pathophysiology and potential drugs for COVID-19

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

Department of Pharmacy
Brac University
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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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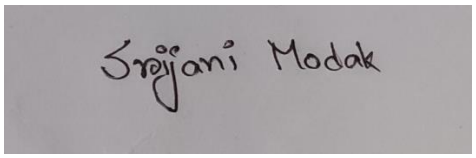

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Approval

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Ethics Statement

The study does not involve any human or animal trial.

Abstract

The ongoing 2019 coronavirus pandemic caused by SARS-CoV-2 has generated enormous obstacles to the healthcare system worldwide. There seem to be no specific therapeutic agent against the virus currently. Infection preventive and mitigation strategies and supportive treatments are the main area of concern for modern health management. A prospective list of repurposed medicines with suitable pharmacological effects and therapeutic effectiveness in the treatment of COVID-19 patients has been suggested by emerging scientific and clinical evidence about virologic SARS-CoV-2. These medications and therapeutic agents include antiviral agents (remdesivir, hydroxychloroquine, chloroquine, lopinavir, favipiravir, oseltamivir, ivermectin) and supportive agents such as; antibiotics, ascorbic acid, corticosteroids, nitric oxide, IL-6 antagonists), biological products, vaccines and many more combinations of therapy.

Keywords: COVID-19, SAR-CoV-2, Treatment, Therapeutic strategies, Transmission.

Dedication

I want to dedicate this project to my parents for their eternal love and affection.

Acknowledgement

I would like to proceed by thanking the Almighty who is the source of our strength and knowledge which have enabled me to complete this project with full diligence.

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List of Acronyms

COVID	Coronavirus Disease
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
HCo	Human Coronavirus
ACE	Angiotensin Converting Enzyme
COPD	Chronic Obstructive Pulmonary Disease
TCM	Traditional Chinese medicine
NSAID	Non Steroidal Anti Inflammatory Drug
RA	Rheumatoid Arthritis
PBMC	Peripheral Blood Mononuclear Cells
ALI	Acute Lung Injury
BALF	Bronchoalveolar Lavage Fluid
ARDS	Acute Respiratory Distress Syndrome
WHO	World Health Organization
FDA	Food and Drug Administration
CT	Computed Tomography
RT-PCR	Reverse Transcription Polymerase Chain Reaction
GammaCoV	Gamma Coronavirus

AlphaCoV	Alpha Coronavirus
BetaCoV	Beta Coronavirus
DeltaCoV	Delta Coronavirus
RdRp	RNA Dependent RNA polymerase
HIV	Human Immunodeficiency Virus
GLN	L-Glutamine
TLR	Toll Like Receptor
ELISA	Enzyme Linked Immunosorbent Assay
BLI	Biolayer Interferometry Binding
ICU	Intensive Care Unit
JAK	Janus Kinase
RBD	Receptor Binding Domain

Chapter 1

Introduction

1.1 Covid-19

The horrific Covid-19 (coronavirus disease 2019) pandemic outbreak around the world took the health care systems by storm by exposing it without proper protection mechanisms to tackle and track such a pandemic (Bourgonje et al., 2020). COVID-19 was first reported in patients with extreme respiratory disease in Wuhan, China. Novel coronavirus is clinically referred to as a severe acute respiratory syndrome 2 (SARS-CoV-2). More than 3 million people have died among more than 1.5 billion infected cases, since its discovery. COVID-19's obvious potential to spread quickly and his propensity to induce serious illness in elderly adults and chronic health problems are troubling (Alanagreh et al., 2020). To reduce its transmission many systems has been adapted by countries around the world. According to a model it is assumed that home confinement can be 100% effective to stop transmission which sadly is not only extremely challenging for all the unaffected people but also it has a potency to disrupt economy, health, education and every system around thus cannot be maintained for a long period of time (Mitjà & Clotet, 2020). Apart from that, to protect people who are at high risk of getting infected such as people in close contacts, doctors and other health care providers, there’s a great need of development of a pre exposure prophylaxis and post exposure prophylaxis treatment. According to Lancet Glob Health (2020), it is very important to start medication as soon as possible after the exposure. Therefore, safety, cost and availability of drug has to be ensured before being considered as a suitable prophylactic system. There is no single specific antiviral therapy yet designed neither discovered for COVID-19. The treatment focuses primarily on symptomatic and respiratory assistance complying with guidelines that has been arranged in each country by the health authority,

whereas lot other countries are following the WHO protocol. To fight this global pandemic development of treatment has become health priority. For this purpose many companies around all over the world are working to develop drug or vaccine but this is not a short process. It might take months to establish a therapeutic system against this viral disease (Alanagreh et al., 2020).

1.2 Coronaviruses

Coronaviruses are wide group of viruses that are known to cause diseases like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) that have a range from the common cold to more serious diseases. Coronaviruses reside to the family Coronaviridae and order Nidovirales which is consists of viruses between 26-32 kilobases in size having a single-strand, positive-sense RNA genome. The family of Coronaviridae carries four genera: Alpha-coronavirus (alphaCoV), Beta-coronavirus (betaCoV), Delta-coronavirus (deltaCoV) and Gamma-coronavirus (gammaCoV). It is believed that bats and mice are reservoirs of alphaCoV and betaCoV. They can induce severe respiratory diseases in humans and gastrointestinal diseases in other species. It is currently less evident which animals act as deltaCoV and gammaCoV reservoirs. (Abd El-Aziz & Stockand, 2020). In addition, coronaviruses are well known for mutating and recombining. When observed under electronic microscope, mature viruses or virions of CoVs appeared having large peplomers which is a crown like structure, arising with the idea of naming this virus as corona which means “crown”. It was not considered as deadly virus prior to 2003 as the symptoms of Covid was only confined by mild symptoms immunocompetent people. When SARS emerged in Guangdong, China in 2003, the entire world was in shock by the first pandemic of 21st century. This resulted in 774 deaths and more than 8000 infected patients. Afterwards, another type of corona virus had emerged in Saudi Arabia nine years later in naming Middle East Respiratory Syndrome Coronavirus termed as MARS-CoV resulted in 861 deaths and

more than 2500 confirmed cases consisting fearfully high mortality rate of 34.40%. COVID-19 is the third novel coronavirus to trigger a major pandemic in the 21st century (Alanagreh et al., 2020). In figure 1 the differences among these three coronaviruses aquired from comaparative ananlysis is shown.

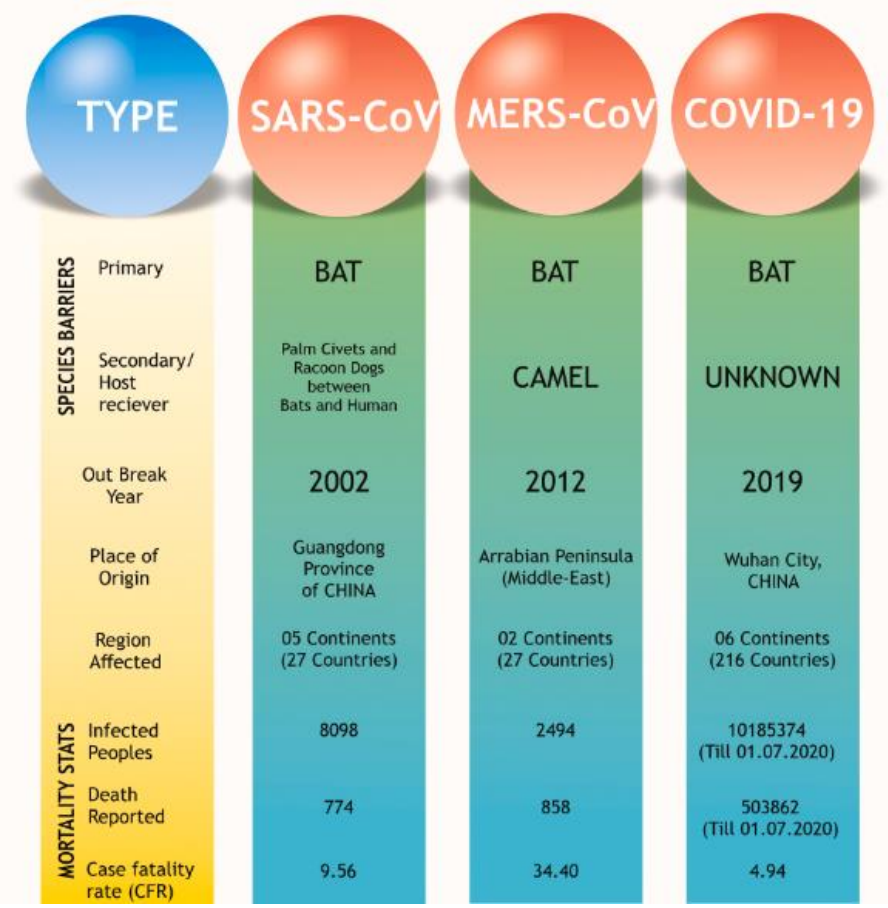

Figure 1: Comparative analysis of three different 21st century coronavirus outbreaks (adapted from Samudrala et al., 2020).

1.3 Diversity of corona virus

Three main factors are the consequence of the diversity of coronaviruses. Firstly, the infidelity of coronaviruses' RNA-dependent RNA polymerase (RdRp) causes their mutation rates to multiply in the order of one per 1000 to 10000 nucleotides, making them extremely flexible. Secondly, their unique and random template results in switching during RNA

replication. Thirdly, since coronaviruses have the largest genomes of 26.4-31.7 kb of all RNA viruses discovered till now, this virus family has been given additional plasticity to accommodate and change genes. These three factors have contributed to the generation of a number of strains, genotypes of one species of coronavirus and also to new species that can adapt to new hosts and ecological changes, often triggering severe outbreaks with destructive effects (Uen, 2009). Again, coronaviruses reside to the subfamily Coronovirinae within the family Coronaviridae. HCoV-229E and HCoV-NL63 exist under alphaCoVs. Under lineage A Betacoronaviruses remain HCoV-OC43, and HCoV-HKU1 whereas the life threatening viruses SARS-CoV and MERS-CoV fit to lineages B and C of betaCoVs, respectively. By analyzing genome, SARS-CoV-2 has been found to be under betaCoVs group in lineage B. CoVs are zoonotic pathogens which means it is originated in animals and has the potency to be transmitted to humans by direct contact. All epidemic causing CoVs including COVID-19 are believed to be originated in bats. Though Bats acts as hosts of many other coronaviruses, there has been an intermediate animal host to transmit it to human. It is suspected that the COVID-19 has come out in the seafood market in Wuhan, China. After analyzing the evolution of COVID-19 virus it has revealed to be mostly similar with bat SARS-like CoV, thus named as SARS-CoV-2 (Cui et al., 2019).

1.4 Primary reservoirs and hosts of coronaviruses

It is necessary to identify the source of origination and transmission to develop preventative measures to control the viral infection. Focus was especially given on raccoon dogsand palm civets by the researchers as a main reservoir of the SARS-CoV infection. However, the only sample isolated out of the civets on the food market has revealed to be positive for the detection of viral RNA, indicating civet palm to be the secondary hosts of the virus. In 2001,

the samples which were collected from healthy Hong Kong individuals for molecular evaluation had given a frequency of 2.5% of SARS-CoVs antibodies. These signs indicated that before the outbreak in 2003, SARS-CoV could circulate in humans. Later on, anti-SARS-CoV antibodies were also found in Rhinolophus bats indicating bats as a vector of viral replication. In Saudi Arabia, the MERS-CoV first appeared in 2012. MERS-CoV has camels as a primary host source. MERS-CoV has also been identified in Pipistrellus and Perimyotis bats in a recent study which indicated bats as the primary host and medium of transmission of this virus. Initially a group of researchers proposed that snakes might be the potential host, but after observation the similarity of genomic of SARS-CoV-2 with SARS-like bat viruses, the claim supported that the main reservoirs may not be snakes but only bats as shown in figure 2. Further study of homologous recombination showed that novel coronavirus receptor-binding spike glycoprotein is derived from SARS-CoV and unknown beta-CoV. However, in order to eliminate the virus, sufficient work is needed to establish the intermediate pathogenic source that is responsible for the viral transmission to humans (Shereen et al., 2020)

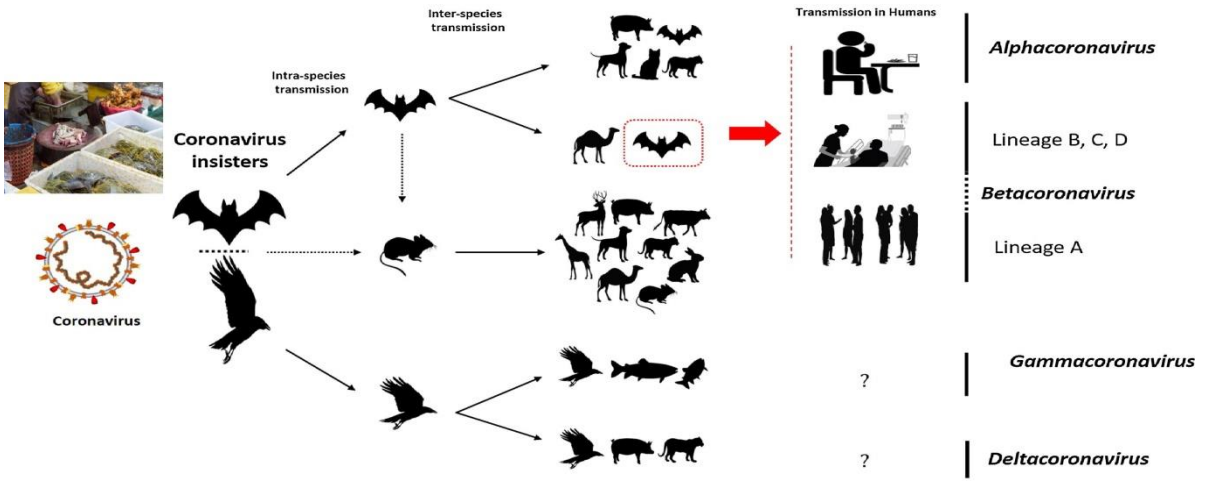

Figure 2: Primary reservoirs and route of transmission of coronaviruses (suspected reservoirs of SARS-CoV-2) (adapted from Shereen et al., 2020).

1.5 SARS-CoV-2

SARS-CoV-2 is a single stranded RNA virus which differs from SARS-CoV and MERS-CoV in genetic characteristics (National Health Commission et al., 2020; Li et al., 2020b). It is the seventh corona virus to infect human (Wu et al., 2020). It has been shown to have above 85% similarity with bat-SARS-like coronavirus in a research study, indicating that bat is its potential natural host (Xu et al., 2020; Zhou et al., 2020). Besides, various wild animals including bamboo rat, swinhoe and badger may be potential SARS-CoV-2 intermediate host (Li et al., 2020c). Again, it is closely related to the bat-like reservoirs of SARS-CoV and MERSCoV, but the former has enormous biological variations in comparison to the other two. SARSCoV-2 is significantly more contagious, infectious and has epidemiological drift that are somewhat distinct. In addition, human transmission adaption capability was never present entirely in MERS-CoV (Sabir et al. 2016). The local and global distribution of SARSCoV-2 is remarkable (Rathore & Ghosh, 2020).

In addition, the primary cause of transmission of the infection to other individuals, including those who are asymptomatic, is infected patients. Humans are infected by or in close contact with the respiratory droplets of infected patients. The Chinese scholar Zhong Nanshan's team released a clinical manifestation of by analyzing 1099 SARS-CoV-2 infected patients. Results were obtained as 43.8% of patients had fever in the initial stage of the infectious disease and 87.9% of them had fever in hospitalized patients only after getting admitted to a hospitali. The most common of all the symptoms were fever and cough (Pan et al., 2020).

Other than that, some patients are also responsible for symptoms of myalgia, diarrhea, and vomiting. These symptoms can lead to the rapid development of acute respiratory distress syndrome (ARDS), metabolic acidosis, and septic shock and in severe cases, dysfunction of coagulation or multiple organs impairment (Huang et al., 2020). According to the symptoms

of the disease, it can be divided into stages consisting of mild, medium, severe and critically ill group of patients (Pan et al., 2020).

1.6 Genome structure and replication

SARS-CoV-2 is a single-stranded, positive sense RNA virus containing 29,891 bases. It is 96% cent similar to the bat coronavirus at whole genome level and shares 79.6% gene identity of the SARS-CoV (Wu et al., 2020). According to Ciotti et al 2020, Phylogenetic genome study of the SARS-CoV-2 has shown that in Wuhan, China, the novel coronavirus is the reason for the outbreak of pneumonia belonging to the genus Betacoronavirus, Sarbecovirus subgenus. Inside the genus beta-CoV, SARSCoV-2 is away from SARS-CoV (approximately 79% similarity) and MERS-CoV by approximately 50% identity that are responsible for causing the epidemics from 2002-2003 and 2012, respectively. But it is closely linked (88% identity) to the two bat like coronaviruses. The analyzed genetic variation to identify the timeline of the common ancestor along with the rate of spread, using 74 publicly shared novel coronavirus genomes. The huge similarity of the genomes indicates that a contemporary common ancestor is shared by them. Otherwise, between the samples, we would assume a larger number of variations. In late November or early December 2019, the rise from bats to humans is most likely to have occurred. Research based on previous studies on coronaviruses indicates that these viruses add on between 1 and 3 changes per month in their genome (rates per year of 3 × 10-4 to 1 × 10-3 per site). The rate of evolution for the SARS-CoV-2 whole genome sequences was calculated by molecular clock calibration at 6.58 × 10-3 substitutions each site every year (95%). The SARS-CoV virus particle is maintained by four different proteins as shown in figure 3: i) the S protein (Spike glycoprotein) that allow the infectious corona virus to be bound to host cells followed by membrane fusion, thereby facilitating the entry of SARS-CoV into host cells; (ii) the

abundant M protein (membrane) which preserves the integrity of the viral particle; (iii) E protein (envelope) is the smallest protein and plays a structural function in the assembling and budding process; (iv) N protein (nucleocapsid) is primarily bound to the SARS-CoV RNA and facilitates nucleocapsid construction (Chauhan et al., 2020). SARS-CoV-2 encodes a receptor binding domain (RBD) spike S protein that functions by binding to human angiotensin converting enzyme 2 (ACE2). Besides, S protein promotes membrane fusion and uptake of virus into human cells, such as endocytosis of the lungs. Upon entering into host cells, covid-19, like other coronaviruses, can take over protein synthesis machines for host cells to synthesize viral proteins, assemble proteins and eventual viral replication (Wu et al., 2020).

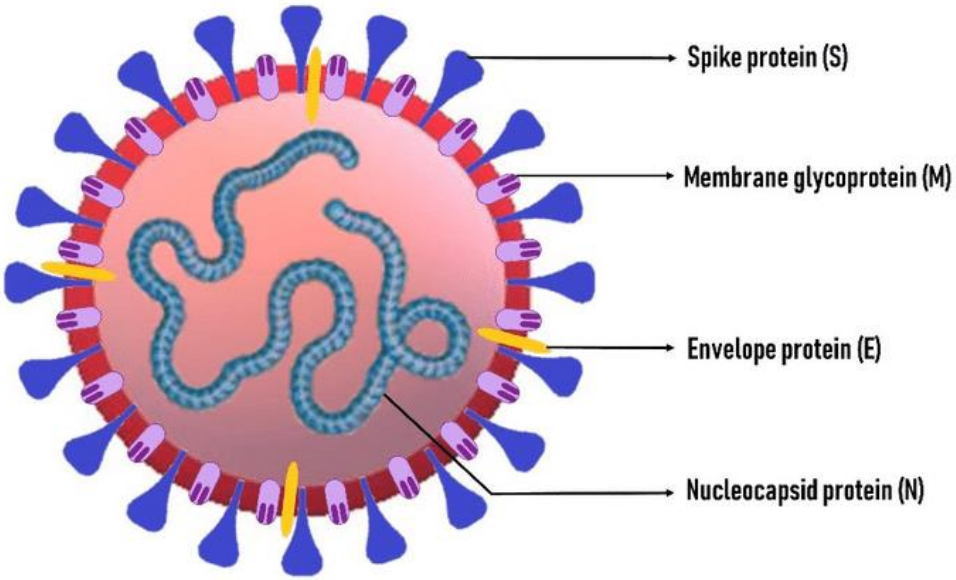

Figure 3: Basic structure of corona virus showing its four basic structural proteins (adapted from Haritha et al., 2020)**.**

1.7 Origin and evolution of the SARS CoV-2 virus

On basis of the phylogenomic interpretation of the currently published 2019-nCoV genomic results, the 2019-nCoV is most precisely linked to two SARS like corona virus sequences which were isolated in bats between 2015 and 2017 9 (Zhang et al 2020). This indicates that a recent common ancestor is shared by the bats' corona virus and the human 2019 novel corona virus. It is therefore possible to consider 2019-nCoV as a SARS-like virus as well as to name it SARS-CoV-2. The two bat viruses were collected from 2015 to 2017 in Zhoushan, Zhejiang Province, China. There is speculation that near Zhoushan or elsewhere, the 2019-nCoV may have originated. The new coronavirus is reported to be isolated from stallholders working at the Wuhan, South China Seafood Market for the first time. It is presumed that wild animals or rodents to be the intermediate hosts of 2019-nCoV, evolved from bat hosts, are also sold in this market. It was speculated that it was possible to sell the intermediate hosts (wild mammals) to the seafood market in Wuhan. In the phylogenomic tree, the novel corona virus have long branches (0.09), suggesting that the SARS-CoV-2 possibly share bat hosts. Similarly, for the bat hosts, the SARS-CoVs (human SARS-CoVs) 2003 had shorter branches (0.03). This suggests that closer to 2019-nCoV, there may be more bat viruses. Based on their phylogenetic relationships, it is possible to divide the 27 2019-nCoV isolates studied in this analysis into at least 6 genotypes which were collected predominantly from four separate locations including Thailand and the three cities from China: Wuhan, Zhejiang, and Guangdong. All of these were observed in individuals who lately visited and had contact with residents of Wuhan. Genotypes VI, V, and IV (Guangdong and Shenzhen) are found in the basal branch of the 2019-nCoV phylogenetic tree, suggesting that the first groups to be infected were those patients infected with these CoV genotypes. In samples from Guangdong province, 3 genotypes were present, suggesting that the six strains got infected by covid-19 from different locations of Wuhan. In Zhejiang Province, two types of genotypes were

detected, indicating that both of the strains were infected at separate locations in Wuhan. In Nonthaburi, Thailand, the two detected strains are of the exact genotype having originated in Wuhan from the same area. Diversification of the sequences between the 24 Covid-19 strains is minimal and they are difficult to distinguish in the phylogenomic tree. The degree of diversification of 2019-nCoV is much smaller compared to the frequent rapid reassortment and mutation of avian influenza. However, the 27 isolates can be grouped into 6 genotypes, suggesting that SARS-CoV-2 has mutated in various patients. The extent of this variation is a cause of concern in the future. Therefore, it is important to be alert for any obvious, rapid mutation (Zhang et al., 2020). It is hypothesized that SARS- CoV's progenitor was produced by recombination within bats and then transmitted to farmed civets or other mammals, which then transmitted the virus by faecal-oral transmission to civets. The virus spread to market civets as the virus-infected civets were shipped to the Guangdong market and developed more mutations before spilling into humans (Cui et al., 2019).

1.8 Incubation period

An incubation time for COVID-19 between 2 and 10 days has been stated by the WHO. Some research, however, indicates that the incubation phase can last longer than two weeks and that a very sustained time of incubation may represent double exposure (Gennaro et al., n.d.). In three different studies, 5.2 days, 5.1 days and 4 days were described as the incubation period for COVID-19. Even then, this time was stated to be between 1 and 19 days in a family cluster of 5 patients. These data suggest that the COVID-19 incubation time was comparable to MERS and SARS and is much prolonged than influenza (Article, 2020). The incubation time for serious cases may vary with respect to moderate cases and may depend on the patient's age and immune response. For patients more than 70 years, this period appeared to be shorter than those aged below 70 years (Wang et al., 2020a).

1.9 Route of transmission

Covid-19 has been shown to have higher transmissibility values. As Covid-19's effective reproductive number (R) is 2.9, which is far higher than the reported effective reproductive number (R) of SARS-CoV having higher pandemic risk than SARS-CoV (1.77) (Hamid et al., 2020). Despite the fact that certain species are believed to be the sources of the virus, human to human transmission along with SARS CoV and MERS CoV is a major transmission mode for SARS CoV-2. Droplet and touch transmission are recognized transmission routes of COVID-19. It can be transmitted by both direct transmission indicating droplet delivery and human-to-human communication and indirect communication which includes objects that are contaminated with virus and airborne contamination (Lot et al., 2020). Nevertheless, for the management of diseases in the population, it is important to clarify or exclude other potential transmission paths (Article, 2020).

Airborne transmission

The person to person contamination of SARS-CoV-2 takes place primarily through respiratory droplets when an infected person coughs, sneezes or even talks or sings. Typically, droplets cannot travel more than six feet and then remain for a short time in the air. Anyhow, SARS-CoV-2 stays intact and contagious in droplets and can remain suspended in the air for up to three hours. Therefore, proper application of disinfectant (particularly in toilets), airborne isolation and ventilation in the room could lessen the rate of spread of covid-19 by aerosol. If a human contacts a SARS-CoV-2 contaminated surface, and then the hands get into close contact with any of the mucous membranes of body such as the nose, mouth or eyes COVID-19 may occur (Lot et al., 2020). Various studies has shown that SARS CoV-2 was observed in experimental models for up to 3 hours in air samples. Gou et al. reported that in several different ward places, air samples were positive. However, when Cheng et al. obtained 8 air samples with or without a surgical mask at a distance of 10 cm from the

patient's chin, they were not able to detect SARS CoV-2. While some environmental samples were positive for SARS CoV2, the other analysis showed that all air samples were negative.

According to a joint WHO-China study, SARS-CoV-2 RNA has been isolated from blood and stools, samples and live stool-cultivated in some COVID-19 patients. Still the mode of fecal oral transmission has not seem to be a crucial factor in propagation of the infection (Lot et al., 2020).

Another important point for transmission is intrauterine or transplacental transmission from infected pregnant women to their fetuses (Article, 2020). As pregnant women are at an elevated risk of COVID-19 contraction, it is as important to find suitable treatment for children as it is important to investigate the possibility of vertical transmission. Also reports stated that immunoglobulin M antibodies of SARS-CoV-2 were observed to be present in blood samples of newborn infant. Therefore, possibility of transmission of SARS-CoV-2 from mother to fetus cannot be excluded (Lot et al., 2020).

1.10 Transmission period

Prior to the onset of symptoms, people infected with SARS CoV-2 could be infectious. In a report, 13% of the patients were infectious prior to symptom onset. 3 out of 8 laboratory confirmed patients were asymptomatic in a family cluster. The problem of touch tracing will be pre-symptomatic transmission. These types of reports suggest that asymptomatic carriers have emerged as a significant focus group which should be taken into account in disease control. Again, viral shedding may be for extended than it was previously considered. The median period of it was reported to be 20 days (IQR 17.0-24.0) in a study of 191 adult patients. Also, the longest reported period of viral shedding in survivor patents was 37 days. In a post-discharge monitoring study of infected patients after clinical recovery, two of the patients were reported to be positive after clinical recovery (BULUT & KATO, 2020).

1.11 Transmissibility and R0

Early reports from China suggest that the reproductive cycle for COVID-19 was between 2.2 and 2.7 days. This implies that every 6-7 days, the number of infected individuals would double. This preliminary evidence is also backed by the reproductive number of the Diamond Princess Cruise Ship outbreak. Sanche et al., however, discovered a serial period of 5.7 days (95 % CI, 3.8-8.9 days). In another analysis, which opted to use the real-time reproduction number (Rt) instead of the simple reproduction number (R0), Yuan et al., showed that their Rt values were 3.1, 4.43, 6.56 and 3.95, respectively, for Italy, Germany, France and Spain. Liu et al . found that in their study of 14 studies, the average R0 was 3.8 (1.4-6.49). This study also showed that different Ro values can be determined even in the same geographic area by using different methods and assumptions. We need more details to establish a more precise R0 value.

1.12 Case fatality rate

According to the WHO Condition Report of 13 April 2020, the total case fatality rate was 6.3. A significant difference is marked in the rates of mortality among countries. In countries with older populations, this rate has been noted to be substantially higher. The median age of people dying from COVID-19 in Italy was 78 years, while it was 62 years for the survivors. The estimated fatality rate in Turkey is 2.1%, which is a major concern to be taken into account. COVID-19-related mortality is a multifactorial process and higher mortality may be attributed to underlying conditions and health care pressures as well as ages (Cemal B, Yasuyuki K, 2020).

It is now a well-known fact that mortality rises with advanced age. It is also well known that performance among these age groups in preventing COVID-19 directly influences the mortality rate in various countries. Moreover, Chinese reports have shown that mortality rates

in older patients could be 3 times higher, particularly those over 80 years of age. ICU mortality was 26 percent in an Italian study, while it was 36 percent after 65 years of age. The median days between onset of symptoms and death have been shown to be lesser in older infected patients, which is another significant point. As of 7 April 2020, 83% of all COVID-19 related mortality in Italy were recorded in the 70 plus age group. While the overall mortality rate was 0.9 percent in a Korean survey, that of patients aged 80 and over was 9.3%. There have also been similar findings recorded from the USA (Cemal B, Yasuyuki K, 2020). The denominator is a significant obstacle in correctly measuring the CFR: the number of persons that are afflicted with the virus. The denominator may be left off from asymptomatic cases of COVID-19, patients with minor signs, or persons who are misdiagnosed, due to its underestimation and overestimation of CFR. Although extremely transmissible, the COVID-19's CFR (Case fatality Rate) tends to be lower than SARS (9·5 %) and respiratory syndrome in the Middle East (34·4 %), but higher than influenza (0·1 %) (Rajgor et al., 2020).

Risks for disease and death

The development of the disease can be rapid having the median survival time in advanced elderly patients can be as low as 5 days. Hypertension, diabetes mellitus, cardiovascular disorders and respitory diseases were the most prevalent comorbidities in a meta - analysis that analyzed 46,248 patients from eight studies. Another result from this research was that it was more likely that these co-morbidities were found in serious patients. Another meta-analysis found that the majority were patients of hypertension, cardiovascular disorders, diabetes mellitus, smoking, chronic pulmonary obstructive disorder, malignancy, and chronic kidney disease (Cemal B, Yasuyuki K, 2020). Chen and colleagues note in a different analysis on the first 799 individuals with disease admitted to a hospital isolation ward in Wuhan, China, for patients with serious or critical covid-19. The investigators compared the

features of 113 (14.4%) patients who have died so far with those of 161 patients who have survived, observing that those who died were 17 years older on average (with no deaths within those under the age of 40 and without deaths among those under the age of 40. 16.8% of deaths from 40-60 years of age), are more likely to be male, and are more likely to be comorbid, such as high blood pressure, diabetes, cardiovascular disease, or chronic lung disease (Jordan et al., 2020).

1.13 Clinical features of patients infected in covid 19:

Fever, dry cough, tachypnea, and shortness of breath are widely known as the first symptoms. Intestinal signs in Covid-19 infected patients are rarely assessed. Additionally, nausea, confusion, fatigue, chest pain were also identified as covid-19 symptoms in another study. Some signs include pain in the mouth, sneezing, nasal inflammation, development of sputum, anosmia and dyspepsia, skin rash, finger or toe discoloration, and viral conjunctivitis. The incidence of cytokine storms, sepsis and RNAaemia in covid-19 has been demonstrated in several laboratory studies. Elevated level of lactate dehydrogenase, C-reactive protein, creatine kinase, aspartate aminotransferase, alanine transaminase, C-reactive protein, creatine kinase, erythrocyte sedimentation rate, white blood cell count, D-dimer level, procalcitonin, urea, and creatinine have been shown in clinical laboratory tests. In COVID-19 patients, reductions in hemoglobin, eosinophil count, lymphocyte count and serum albumin were observed. Ground-glass opacity in the lungs has been the most common radiological observation in infected patients. SARS-CoV-2 has the potency to affect the cardiovascular system, the gastrointestinal tract and cause acute kidney failure (Lot et al., 2020).

Children

Children infected with covid-19 have shown to have milder effect and improved clinical results, unlike adults. Among infected patients below 18 years especially children below 1

year of age tend to have the greatest risk of experiencing a serious type of the disease. While early findings found that children infected with covid-19 were less prone to have serious symptoms than other age groups. Whereas, another study has shown that children are as likely as adults to experience COVID-19. For children, however, intervention and seeking adequate care is as critical as for adults (Lot et al., 2020). Insights into less serious pathophysiological pathways in children may be useful for adults in high and elderly people to devise therapeutics. Early closure of schools and day-care centers resulted in less frequent exposure and, thus, decreases children's infection rate. ACE-2 which is the primary target of SARS-CoV-2 C receptor expression decreases with age by limiting angiotensin-2 mediated pulmonary capillary leak and inflammation. ACE-2 has lung protective effects. High and persistent viral loads are associated with serious COVID-19 illness in adults. Because of qualified immunity, children have a high innate immune response, leading to possibly rapid regulation of infection at the site of entry. In extreme infections, which are not seen in infants, adult patients exhibit suppressed adaptive immunity and defective over-active innate immune response. These may be linked with elderly immune-senescence. Excellent pediatric alveolar epithelium regeneration potential can lead to early recovery from COVID-19. Children have risk variables, such as co-morbidities, alcohol, and obesity, less often. But young infants and children with pre-existing diseases can be high-risk classes and need to be monitored carefully. Children lack studies explaining immune-pathogenesis in COVID-19 and require urgent care (Behl et al., 2020).

1.14 Long term clinical manifestation of the infection

For COVID-19, various reports, including cough, fever, sore throat, shortness of breath, diarrhea, and exhaustion have been identified typical clinical manifestations. Nonetheless, there is massive evidence that patients infected with COVID-19 also have cardiac and neuropsychiatric complicacy. Report of a research indicated that neurological signs were

observed in about 36% of patients. This research states that in acute cases of COVID- 19, seizures, impairment of consciousness and various other neurological disorders have commonly appeared. This requires involvement of direct and indirect both type of nervous system activity. Many case studies have been conducted to find out multiple neurologic disorders after this report. Anosmia, ageusia, stroke, acute necrotizing hemorrhagic encephalopathy, acute inflammatory demyelinating polyradiculopathy (AIDP), toxic metabolic encephalopathy, headache, myalgia, central respiratory failure, myelitis, ataxia and multiple neuropsychiatric symptoms are the recorded manifestations (Jasti et al., 2020). Viruses in general can activate a variety of positive and negative host responses once within the human body. These responses involve apoptosis, autophagy, stress response and innate immunity. Though, at least 80% of individuals afflicted with SARS-CoV-2 are suspected to have an asymptomatic or moderate symptom which is definitely owing to the activity of good response. These healthy responses activate to stimulate the inherent immune response of the body by triggering the antiviral defensive mechanisms of the body which consists of natural killer cells, antiviral T cells and interferon induction (IFN). Unfortunately, patients with compromised health problems such as cardiovascular and pulmonary probiotics, diabetics, obesity, hypertension, chronic obstructive pulmonary disorder (COPD), pulmonary fibrosis, asthma, and interstitial lung impairment will undergo more serious pulmonary disease in around 20% of infected individual, including the immune suppressed and aged. A significant thing to mention is that ARDS happens later in the course of the condition and is followed by acute lung injury (ALI) (Wu et al., 2020).

There is a severe inflammatory reaction in critical COVID-19 patients. Multiple immune pathways and pro-inflammatory cytokines in peripheral blood mononuclear cells (PBMC) in bronchoalveolar lavage fluid (BALF) were caused by SARS-CoV-2 infection, signaling prolonged inflammation along with cytokine storm. Prolonged cytokine release caused by

SARS-CoV-2 infection associated with lung damage and pathogenesis of covid-19. It is estimated that nearly 20% of infected patients with more serious SARS-CoV-2 infection are more likely because of genetics, epigenetics and various other causes including weaken innate immune response to the virus combined with elevated viral load contributing to cytokine storm, inflammatory stress response and severe ARDS-secondary lung cell damage. While there is a strong awareness that in COVID-19 patients, the respiratory system is significantly impaired, research shows effects in other organs as well. Also, emerging data suggest that SARS-CoV-2 can cause other major organs including the brain and heart, to be affected. Almost 20% of infected hospitalized patients acquire symptoms of cardiovascular injury. In addition, neurological effects have been reported in patients, and both humans and laboratory animals have been infected with SARS-CoV-2 in the brainstem (Wu et al., 2020)

1.15 Aim of the study:

The aim of the study is to summarize the currently available clinical treatment interventions in conjunction with their mechanism of action and therapeutic effects.

Chapter 2

Pathophysiology of Covid-19

2.1 SARS-CoV-2 entry and replication

There are 5 stages in the life cycle of the virus with the host: attachment, penetration, biosynthesis, maturation and release. They join host cells by endocytosis or membrane fusion (penetration) once viruses bind to host receptors (attachment). Viral RNA joins the nucleus for replication once the viral contents are released within the host cells. To produce viral proteins (biosynthesis), viral mRNA is used. Then, new viral particles (maturation) are formed and released. Four structural proteins are composed of coronaviruses; spike (S), membrane (M), envelope (E) and nucleocapsid (N). The Spike consists of a transmembrane trimetric glycoprotein, which defines the diversity of coronaviruses and host tropism, protruding from the surface of virus. The S protein has been identified as an essential factor for the entry of the virus into the host cell. The spike protein binds to the host cellular receptor that is ACE2 receptor for SARS-CoV and SARS-CoV-2. Initially, the entry of SARS-CoV inside host cells was established to be achieved by direct fusion of membrane between the plasma membrane and the virus. Belouzard et al. found that membrane fusion and viral infectivity were mediated by a crucial proteolytic cleavage event of the SARS-CoV S protein at position (S2'). The Spike consists of two functional subunits; the S1 subunit is responsible for binding to the receptor of the host cell, and the S2 subunit is responsible for viral and cell membrane fusion. As a functional receptor for SARS-CoV, angiotensin converting enzyme 2 (ACE2) has been identified. Structural and functional research has shown that the spike protein of SARS-CoV-2 is also connected to ACE2. The ACE2 expression was elevated in the lung, heart, kidney, bladder and ileum. Also ACE2 expression was high in pulmonary epithelial cells in the lungs. Whether SARS-CoV-2 binds to any other

receptor or not needs more investigation requires. Following the attachment of SARS-CoV- 2 to the host membrane protein, the S protein undergoes protease cleavage. A model was proposed with two step sequential two-step protease cleavage for the purpose of activating SARS-CoV spike protein. This model is comprised of priming cleavage at the S1 / S2 cleavage site with activation of cleavage at the S'2 site which is a position adjacent to the S2 subunit fusion peptide. The S1 and S2 sub-units remain non-covalently bound after cleavage at the S1 / S2 cleavage site and the distal S1 sub-unit contributes to the stabilization of the membrane-anchored S2 sub-unit at the pre-fusion. Subsequent cleavage at the S'2 site is likely to trigger the membrane fusion spike via permanent, conformational changes. The coronavirus spike is rare among viruses because it can be split and triggered by a number of different proteases. The presence of furin cleavage site ('RPPA' sequence) at the S1/S2 site is the characteristics distinctive to SARS-CoV-2 among coronaviruses. In a dramatic contrast to the SARS-CoV spike, which was incorporated into assembly without cleavage, the S1 / S2 site of SARS-CoV-2 was entirely subject to cleavage during bio-synthesis (Shereen et al., 2020). An irregular two-step furin activation for membrane fusion has also evolved with MERS-CoV. Besides membrane fusion, SARS-CoV entry was also mediated by clathrin dependent and independent endocytosis. The viral RNA genome is released into the cytoplasm after the virus reaches the cells and is translated into two polyproteins and structural proteins, after which the viral genome starts replicating. The newly developed envelope glycoproteins are incorporated into the ER or Golgi membrane and the combination of genomic RNA and nucleocapsid protein forms the nucleocapsid. Then, the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) is germinated by viral particles. Finally, the vesicles that hold the particles of the virus combine with the plasma membrane to release the virus as given in figure 4 (Madabhavi et al., 2020). The wide ranging expression of furin contributes to extreme pathogenicity of this virus (Yuki et al., 2020).

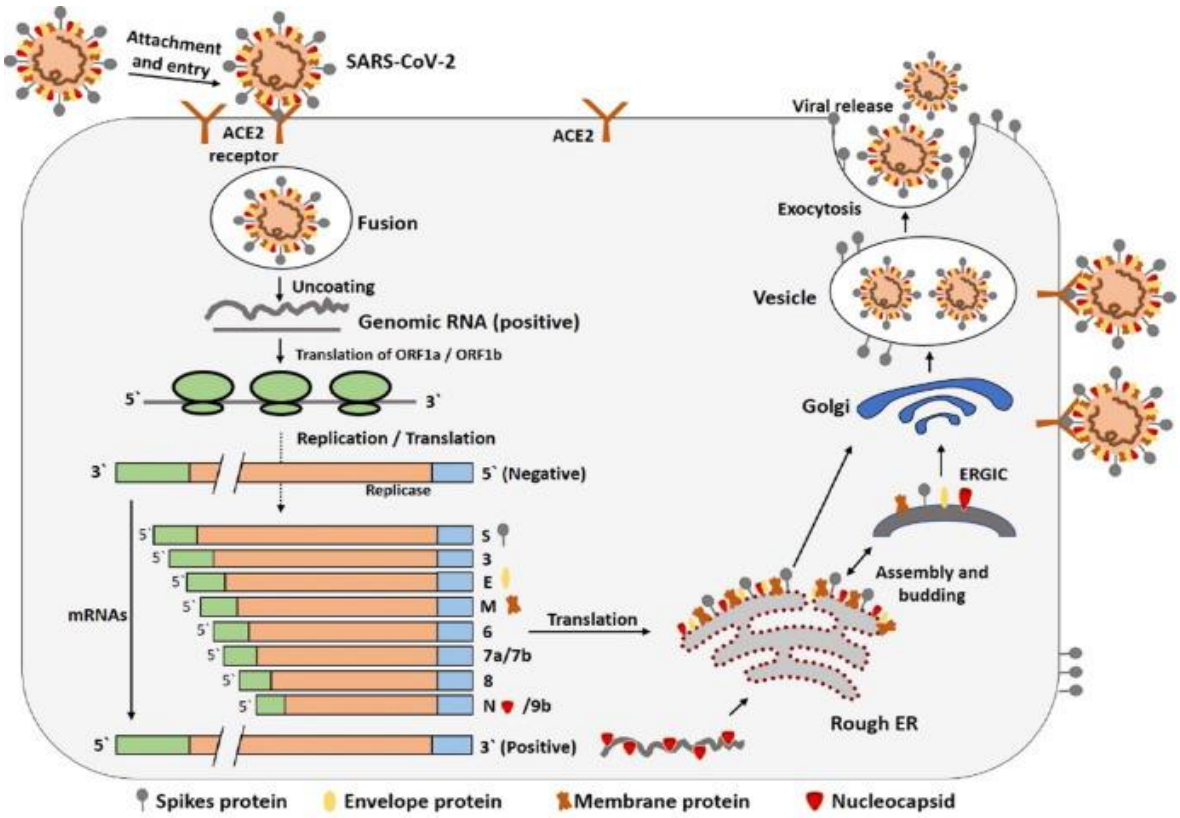

Figure 4: Life cycle of SARS-CoV-2 consists many stages. At staring of the life cycle of SARS-CoV-2, S protein binds to ACE2 receptor in host cell. After receptor binding, viral envelope fusion is influenced by conformational change in S protein. This happens in endosomal pathway. Then RNA is released by SARS-CoV-2 into the host cell. Genome RNA is converted into viral replicase polyproteins. These proteins are then cleaved by viral proteinases into tiny products. A series of subgenomic mRNAs are formed by polymerase. In the ER and Golgi, viral proteins and the RNA genome are finally assembled into virions and then transported through vesicles and released from the cell (Yuki et al., 2020).

2.2 ACE2 expression

In human physiology, ACE2 is a homologue of angiotensin converting enzyme. It plays an essential part in the renin-angiotensin-aldosterone (RAAS) mechanism which includes the blood pressure regulation also homeostasis of electrolytes. The liver-generated angiotensinogen is activated by renin and results in the development of angiotensin I (Ang I).

Consequently, ACE is an enzyme that act by catalyzing Ang I to Ang II transfer. The active component of RAAS which is Ang II, exerts its activity by its effects primarily through type 1 angiotensin II receptors (AT1R). ACE2 regulates bradykinin metabolism in the lungs in addition to its roles in RAAS by inactivating bradykinin. Thus it inhibits symptoms such as vasodilation and vascular permeability elevation. ACE2 has been recognized as a primary regulator of dietary amino acid homeostasis in the gastrointestinal tract, expression of antimicrobial peptide, local innate immunity and microbial ecology of gut. In reality, gut microbiota transplantation from ACE2 knockout mice resulted in an elevated tendency of developing serious inflammation in colon lining (Bourgonje et al., 2020). Additionally in its peptidase domain, ACE2 consists of a structural dimer of two units which facilitates the RBD. Polar interactions promote communication between ACE2 and SARS-CoV-2. An arch shaped helix of the ACE2 peptidase domain interacts with the S protein's loop region of RBD. The other helix and loops bind the antiparallel strands to the RBD and organize the domain of peptidase. The amino acid interactions found in the SARS-CoV-2 RBD and the ACE2 peptidase domain are considered as essential elements of the nature of the inhibitor. SARS-CoV-2 amino acids have been found to interact with ACE2 at the amino acid level. When compared to SARS-CoV, the binding affinity of the RBD domain of SARS-CoV-2 and PD of ACE2 is greater. It was stated that the amino acid LYS417 had a salt bridge interaction with ACE2's ASP30 in SARS-CoV-2. The positive charged patch led to the electrostatic potential introduced by LYS417 in SARS-CoV-2 and absent in SARS-CoV on the surface of RBD (Chauhan et al., 2020).

2.3 The host defense against SARS-CoV-2

Early in infection, via the viral structural spike (S) protein that attaches to the angiotensin-converting enzyme 2 (ACE2) receptor, SARS-CoV-2 targets cells, such as nasal and bronchial epithelial cells and pneumocytes. Type 2 transmembrane serine

protease (TMPRSS2) present in the host cell, promotes viral uptake by cleaving ACE2 also by activating the SARS-CoV-2 S protein. This facilitates the entry of the virus into the host cell. In addition, lymphopoiesis is disrupted by the inflammatory response consisting of both the type of innate and the adaptive immune response due to which lymphocyte apoptosis increases. In extreme COVID-19, immunological research is mainly published with patients. Lymphopenia, especially the reduction in peripheral blood T cells, has been documented in patients with serious diseases. Elevated plasma concentrations of proinflammatory cytokines, including interleukin (IL)-6, IL-10, granulocyte colony stimulating factor (G-CSF), monocyte chemo-attractant protein 1 (MCP1), macrophage inflammatory protein (MIP)1 alpha, and tumor necrosis factor (TNF)-alpha were recorded in patients with serious diseases. SARS-CoV-2 causes infection to endothelial cells of pulmonary capillary along with epithelial cells which leads to the response after inflammation and inducing an influx uptake of monocytes and neutrophils. Autopsy reports have shown alveolar wall to go through diffuse thickening with infiltrating space of mononuclear cells and macrophages in addition to endothelialitis. After early-phase acute respiratory distress syndrome (ARDS) follows pulmonary edema that fills the alveolar spaces with hyaline membrane formation. Bradykinin dependent lung angio-edema can lead to death. Collectively, the characteristic features of COVID-19 are destruction of endothelial barrier, hindrance in oxygen delivery to alveolar capillary along with impairment of the ability of oxygen diffusion. Sudden activation of severe coagulation and intake of blood clotting factors occur in severe COVID-19. A Wuhan, China, study suggested that 71% of 183 infected individual who died from COVID-19 met diffuse intravascular coagulation requirements. Inflammation of lung tissues and endothelial pulmonary cells can progress to the formation of microthrombi contributing to a high incidence of thrombotic complications

in severely ill patients, such as pulmonary embolism, deep venous thrombosis and thrombotic arterial complications (e.g. limb ischemia, ischemic stroke, myocardial infarction) (Wiersinga et al., 2020). In parallel to respiratory symptoms, pulmonary thrombosis and embolism has been found in serious illnesses. This is associated with the observation that in serious diseases, elevated d-dimer and fibrinogen levels have been observed. The endothelium work involves encouraging vasodilation, fibrinolysis, and anti-aggregation. Hypercoagulable profiles shown on serious diseases are likely to suggest severe endothelial damage because endothelium plays a critical role in thrombotic activity (Yuki et al., 2020). The development of viral sepsis can further lead to multiple organ failure, identified as life-threatening dysfunction of organs due to a dysregulated host response to infection (Wiersinga et al., 2020).

2.4 Role of antigen in coronavirus infection

While the virus reaches the cells, the antigen presentation cells (APC), which are a core part of the anti-viral immunity of the body, will be presented with its antigen. The main histocompatibility complex (MHC or human leukocyte antigen (HLA) in humans) is presented by antigenic peptides and then recognized by cytotoxic T lymphocytes (CTLs) specific to the virus. Therefore, it will aid our understanding of COVID-19 pathogenesis by understanding the antigen presentation of SARS-CoV-2. Unfortunately, there is still no study on it, and we can only obtain some knowledge from previous SARS-CoV and MERS-CoV studies. SARS-CoV antigen presentation is primarily dependent on the molecules of MHC I, but MHC II also contributes to its presentation (Madabhavi et al., 2020).

Humoral and cellular immunity

Subsequently, antigen activates the humoral and cellular immunity of the body which is regulated by B and T cells unique to the virus. The antibody profile against the SARS-CoV

virus has a standard IgM and IgG development pattern, similar to common acute viral infections as conveyed in figure 5. At the end of week 12, SARS-specific IgM antibodies vanish, while IgG antibodies may remain for a long period of time, which suggests that IgG antibodies can deliver a primary protective role. Again, SARS-specific IgG antibodies are mainly S and N protein specific. The most recent study indicates that the amount of CD4+ and CD8+ T cells identified in the peripheral blood of patients infected with Covid-19 is substantially minimized, while its status is immoderate, as shown by the elevated proportion of double-positive fractions of HLA-DR and CD38. In a similar manner, response in acute phase patients with SARS-CoV is collaborated with a significant decrease in CD4+ T and CD8+ T cells. Even without the presence of any antigen, CD4+ and CD8+ memory T cells can be persistent for few years in part of individuals recovered from the SARS-CoV and may cause proliferation of T cell, DTH response, and IFN-γ development. After six years of infection with SARS-CoV, memory responses of T cells uniqe to the SARS-CoV S peptide library could still be detected in 14 out of the 23 recovered SARS patients. These findings can be used to generate further information on the rational design of SARS-CoV-2 vaccines (Madabhavi et al., 2020).

2.5 Cytokine Storm in COVID-19

A major study has shown that, ARDS is the leading cause behind COVID-19 deaths. The typical immunopathological case for infections with SARS-CoV-2, SARS-CoV and MERS-CoV is ARDS. Cytokine storm is a fatal unregulated systemic inflammatory response of the body. It results from the release of enormous amounts of pro-inflammatory cytokines (IFN-alpha, IFN-γ, IL-1β, IL-6, IL-12, IL-33, TNF-alpha, TGFβ etc.) and several chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10 etc.) as shown in figure 5 released by immune effector cells from SARS-CoV infection, is one of the main mechanisms for ARDS. Individuals with extreme MERS-CoV infection, comparable to those with SARS-

CoV, display elevated serum levels of IL-6, IFN-aa, and CCL5, CXCL8, CXCL-10, relative to those with mild-moderate disease. The cytokine storm can cause the immune system to affect the body violently, cause ARDS along with multiple organ failure which eventually takes turn to fatality in serious cases of SARS-CoV-2 infection very similar to what happens in SARS-CoV and MERS-CoV infections (Madabhavi et al., 2020).

2.6 Coronavirus immune evasion

SARS-CoV and MERS-CoV use various methods to prevent immune responses in order to better grow in host cells. By pattern recognition receptors (PRRs), the evolutionarily established microbial structures called pathogen-associated molecular patterns (PAMPs) can be identified. SARS-CoV and MERS-CoV can, however, induce the formation of double-membrane vesicles lacking PRRs and then replicate in these vesicles, thereby preventing their dsRNA from being detected by the host. IFN-I (IFN-alpha and IFN-beta) acts by showing a protective effect on infection with SARS-CoV and MERS-CoV. Although in case of infected mice the IFN-I pathway is inhibited. MERS-CoV accessory protein 4a can, by direct interaction with double-stranded RNA, block the induction of IFN at the level of MDA5 activation. Furthermore, ORF4a, ORF4b, ORF5, and MERS-CoV membrane proteins inhibit IFN regulatory factor 3 (IRF3) nuclear transport and IFN β promoter activation. The coronavirus can also affect the antigen presentation. After MERS-CoV infection, for instance, gene expression linked to antigen presentation is down-regulated. Therefore, in its treatment and unique drug production, disrupting the immune evasion of SARS-CoV-2 is crucial (ZHANG et al).

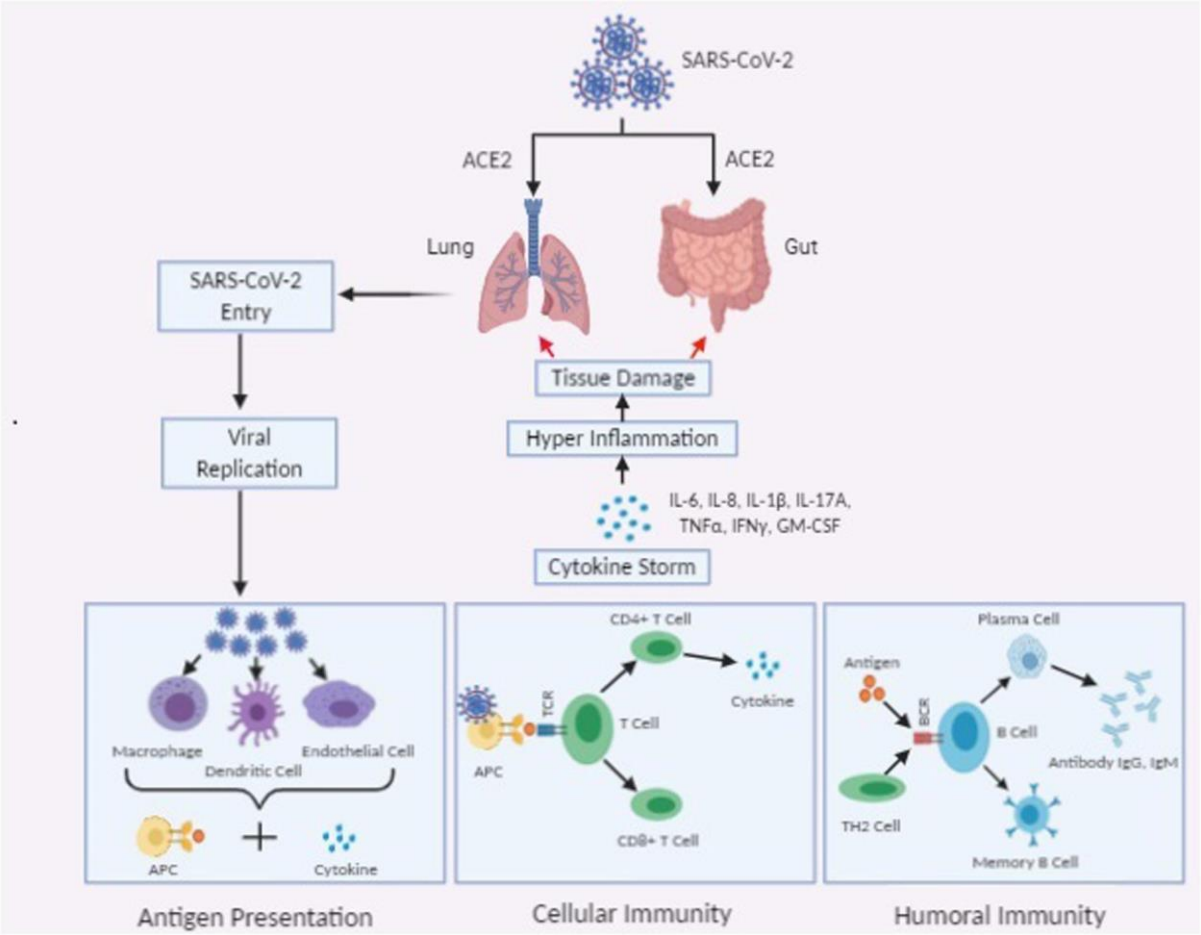

Figure 5: Immunopathogenesis of SARS-CoV-2 virus (adapted from Chatterjee et al., 2020).

Chapter 3

Potential therapeutic drugs For Covid-19

Due to the absence of specific and established treatment regimens, interventions against COVID-19 infections include early detection, prompt notification, isolation and supportive treatment, are essential lines of treatment. Present social activities include the prompt distribution and management of disease knowledge and social directives and person dependent practices such as strengthening personal sanitation, wearing face coverings or masking, sufficient rest, and ensuring spaces with well ventilation as some of the first line of acts to fight against the COVID-19 pandemic. Current health treatment requires infection control, appropriate control procedures and supportive treatment, including additional oxygen and mechanical ventilation. Though several countries and companies are working for a SARS-CoV-2 vaccine, it will take certain amount of time to cover the mass population. Pressure has now been developed to find another medicine to fight the virus effectively. This campaign has mainly concentrated on repurposing generic medications. Many medicines that have shown effectiveness in treating the 2019-nCoV infection have been noted by WHO health authorities. Antivirals possess the ability to weaken the viruses to invade cells and refrain them from spreading or transferring from infected cells to others, have been the main cure so far for this virus (Abd El-Aziz & Stockand, 2020). The treatment of patients with SARS-CoV-2 is currently being considered usually repurposes the medicinal medications available and is focused on symptomatic symptoms. In the treatment regimen, antibiotics, antiviral therapy, systemic corticosteroids, and anti-inflammatory medications are frequently used for ARDS, accompanied by secondary infections. Neuraminidase inhibitors, RNA synthesis inhibitors, convalescent plasma and conventional herbal drugs were also used in the treatment of COVID-19 in addition to antiviral interferers and antibiotics. The feasibility of

these treatment regimens, however, needs to be confirmed by properly planned clinical tests (Wu et al., 2020).

3.1 Antiviral drugs

There is no specific successful antiviral therapy for COVID-19 at present. There is an immediate need for appropriate medications, while most COVID-19 infected patients experience a mild to moderate infection, up to 5-10% may have a serious and potentially life threatening disease. Optimized patient safety is the foundation of healthcare. More than 300 clinical trials have been undertaken, and others will be released in the next couple of months. To test remdesivir, hydroxychloroquine and lopinavir-ritonavir with or without interferon beta, WHO has launched a 'Solidarity' clinical trial for SARS-CoV-2 medication. Several other antiviral and immunomodulating drugs are in varying phases of Covid-19 assessment. It is highly advised that patients be enrolled into ongoing research at the present, which will offer most important information on the effectiveness and safety of multiple interventions for COVID-19, provided that it was not possible to decide whether the advantages outweigh the harms for other procedures. Antivirals would not be known to be successful or safe to treat COVID-19 unless used throughout the form of randomized controlled trials. Nearly 30,000 people acquired Ebola viral disease during the 2014 Ebola outbreak, and various therapies, including hydroxychloroquine, favipiravir, remdisivir, monoclonal antibodies, antisense RNA, and convalescent plasma, among several others were tested against this virus. The aim was to decide which was successful against Ebola with such a great range of clinical interventions given to infected patients. Ultimately, none appeared to be successful or safe, precisely as nearly every experiment was single-group procedures without parallel controls, resulting in no conclusive effectiveness or safety inference. The vast majority of COVID-19 patients would perform better without further medication, so there's no need for therapies in most cases. To wait until infected patients get seriously ill before initiating care, however,

could allow them to skip an initial phase of treatment within which the progression of the disease is even more possible. It has been understood that antiviral treatment is more likely to be effective for both influenza and SARS when started early during the course of the disease. Adverse outcome indicators can be effective in forecasting who would perform worse and who may benefit more from application of early antiviral drugs. It is rational to initiate antiviral therapy as early as possible in patients with COVID-19 as well, particularly in the co-existence of adverse outcome predictive variables. From current understanding and observation, concurrent use of antiviral medications for COVID-19 patients should be considered also potential adverse effects also drug-drug interactions should be considered. (Şimşek Yavuz & Ünal, 2020)

Hydroxychloroquine and Chloroquine

Hydroxychloroquine (HCQ) and Chloroquine (CQ) are two drugs that are commonly used as antimalarial, antiviral, and antirheumatic agents (Bourgonje et in 2020). In vitro findings and limited clinical trials indicating antiviral effect of these drugs to fight against SARS-CoV-2 infection have recently emerged. It was assumed that beneficial effects resulted from blocking the entry of virus into host cells by elevating endosomal pH and interfering with ACE2 glycosylation. Some cellular activity and molecular pathways associated with activation of immune system may be blocked by hydroxychloroquine and chloroquine. Inhibition of expression of MHC class II, antigen appearance and immune activation also inhibition of the development of different pro-inflammatory cytokines including IL-1, IFNa and TNF. These cytokines may defend against resorption that is mediated by cytokine interfering with the signaling pathways of the toll like receptor (TLR7 and TLR9) with the activity of cyclic GMP-AMP (cGAMP) synthase, partially by aggregation of phagocytic cell lysosomes and auto phagosomes. Analogs of Chloroquine are weak diprotic bases and capable of penetrating and concentrating through organelles such as endosomes and

lysosomes that are acidic. This phenomenon contributing to enhanced intra-vesicular pH, preventing endosome prevention and preventing cell fusion of virus. The possible role of these medications in the therapy of COVID-19 has been translated into this pathway. In addition, experiments have also shown that these medications interact with ACE-2 receptor glycosylation, which inhibits the localization of the SARS-CoV-2 receptor and subsequent infection. (Şimşek Yavuz & Ünal, 2020). Two studies conducted in France revealed that HCQ, especially when combined with Azithromycin, could lead to a reduction of the viral load within 6 days. However, some methodological constraints hampered these studies. Similarly, two Chinese studies were conducted: no substantial difference was reported by one study between treatment with HCQ and usual standardized supportive control in nasopharyngeal viral carriage, while the other study showed a lesser period of clinical recovery compared to placebo for patients receiving HCQ. However, it was not possible to include seriously ill infected patients in the above sample, which is essential since this relatively small group of patients is at a greater risk of extreme HCQ / CQ side effects, including hepatic insufficiency, ventricular arrhythmias, and cardiac toxicity. Indeed, recent research has raised questions about the possibility of potential hazards, as higher doses have been linked to increased mortality and a mild prolongation of the QT interval, especially when combined with azithromycin and/or oseltamivir. Another study found that in critically ill patients, HCQ / CQ could not help because its administration was not related with either a substantially lesser or a higher risk of a composite endpoint of intubation or fatality. Therefore, information on HCQ/CQ usage for COVID-19 treatment currently available are not only inconclusive but also seem far away from promising. Therefore, future prospective randomized clinical studies should assess if treatment with HCQ / CQ will be an effective therapeutic option for patients with COVID-19 and also what would be the most effective period to begin treatment within the disease course (Bourgonje et al., 2020).

Favipiravir

Favipiravir is an analog of guanine that is intended to treat of influenza. RNA-dependent RNA polymerase can be blocked by RNA viruses including Measles, Chikungunya, Yellow Fever, Ebola, Norovirus, and Enterovirus. In addition, scientists have confirmed its efficacy against Covid-19 from one recent analysis. In randomized clinical trials, patients with COVID-19 are examined to assess the effectiveness of Favipiravir + Interferon-alpha and favipiravir along with baloxavir marboxil which is an approved Influenza inhibitor that targets the cap- dependent endonuclease (Lot et al., 2020). Favipiravir is the first medication licensed by the national medical of China-administered drugs for the treatment of COVID-19. An open-label FPV control testing was performed on COVID-19 patients by Cai et al. In these studies, 35 patients received FPV treatment, and 45 patients were treated with a mixture of lopinavir and ritonavir (LPV/RTV). It was observed that FPV-treated patients tend to have quicker viral clearance and improved improvements in chest imaging than LPV/RTV-treated patients. Chang et al. performed COVID-19 patient trials by prescribing Favipiravir and arbidol. There were 240 patients in all. Among both, 120 patients received favipiravir and 120 patients received arbidol medication. It was found that after 7 days, no improvement was observed in both therapies. Favipiravir showed substantial improvement after 7 days of therapy for cough and pyrexia (Bhavana et al., 2020).

Remdesivir

In the United States the Food and Drug Administration licensed the antiviral drug remdesivir for use in adult and pediatric patients of 12 years of age and older and weighing at least 40 kilograms (around 88 pounds) for treatment of COVID-19 that only involves hospitalized patients. Remdesivir should just be provided in hospitals or healthcare settings are capable of delivering emergency care equivalent to inpatient medical care. Remdesivir is the first COVID-19 treatment to obtain approval from the FDA. Nucleoside analogs are effective

reagents in the fight against infection by viruses. Remdesivir will prevent the further proliferation of SARS-CoV, MERS-CoV and Ebola viruses in vitro as it is a well-characterized adenosine analog. Moreover, Remdesivir has the potential to be incorporated as an RNA-dependent RNA polymerase (RdRp) substrate into the progeny virus RNA chain, which inhibits viral genomes replication as shown in figure 6 and thus causes the virus to terminate maturely. Remdesivir has also been verified to substantially interfere with the achievement of the SARS-CoV-2 host cell life cycle . Clinical improvement of severely ill COVID-19 patients from a number of countries in 36 of 53 patients (68%) was reported after treatment with remdesivir in the latest study (Huang et al., 2020).

Remdesivir has been used in several clinical trials because of its excellent efficacy. The outcomes of a randomized, placebo-controlled, double-blind, multicentre trial indicated that more clinical trials need to confirm whether intravenous administration of remdesivir will shorten the time for improvement clinically in those treated earlier. However, in this clinical trial, no significant clinical upgrade were seen in the remdesivir community compared with that of placebo group .Indeed, after obtaining remdesivir by intravenous administration in the United States, an infected patient with corona virus 2019 recovered with success, which further suggests that remdesivir will in the future be rapidly used as a therapeutic treatment for corona virus 2019. Remdesivir was, however, shown some side effects in the hospitals including hypotension, elevated liver enzymes, and decreased renal function. It is not clear about the mechanism that might be responsible for the side effects of remdesivir. In order understand the mechanism of it, further study is required. Collectively, remdesivir is a moderately effective therapeutic agent candidate for anti-SARS-COV-2. The first drug for treatment of patients infected by Covid-19 was approved by the FDA.

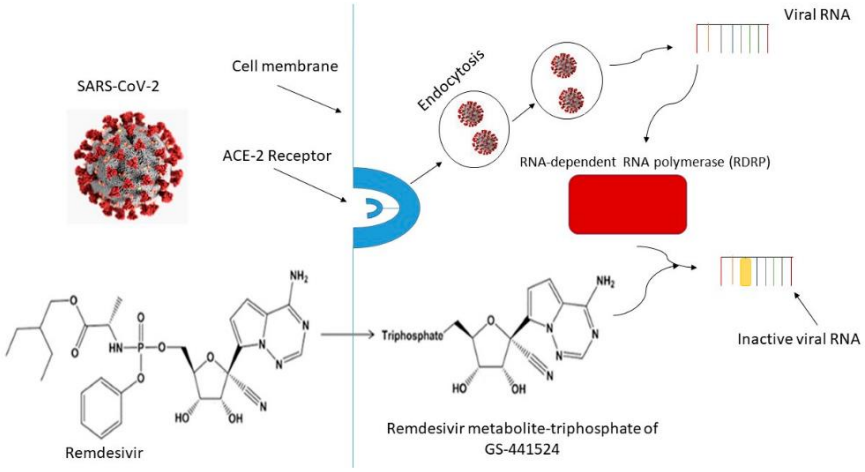

Figure 6: Mechanism of action of remdesivir by blocking RNA replication (adapted from Al-Tannak et al., 2020).

Lopinavir/Ritonavir

Lopinavir is an inhibitor of Human Immunodeficiency Virus 1 (HIV-1) protease inhibitor. Ritonavir can delay the metabolism of lopinavir in order to elevate the anti-HIV-1 effect of Lopinavir. Thus these two drugs are often prescribed in combination. Mechanism studies have shown that a combination of lopinavir and ritonavir can inactivate 3-chymotrypsin-like cysteine protease (3CLpro) which causes splits protein precursors to transform these into a number of active proteins needed for the SARS-CoV-2 life cycle. A case series consisting 10 patients revealed Lopinavir to potential of easing COVID-19 symptoms. After using lopinavir and ritonavir with arbidol combination therapy, the rate of being negative for COVID-19 at 7 days and 14 days was considerably improved. Again, there has been a decrease in the viral load of a infected patient receiving lopinavir/ritonavir combination treatment in Korea and also fully cleared in some days. In addition, a retrospective study result demonstrated lopinavir as an important medication for the treating COVID-19. However, as seen in a randomized, controlled, open-label trial, no advantage was found in COVID-19 patients undergoing combined therapy with lopinavir/ritonavir. Importantly, the National Health

Commission of China prescribed a combination of lopinavir/ritonavir for COVID-11 treatment. However, the combination of lopinavir / ritonavir can result in severe gastrointestinal effects while used for COVID-19 treatment, the cause of which still remains beyond knowledge. Of note, in conjunction with other drugs, the combination of lopinavir / ritonavir can be used to improve adverse effects including probiotics, soluble fibre, and L-glutamine (GLN) (29). In comparison with tablet form, film-coated tablet formulation of lopinavir/ritonavir produce reduced gastrointestinal adverse reactions than when administered in tablet formulations (Huang et al., 2020).

In 199 patients with Covid-19, a randomized clinical trial investigated the role of lopinavir and ritonavir: 99 of infected patients were being treated with lopinavir/ritonavir therapy while 100 of them received regular therapy. The investigators reported that patients that had been treated with lopinavir/ritonavir failed to display any remarkable difference in the risk ration of early clinical progress or a 28-day decrease in mortality. In comparative story the group of patients treated with lopinavir/ritonavir has shown clinical success than the control group getting discharged 5 days prior from the ICU. While there is a shortage of major clinical trials testing the medicinal effect of these antiviral drugs in COVID-19, there is anticipation that the available research would include patients with extreme disease only. Thus further studies in future would indicate that the effect of these antiviral medicines should be assessed earlier in COVID-19 (Bourgonje et al., 2020).

Nitazoxanide

Nitazoxanide and tozoxanide (an active metabolite of Nitazoxanide) exhibit potential to fight against SARS-CoV-2 virus. In addition to coronaviruses, it also demonstrates broad-spectrum in vitro antiviral activity against influenza, respiratory syncytial virus, parainfluenza, rotavirus and norovirus. It is suspected that this broad-spectrum antiviral effect is due to the

mechanism of action which is based on interference with host-regulated viral replication pathways rather than virus-specific pathways. By widely amplifying the cytoplasmic RNA sensing and type I IFN pathways, nitazoxanideup regulates the innate antiviral mechanisms. By controlling the specific host pathways that viruses target to circumvent cellular defenses of host body, nitazoxanide interferes with viral infection. Nitazoxanide is going through tests for clinical trials for the treatment of influenza and other acute respiratory infections because of its broad-spectrum antiviral activity (Şimşek Yavuz & Ünal, 2020).

Ivermectin

Ivermectin is a broad-spectrum antiparasitic agent approved by the FDA, which has been shown to have antiviral efficacy in vitro against a wide variety of viruses in recent years. It is reported to inhibit integrase protein nuclear import and HIV-1 replication being an inhibitor of the interaction between integrase protein of the human immunodeficiency virus-1 (HIV-1) and the importin (IMP) heterodimer which is responsible for nuclear import of integrase protein. Other acts of ivermectin have been documented, but nuclear imports of host and viral proteins have been shown to be inhibited by ivermectin.

A number of RNA viruses including influenza, dengue and West Nile viruses, have been reported to restrict infection by the use of it. Similarly, ivermectin has been shown to be successful against both in vitro and in vivo DNA virus pseudorabies (PRV) viruses, with ivermectin treatment showing improved survival in mice infected with PRV. The efficacy of ivermectin against Zikavirus was not observed, but the authors acknowledged that the limitations of the study justified the reassessment of the anti-Zika virus activity of ivermectin. Ivermectin was found to be a SARS-CoV-2 inhibitor in an in vitro analysis, with a single addition to Vero-hSLAM cells 2 h after SARS-CoV-2 infection, capable of effecting a reduction in viral RNA by ~5000 fold at 48 h. It is hypothesized that this possibly interrupts

the immune evasion mechanism of the virus by inhibiting IMP alpha / β1-mediated nuclear import of proteins of the virus. There is a need for more in vitro, in vivo and clinical trials to evaluate its function in COVID-19 management (Şimşek Yavuz & Ünal, 2020).

Galidesivir

Galidesivir is an analog of adenosine that was developed specifically to treat HCV, and in preclinical trials against several RNA viruses, including SARS-CoV and MERS-CoV, its effectiveness against Yellow fever demonstrated its antiviral function. It is now in main clinical trials to test its efficacy in healthy people. So, against SARS-CoV-2, it would be useful (Lot et al., 2020).

Arbidol

Arbidol is a non-nucleoside antiviral and immunomodulatory medication that could be selective against COVID-19 for the treatment and prevention of influenza. There are several clinical studies in progress to examine its efficacy towards COVID-19 (Lot et al., 2020).

Table 1: Investigated antivirals for therapeutic treatment of Covid-19 in clinical trial (Şimşek Yavuz & Ünal, 2020).

Groups	Name of Drugs	Mechanism of action	Dosing
Inhibitors of viral RNA polymerase	Remdesivir	Adenosine Nucleotide analogue, prodrug, RdRp inhibitor	Loading dose (Day 1): 200 mg IV as a single dose. Maintenance dose (from Day 2): 100

			mg IV once a day
	Favipiravir	Guanosinenucleotid analogue, prodrug, RdRp inhibitor	Loading dose: 2*1600mg Maintenance dose: 2* 600mg/day
Inhibitors of viral protein synthesis	Lopinavir/ritonavir	Protease inhibitor	Day 1-10: 400mg/100 mg * 2/day, orally.
Viral entry inhibitors	Hydroxychloroquine	Increases endosomal pH required for virus/cell infusion and by interferes with the glycosylation of cellular receptors.	Day 1-5: 2*200mg/day, orally
	Chloroquine		Day 1-5: 2*500 mg/day, orally
Imunomodulators	Ivermectin	Inhibition nuclear import of host and viral proteins through inhibition of importin 1 heterodimer	Day 1-5: 200 mcg/kg/day for five days.

3.2 Analgesics and anti-inflammatories

Analgesic is one of the most common medications recommended by medical professionals. They contain acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. It has been advised to consider these as the first line of analgesia and antipyretic drug for COVID-19 patients. The effect of acetaminophen on patients with Covid-19 has not been reported by any published studies. The bulk of the debate around analgesia, anti-inflammatory drugs and COVID-19 circulates surrounding NSAIDs. This started following research and guidelines linked to an increased frequency of COVID-19 infections with the use of anti-inflammatory drugs. These were postulated because of the interaction of NSAIDs with ACE. It was also proposed that the signs of infection may be obscured by NSAIDs, delaying diagnosis. Subsequent analyses, however, have shown that no published reports have shown that the use of anti-inflammatory drugs is currently associated with an increased or worsening incidence of infections with COVID-19. Indeed, a previous in vitro also in vivo study investigating the effectiveness of indomethacin on Covid-19 showed that by inhibiting replication of the virus and providing protection the damaged host cell caused by viruses, indomethacin exhibited strong antiviral activity. Consequently, subsequent research and guidelines, including a declaration by the WHO, released official statements stating that it was not possible to prevent the use of NSAIDs on the basis of available established facts. Opioids are known to acquire the potency of weakening the immunity, followed by a possible rise in the incidence and severity of infection risk, although the importance of Covid-19 remains uncertain. The international panel also recommends that even if morphine and fentanyl shown to have the most immunosuppressive activity, buprenorphine is considered to be the safest drug to be used for immunocompromised or elderly patients vulnerable to infection. In addition, it is important to note that there is a higher risk of using opioid patches of respiratory failure in patients who are suffering from fever as fever elevates absorption.

Additionally, opioids possess the potential for immunosuppression along with to respiratory depression and should thus be used with caution in patients with COVID-19 (Heng & Tan, 2020).

3.3 Immunosuppressive agents:

Anti-cytokine therapy

The prevailing understanding is that a cytokine storm will trigger SARS-CoV-2 infection or complicate it further, suggesting that the progression of the disease can be amplified by suppressing cytokine pathways. Interleukin-6 (IL-6) is thought to play a key role among the other. IL-6 is a cytokine with both anti-inflammatory as well as pro-inflammatory effects. Almost every stromal and immune system cells (monocytes, lymphocytes, macrophages, endothelial cells, mast cells, dendritic cells) can contain it and it is expected to play a vital role in the production of cytokine storms. Anti-IL6R treatment is, in accordance with this logic, a possible clinical option to COVID-19. COVID-19 is being examined against commercially available humanized monoclonal antibodies against the IL-6 receptor (tocilizumab and sarilumab) (Bourgonje et al., 2020).

Tocilizumab

Tocilizumab acts by stopping the immune system by blocking IL-6 and is thought to also assist with the control of excessive cytokine release. Research on tocilizumab began with a study conducted in France that indicated that patients who received tocilizumab needed a reduced number of ventilation or die. Another research reported from Italy showed that those receiving tocilizumab had a lower mortality risk, while ventilators were required for about the same percentage of patients from each groups. Then again, tocilizumab did not help early-stage pneumonia patients with COVID-19. The manufacturer's phase 3 analysis also found

that tocilizumab did not benefit patients with serious pneumonia in hospitalized COVID-19 patients. There have been equivocal findings in larger studies, and that may be partially because of the various types of people who were included while conducting the studies. One research looked at early treatment with tocilizumab in 3,924 patients in the hospital intensive care unit (ICU) with extreme COVID-19. There was a lower mortality rate in patients receiving tocilizumab within the first 2 days of getting admitted to the ICU (29 percent) compared to those who did not receive it (41 percent). Another study in 243 hospitalized patients with moderate COVID-19, on the other hand , found that tocilizumab was not successful in preventing the need for breathing tubes (intubation) or death in patients. Eleven percent of patients who received tocilizumab were intubated or died on day 28 of this study, compared with 13 percent of patients who did not receive the drug. This disparity was not statistically different.

Tocilizumab is a recombinant humanized monoclonal antibody which binds to the interleukin-6 (IL-6) receptor and blocks it from functioning. It is used for patients with severe COVID-19 and elevated IL-6 levels; the agent is being evaluated in a clinical trial.

Sarilumab

Regeneron Pharmaceuticals and Sanofi have introduced sarilumab (branded as Kefraza), a humanized mAb, to relieve rheumatoid arthritis (RA). Regeneron Pharmaceuticals and Sanofi (and in collaboration with Northwell Health's Feinstein Institutes for Medical Research) scheduled a phase 2/3 randomized double-blind placebo-controlled clinical trial for March 2020 aimed at enrolling 400 COVID-19 patients, assessing percent improvement in C-protein (Phase 2 only) and time to recover on a 7-point scale (based on mortality and type of medical facility). The findings of this report have still not been made available to the public since the time of this report (Wu et al., 2020).

Janus kinase inhibitors

As a possible targeted treatment for COVID-19, inhibition of the JAK-STAT signaling pathway has also been proposed and multiple drug trials are underway. JAK2-blocking inhibitors, such as fedratinib, have been proposed to inhibit viral entry and battle a host inflammatory cytokine storm portion without alteration of interferon signalling. Via ACE2-mediated endocytosis, SARS-CoV-2 reaches host cells. The JAK inhibitor baricitinib can restrict viral entry ito the host cell and intracellular aggregation of viral particles by blocking AAK1 and GAK, along with several other high-affinity inhibitors of these controllers. During the hyper inflammatory process, in which elevated cytokine levels exist, baricitinib can be of specific importance, signaling along the JAK-STAT pathway. However, it is also important to assess the best time to prescribe cytokine inhibitors and to await the findings of the aforementioned clinical studies (Bourgonje et al., 2020).

Glucocorticoid

A steroid hormone that is secreted by the human adrenal gland is glucocorticoid, also known as adrenocortical hormone. Glucocorticoids can influence the host's biosynthesis and metabolism as one of the most significant physiological hormones. Significantly, there is also significant anti-inflammatory activity in glucocorticoids. Long-term glucocorticoid use, however, often causes significant adverse effects including an elevated risk of osteonecrosis, endocrine disorders and heart failure. The therapeutic application of glucocorticoids was an unavoidable alternative for critically ill patients in China during the 2003 outbreak of SARS. To prevent acute pulmonary damage and acute respiratory distress syndrome, glucocorticoid acts by suppressing cytokine storms and chemokines caused by SARS-CoV-2. While glucocorticoid treatment for SARS-CoV-2 virus is not supported by clinical evidence, glucocorticoid may serve as adjuvant therapy for critical COVID-19 patients. Glucocorticoid [almost 1-2 mg/(kg-day) methylprednisolone] was prescribed as an alternative therapy in the

6th edition of the Corona Virus Disease 2019 Diagnosis and Treatment Plan. Of note, glucocorticoid can attenuate host immunity by inhibiting signaling of toll-like receptor 4 (TLR4) and activation of T cells, which can lead to secondary infection of other pathogens. However, by combining thalidomide and glucocorticoid with a decreased dose of glucocorticoids, some side effects can be partially restored. Therefore, when glucocorticoid is used to alleviate Covid-19 patients' inflammation, the usage and dosage should be moderately administered according to the patient's condition. Collectively, additional randomized controlled trials are required to assess the safety and efficacy of glucocorticoids in patient infected with Covid-19 to relieve inflammatory symptoms (Huang et al., 2020).

Dexamethasone

Dexamethasone has been used for several years to treat various health problems, such as autoimmune conditions and allergic reactions, and is a popular corticosteroid (steroid) drug. Many drugs, including dexamethasone, are being tested by Rehabilitation, a randomized clinical trial in the UK, to see if any are successful against COVID-19. Researchers found that 2,104 COVID-19 hospitalized patients who received a low daily dose of dexamethasone (either by mouth or IV injection) had a lower mortality rate at day 28 compared to 4,321 patients who did not receive it (23 percent versus 26 percent , respectively). This distinction was important. For patients who were on a ventilator or requiring more oxygen, the drug appeared to be most helpful. For those with less serious symptoms, there was no benefit. Additionally, based on a meta-analysis that looked at results from seven different trials, death rates were lower in hospitalized patients who had been dosed one of three different corticosteroids — dexamethasone, hydrocortisone, or methylprednisolone — compared to those who took none (32% vs. 40 %).

3.4 Antibiotics

Broad-spectrum antibiotic use is widespread in COVID-19 patients. A recent study of 203 American physicians found that in patients with COVID-19, antibiotics are very widely prescribed medications, second only to acetaminophen. Only 29.1 percent of respondents opted not to prescribe an antibiotic as one of the two alternatives for patients on the ward. Such an approach was the most prevalent among Slovenian respondents and was absent in North America. The decision on the use of antibiotics was based on clinical presentation and less so on radiology or laboratory markers. Among the laboratory inflammation markers, responders found procalcitonin to be the most significant factor in affecting the decision to prescribe antibiotics. In a large Chinese series of COVID-192 patients, the percentage of elevated procalcitonin was confirmed to be relatively low and may, as such, be a good marker of bacterial superinfection. In this area, more studies are needed. The flora that causes bacterial superinfection in COVID-19 is currently unknown and appears to be scarce, but most participants agreed that it is warranted to cover agents that cause atypical pneumonia and staphylococci. A recent study from North California, USA, showing very few cases of Mycoplasma pneumoniae and no infection with Chlamydia pneumoniae, does not support the coverage of atypical pathogens. The need for an anti-staphylococcal antibiotic which indicate the experiences with influenza bacterial superinfection is often caused by *S.Auroraeus*.

Azithromycin

Azithromycin (AZ) is a broad-spectrum macrolide antibiotic with a long half-life and a large volume of distribution. An antibiotic widely used to treat bacterial infections such as bronchitis and pneumonia is azithromycin. Some in vitro activity against viruses such as influenza A and Zika has been shown, but it has not worked against the coronavirus that causes MERS.

For COVID-19, one study group tested azithromycin in combination with hydroxychloroquine. They recorded that after 8 days, 93% of patients cleared the virus, but there was no control group, so it is not know if people without the drugs would have cleared the virus on their own. In vitro antiviral activity of AZ against viral pathogens with 50% inhibitory concentrations ranging from ~ 1-6 μM, with the exception of H1N1 influenza, AZ has been reported to exhibit anti-inflammatory activity in numerous studies. When using azithromycin and hydroxychloroquine together, there are questions about potentially serious side effects. For COVID-19, the NIH currently advises against the use of azithromycin.

Doxycyline

In clinical trials it has been shown that doxycycline has anti-inflammatory effects at minimal (20-40 mg/day) and elevated (100 or 200 mg/day) doses, inhibiting metalloproteases or modulating the activities of pro-inflammatory cytokines IL-6,IL-8, and tumor necrosis factor-alph, in regard to its well-defined antibiotic influence (bacteriostatic function by inhibition of bacterial protein synthesis). As a result, low-dose doxycycline has been found to be more effective than increased doxycycline in preventing the activation of pro-inflammatory cytokines (such as IL-6) in autoimmune conditions. On systemic ingestion, doxycycline is quickly nearly fully absorbed. Long-term medication with doxycycline as well as hydroxychloroquine for ailments like Q fever endocarditis has been linked to abnormal excess weight and changes in the gut microbiota. This mixture, rather than hydroxychloroquine and azithromycin, may be more useful and have less side effects, particularly when administered at home. Clinical studies are required to determine their effectiveness and safety in COVID-19 patients who are suspected or proven (Conforti et al, 2020).

3.5 Anticoagulant treatment

Upon witnessing increased risk of thrombotic events in COVID-19, current guidelines propose routine usage prophylactic systemic anticoagulation. Unless contraindicated, the International Society on Thrombosis and Haemostasis previously proposed that prophylactic low-molecular-weight heparin (LMWH) be issued to both hospitalized COVID-19 patients and those not admitted to the ICU. However, according to a recent study, COVID-19 patients admitted to the ICU were still at high risk for PE, even though they were given prophylactic low-dose LMWH. This prompted the Dutch Federation of Internists to recommend a double dose of LMWH in ICU patients with COVID-19, as this reduces the chance of bleeding. Other guidelines suggested using unfractionated heparin instead of LMWH for prophylactic systemic anticoagulation due to heparin resistance, which could be required in broad doses. However, anticoagulant medication is unlikely to have a strong disease-modifying impact, and it is important to remember that the initial viral load, and even the systemic inflammatory response are the motivating forces for COVID-19 VTE. Further studies are required to determine the most suitable procedure for thrombosis prophylaxis in COVID-19 (Bourgonje et al., 2020).

3.6 Traditional Chinese medicine

In China, the SARS-CoV-2 combat experience has thoroughly confirmed that TCMs provide a significant role in the prevention and treatment of Covid-19 till effective medicines and vaccines are successfully produced. The combination of TCM and chemical drug therapy approaches increased therapeutic effectiveness, shortened patient stay time and decreased the critical fatality rate (Xia et al., 2020).

3.7 Biological products

As the worldwide COVID-19 disease situation is becoming increasingly serious, in many countries all over the world, biological products for COVID-19 control have begun to be manufactured. Biological products basically focus on stimulating the immune system to generate immune components with antiviral potency. One of the very first countries to bring the COVID-19 prevention and treatment, China has developed a prototype of biological products, such as IFN, vaccines and convalescent plasma targeting SARS-CoV-2 (Pan et al., 2020).

Interferon α

Like IFN-alpha1b and IFN-alpha2b, recombinant human interferon-alpha (IFN-alpha) acts as broad-spectrum antiviral, anti-tumor, cell proliferation suppression along with immunity booster in patients. By enhancing macrophage phagocytosis, lymphocyte cytotoxicity to target cells, and natural killer (NK) cell vitality, IFN-alpha bound to target cells stimulates cells by production of a variety of antiviral proteins that block cellular virus replication and boost immune ability (Chen et al., 2016; Sugita et al., 1987). IFN-alpha2b is commonly used for the treatment of such viral diseases including acute and chronic viral hepatitis, shingles, and genital warts. Presently, IFN-alpha nebulized inhalation has already been tested clinically for the management of COVID-19 in association with several other antiviral drugs, such as ribavirin, and has had a successful therapeutic effect. However, generation of microbial aerosols during IFN-alpha nebulized inhalation should be controlled due to the possibility of aerosol transmission in Covid-19 infections (Chen et al., 2020). Some hospital security and disinfection should be done to minimize the chance of exposure by medical staff. The Chinese Clinical Trial Registry has declared that a clinical trial demonstrated the effects of new high-efficiency recombinant IFN and IFN-alpha compounds for COVID-19 management (Pan et al., 2020).

Bamlanivimab

A public health emergency justifying the emergency use of medicines and biological products during the COVID-19 pandemic has been announced by the Secretary of the Department of Health and Human Services (HHS). This EUA, submitted by Eli Lilly and Company, has been released by the FDA for the unapproved product bamlanivimab for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older, weighing at least 40 kg) with direct positive SARS-CoV-2 viral test results and who are at high risk of progression to serious COVID-19 and/or hospitalization.

3.8 Vaccines

Treatment via vaccination is an efficient way to prevent further infection or improve the severity of diseases (Wang and Wang, 2020). It takes a long time to produce vaccines, including the isolation and sorting of virus strains, in vitro tests, laboratory experiments, clinical trials, and regulatory approval. In total there were 115 COVID-19 candidates of vaccine worldwide are under production as of April 8, 2020, 78 of which have been confirmed. Five applicants for the fastest-growing vaccine have reached the clinical development stage (Thanh Le et al., 2020). Inactivated vaccines, recombinant protein vaccines, adenovirus vector vaccines, live influenza virus vector attenuation vaccines, and SARS-CoV-2 nucleic acid vaccines are being produced. The most successful direction to vaccine production for rapidly emerging viral diseases is inactivated vaccines (Pan et al., 2020).

There are already more than three SARS-CoV-2 vaccines available. There are nine vaccines permitted or licensed in at least some countries as of the end of January, according to the Regulatory Affairs Practitioners Society, an international organisation representing individuals engaged in the regulation of health care and related services: Pfizer/BioNTech

vaccine, Moderna vaccine, Oxford-AstraZeneca vaccine, two Russian vaccines (Sputnik V and EpiVacCorona), three Chinese vaccines (by Wuhan Institute of Biological Products/Sinopharm, Beijing Institute of Biological Products/Sinopharm and Sinovac) and one from India (by Wuhan Institute of Biological Products/Sinopharm, Beijing Institute of Biological Products/Sinopharm and Sinovac) (Bharat Biotech, ICMR). Another 58 applicants for vaccines were identified as being in separate production stages. Among these distinct candidates, various forms of vaccines exist. Some, like the variants of Pfizer/BioNTech and Moderna, are mRNA vaccines that produce synthetic RNA, that is, a single-stranded RNA molecule that complements and injects into the body one of the DNA strands in a gene. These vaccines trigger one's cells and induce them to generate proteins identical to those correlated with a common pathogen (a disease-causing agent) and prepare to use those proteins to defend against the virus. In order to prepare the immune system to identify and defeat them, more conventional vaccinations inject damaged or dead forms of a given pathogen, or fragments from such pathogens, into the body. Among these distinct candidates, various forms of vaccines exist. Some, like the variants of Pfizer/BioNTech and Moderna, are mRNA vaccines that produce synthetic RNA, that is, a single-stranded RNA molecule that complements and injects into the body one of the DNA strands in a gene. These vaccines trigger one's cells and induce them to generate proteins identical to those correlated with a common pathogen (a disease-causing agent) and prepare to use those proteins to defend against the virus. In order to prepare the immune system to identify and defeat them, more conventional vaccinations inject damaged or dead forms of a given pathogen, or fragments from such pathogens, into the body (Matthew, 2021).

3.9 Stem cells

By controlling the immune system and enhancing the microenvironment, stem cell therapy may facilitate endogenous damage recovery and prevent the progress of acute inflammation

in the lungs, thus lessening respiratory distress symptoms. Studies have demonstrated that mesenchymal stem cells (MSCs) might be useful to treat MERS-CoV effectively (Zumla et al., 2015). Currently, COVID-19 stem cell therapy relies predominantly on MSCs and NK cells, with MSCs being the most widely used. Findings revealed a decrease in IL-6 and CRP levels of the major inflammatory factors decreased, the ratio of neutrophils to lymphocytes decreased continuously, and the absolute values of T cells, NK cells, and B cells continued to increase. CT scan imaging findings showed that lung inflammation steadily subsided without any adverse reactions (Gu et al., 2020). MSCs have also been found to be healthy and reliable for COVID-1919 chronically ill patients. While the value of stem cell therapy against COVID-19 is certain, more evidence and findings are also required to affirm the safety and efficacy of treatment with COVID-19 (Pan et al., 2020). Stem cell therapy is proving to be successful in treating critically ill COVID-19 patients in other regions of the world too, according to Technology Networks. Sun Yanrong, deputy head of the China National Biotechnology Development Center, has said the therapy of stem cells has already been used in more than 200 cases in Wuhan, China's most affected region (Lynn, 2020)

3.10 Plasma therapy

The antibodies developed by plasma cells against SARS-CoV-2 will neutralize the virus to reduce its pathogenicity. Since the outbreak of COVID-19, scientists have been dedicated to the production of antibodies to SARS-CoV-2. Among four of the retained structural proteins found in SARS-CoV-2, the spike (S) protein, the membrane (M) protein, the nucleocapsid (N) protein and the narrow envelope (E) protein in which the S protein demonstrates outstanding antigenicity. The SARS-specific human monoclonal antibody as defined by the enzyme-linked immunosorbent assay (ELISA) and biolayer interferometry binding assay (BLI) will bind to the S protein SARS-CoV-2, although the clinical effectiveness of this needs to be further checked. In addition, antibodies within convalescent plasma have been

documented to be able to neutralize SARS-CoV-2 effectively and easily. Convalescent plasma may be a possible therapy for COVID-19 patients admitted to the intensive care unit (ICU) as reported in a research study with a limited sample size. Additionally, the extraordinary effectiveness and viability of plasma therapeutics of COVID-19 was also seen in another medical study. However, since an optimal medicinal plasma should be consistent with the patients, plasma therapy is constrained by the absence of its origins. The collection, preservation, and distribution of plasma will also be central to the production of plasma therapy. Collectively, plasma therapy needs validation in broader trials to treat COVID-19 patients with systemic, serious, and essential conditions (Huang et al., 2020).

3.11 Vitamins and minerals

These have been extensively studied in COVID-19, along with dietary supplementation. Many proponents recommend that nutritionally deficient COVID-19 patients should obtain dietary assistance immediately after diagnosis and that patients who are not malnutritioned, should continue achieving sufficient nutrition from daily intake. This is because of to the possible protective anti-inflammatory, antimicrobial and immunomodulatory actions of vitamins and minerals in patients with COVID-19. To stimulate the immune system and reduce the severity of symptoms vitamin A, B, C, D, E and minerals such as selenium, magnesium and zinc play important role. Vitamin B3 has also been shown to substantially suppress neutrophil penetration into the lungs during ventilator-induced lung damage in an in vivo experiment that was previously done on mice receiving mechanical ventilation. In several researches, including clinical trials, the antioxidant ability of vitamin C is also illustrated. In a randomized, double-blind, placebo-controlled, multicentre trial, 167 patients with acute respiratory distress syndrome due to sepsis were categorized to receive either a high-dose of vitamin C in intravenous infusion or placebo, and while vitamin C did not substantially increase the scores of organ dysfunction or change inflammatory and vascular

damage markers, the trial reported significant reduction in mortality in patient with high dose of vitamin C. Vitamin C supplementation has also been found in older studies to reduce the risk of pneumonia. Therefore, a project to measure the effects of vitamin C on COVID-19 has been reported and is in progress. Another essential vitamin that has been researched and reported for multiplying COVID-19 is vitamin D. It has been reported that vitamin D can mitigate the risk of infection in a number of pathways, including lowering the incidence of virus replication, minimizing pro-inflammatory cytokine concentrations, and increasing anti-inflammatory cytokine concentrations. Nonetheless, retrospective trials and clinical studies performed on the impact of vitamin D and the subsequent risk of infection of the respiratory tract have been contradictory, with some indicating a decrease in risk, while others do not. It has been postulated that these contradictory findings are attributed to the variability of the patient population along with dosage of vitamin D, causing more carefully designed vitamin D tests to be performed before making any definitive conclusion about the impact of vitamin D on patients with covid-19 (Tan, Hong, Saha, Murphy & Hui, 2020). All over, vitamin D, C and Zinc has shown the strongest evidence of being an integral part of immune system by taking part in maintenance and functionality of immune cells (Souza, Vasconcelos, Prado & Pereira, 2020). According to the above facts, as per standard clinical practice, orthopedic surgeons who typically prescribe vitamins should then continue to prescribe to COVID-19 patients. According to the above facts, as per standard clinical practice, orthopaedic surgeons who typically prescribe vitamins should then continue to prescribe to COVID-19 patients (Tan, Hong, Saha, Murphy & Hui, 2020).

3.11 Resveratrol

In this subpopulation of SARS-CoV-2-infected patients, the correlation between obesity and progression to hypoxic respiratory failure in patients with COVID-19 requiring mechanical ventilation has contributed to the inference that leptin and adipokine may play a key role. Due

to triple action, resveratrol, an antioxidant and nutritional substitute, has been proposed to be of potential therapeutic benefit. Second, resveratrol lowers leptin levels in certain experiments. Second, Ang II could be suppressed by resveratrol, which could decrease inflammation. Third, antioxidant effects in the lungs may decrease lung damage caused by oxidative stress. This food supplement is safe to use (up to 2-3 g a day) and can be studied as an adjunct to other therapies in COVID-19 patients.

Chapter 4

The major obstacle in research progress

In order to discover the dynamics of viral pathogenicity from the entrance to transmission and devise therapeutic strategies, animal models play a critical role. Different animal models were previously used to investigate the replication of SARS-CoV, showing the symptoms of serious infection. Since the entire genome of the 2019-new coronavirus is more than 80 percent identical to the previous human SARS-like bat CoV, the infectious pathogenicity of SARS-CoV-2 can be studied by previously used animal models for SARS-CoV. Both SARS and Novel coronaviruses identify the human ACE2 cell receptor. In conclusion, genetically engineered hamsters or other small animals, mediated by TALEN or CRISPR, may be used to research the pathogenicity of novel coronaviruses. SARS-CoV has been reported to replicate and cause serious rat disease, where a sequence analysis revealed a glycoprotein spike mutation. Thus, the development of spike glycoprotein targeting therapeutics against novel coronaviruses could be another suitable alternative. Mice models and clinical isolates have recently been used to establish some therapeutic strategy against COVID-19 induced by SARS-CoV-2. Artificial intelligence prediction has been used in a related study to investigate the inhibitory effect of the drug against SARS-CoV-2. Infected patients with SARS-CoV-2 were also used for randomized clinical trials. It is now essential for scientists worldwide to collaborate on the design of an effective model and to investigate the in vivo mechanisms associated with SARS-CoV-2 pathogenesis (Shereen et al 2020).

Chapter 5

Discussion

This analysis explicitly indicates that the available results are not adequate to conclude that any COVID-19 eradication therapy can be used at the therapeutic stage. Both individual trials lack comparable evidence, since it is uncertain if the patient has recovered due to the use of a new treatment or the general clinical treatment received. However, most in vitro experiments indicate likely beneficial results, but the evidence is too preliminary to be considered as a rationale for clinical application. The motivation for the use of antiviral drugs to combat the viral disease, COVID-19 infection, is clear. The interest in the use of antimalarial medications, however, derives from the unexpected discovery that hydroxychloroquine has positive impact on the prevalence of HIV patients. Nevertheless, it is important to assess the positive effects of chloroquine in patients with COVID-19 by well performed clinical trials. The safety profile of these two antimalarial drugs is, however, an aspect that requires close consideration. The toxicity of chloroquine is well known, however it is frequently underestimated that a significant population of patients with early rheumatoid arthritis use hydroxychloroquine as a comparatively safe medication. Therefore, instead of more toxic chloroquine, the focus of the trials will need to be on hydroxychloroquine (Rabby, 2020).

Chapter 6

Conclusion and future works

Human health and survival have been endangered worldwide since the 2019-nCoV crisis. The production of suitable medicines, sadly, is time-consuming and consists of various procedures. As the viral outbreak ended, the production of several new drugs for SARS-CoV ceased to advance. However, unlike SARS, COVID-19, like influenza, can become a chronic illness and coexist with humans. Screening for effective therapies among existing medications is certainly wise for unexpected viral infections. This article reviewed potential therapeutic agents that can be prescribed to treat the infectious disease. These medications, however, do have certain drawbacks, with either low specificity or minimal medicinal effects. The creation of new, broad-spectrum antiviral drugs to fight a wide variety of HCoVs in the long run will become a COVID-19 therapy and the ultimate treatment plan to deter emerging HCoV infections.

In future a comparative analysis of the efficacy and their concurrent side effects of the therapeutic agents used in the clinical trials all over the world can be done.

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