
Covid-19: A Pandemic Outbreak

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Abstract

A pandemic disease which is widely spreading all over the world leading to deaths of millions of people. A novel coronavirus (CoV) known as COVID-19 or nCoV-2019 or 2019 novel coronavirus identified by World Health Organization (WHO) is currently maintaining all the data of COVID-19 and it was started in December 2019 in Wuhan, Hubei province, China. Coronavirus is a harmful disease and fastly spreading disease. The WHO declared coronavirus as a global pandemic on March 11, 2020. The first case was occurred in Wuhan, Hubei province, china which showed the first symptom of respiratory illness. The family of SARS is MERS-CoV, SARS-CoV, and SARS-CoV-2. MERS-CoV is an epidemic; SARS-CoV is also a pandemic which was long lasted in the year 2009 now SARS-CoV-2 which has been started in the year 2019 and still it is going on. The symptoms which reflects that a person he/she who is suffering from COVID-19 is respiratory illness, fever, cough, shortness of breath, difficulty in breathing, change in taste of mouth, fatigue. The coronavirus is affected to all age groups but especially to those people who are old in age and are suffering from diseases like diabetes, cardiovascular diseases, chronic respiratory diseases, cancer, hypertension, and chronic liver diseases. It can spread from one person to another person very easily through droplets or aerosols or particles and transfer from hands. People who are 6 feet to infected people have 100% chances of being affected to virus. The incubation period for an infected person should be atleast 2-14days. If the normal person meets the infected person the person should see for 14 days if he/she is not infected then he/she is not confirmed with COVID-19. The preventive measures are get vaccinated as soon as possible, should keep physical distance from every person atleast 1 m, should wear mask and gloves compulsory, while cough or sneeze bent your elbow. The COVID-19 is tested or diagnosed by RT-PCR test. It is available in the form of kits and it is developed and is available in all clinical labs. RT-PCR results shows just 30-75% accurate because it shows incorrect use of kits or shows not enough virus in our blood at the starting stages of infection. The current outbreak has much importance in bioinformatics in drug designing. Some databases and tools are used to design drug using lopinavir and remdesivir.

Keywords: COVID-19, nCoV-2019, pandemic, WHO, MERS-CoV, SARS-CoV, SARS-CoV-2, respiratory illness, fever, cough, fatigue, RT-PCR.

1. Introduction

Severe acute respiratory syndrome was the first infectious and pandemic disease which is still going on and is identified this disease as the 21st century. This respiratory disease was originated from the Guangdong province in China and this disease was identified in the month of November. A global leader of health WHO lead to identify this disease in the month of April and announced in the public that it is a new corona virus SARS-CoV-19, by late news it has been already spread throughout the world [Stephanie and Shari,2021]. The new corona virus is pronounced with many names such as SARS-CoV-19 or COVID-19 or severe acute respiratory syndrome and it is an advanced raising infectious disease which is caused from its SARS-CoV strain. SARS-CoV is a novel corona virus which has spread all over the world [Kenneth McIntosh, Martin and Allyson, 2020]. Spike protein of corona virus acts as a target for the development of vaccines and therapeutics for stopping and curing of SARS-CoV-19. COVID-19 has four protein layers in it – the first layer or outer most layer is spike protein and is denoted as ‘S’, the second layer is Envelope protein and is denoted as ‘E’, the third layer is Membrane protein denoted as ‘M’, the last and the fourth layer or inner layer is Nucleocapsid protein is denoted as ‘N’. The gene is packed in the form of nucleocapsid which is present inside like a helical capsid and it is together by an envelope protein. Viral envelope contains three structural proteins: The membrane protein and the envelope protein which are involved in the function of virus assembly, then spike protein stops the virus entry into host cells [Subramaniam, Adolfo and Ponmalai, 2021]. The spike protein of corona virus includes three segments in it – a large ectodomain, a single transmembrane anchor, a short intracellular tail. The ectodomain segment contains two subunits ie. S1 and S2 where S1 subunit implies to receptor binding and S2 subunit implies to membrane fusion. Spike protein is present in the form of clove-shaped trimer with three S1 heads and one trimeric S2 stalk. In the entrance of virus, the S1 binds to receptor on the cell surface of host and gets attached to virus and S2 combines the host and viral membranes permits the viral genes to enter the host cells. The spike protein allows humoral and cellular immune responses to act against SARS-CoV. The vaccines are made based upon SARS-CoV full length spike protein and their receptor-binding domain which includes DNA, viral vector, and subunit-based vaccines. The additional anti-SARS-CoV therapeutics includes peptides, antibodies, organic compounds and short interfering RNA’s which mainly focuses on spike protein.

COVID-19 is present in the form of an envelope, single and positive-strand RNA virus. Its RNA gene converts a non-structural replicase polyprotein into structural proteins. It is a zoonotic virus apart from this the hosts forms its natural main cause to disease which is caused from bats. Before getting affected to smaller organisms it gets affected to humans [Anshumali et al., 2021]. The spike protein is composed of trimers which belongs to the family of class I viral fusion glycoproteins in that HIV glycoprotein 160, Influenza hemagglutinin, paramyxovirus F and Ebola virus glycoprotein. Spike protein converts a surface glycoprotein which comes before and assumes to be 1,225 lengths in amino acids. The amino acid terminus and the most of the other proteins are assumed to be present outside the surface of the cell or the virus particles. The assumed spike protein includes a signal

peptide which contains amino acids at 1-12 position in the N-terminus location; in extracellular domain it is present at 13-1,195 position, in transmembrane domain it is present at 1,196-1,215 position, in intracellular domain it is in 1,126-1,225 position. The spike protein can be split into S1 and S2 subunits in the form of proteases which includes trypsin, factor Xa and Cathepsin L. The trypsin splitting site occurs between R667-S668, and in Cathepsin L it splits and marked to T678-M679 in the spike protein [Edison et al., 2020].

1.1 History of Covid-19

In 2019, based on the outdated analysis which is starting from December 2019, the number of increasing in COVID cases is 19 in Hubei which is gradually increasing and by the 20th December cases had reached to 60 and by the end of the month it has reached to 266 in number. On 24 December 2019, the Wuhan Central Hospital sent a unsolved case of BAL sample (Broncho-alveolar Lavage fluid) to a company of sequencing named Vision Medicals [Onyeka et al., 2021] [Buddhisha et al., 2020]. On 27 and 28 December, the sequencing company named Vision Medicals intimated that the results of the test were showing as a new corona virus to Wuhan Central Hospital and Chinese CDC. The unknown case of pneumonia was identified on 26 December and was treated by Dr.Zhang Jixian who works in Hubei provincial hospital informed to the CDC member Wuhan Jianghan on 27 December. On 30 December 2019, a report convey that Wuhan Central Hospital to the company CapitalBio Medlab mentioned that the positive result found wrong for covid having a great loss for a group of doctors at wuhan central hospital to warn their colleagues and other hospital authorities about this error in positive result. Among eight doctors one was Li Wenliang, were later arrested by the police by spreading wrong rumors. Ai Fen was scolded by their seniors by raising the alarm. The same evening, the Wuhan Municipal Health Commission made the first announcement in people of pneumonia spread all over the world but still there is no known cure of this disease and telling them that it is now around 27 positive cases, and the research has been activated on this disease [Franziska et al., 2021]. On 31 December, the WHO office in china was intimated with the number of cases of pneumonia in Wuhan. A search was launched on January 1, 2020. According to Chinese official resources, the old cases of covid were mainly connected from Huanan seafood wholesale market, which also sell active animals [Ben Hu et al., 2021]. In May 2020, the director of Chinese center for disease control and prevention named George Gao, mentioned that we have collected the animal samples from that seafood market and the result was negative of this virus and telling that this market was not the main cause of initial spreading all over the world. In March 2021, the WHO mentioned the test report on the possible zoonotic source of the virus [Yan et al., 2020]. The WHO made a conclusion that human spreading was through a primary animal host and it was briefly explained, with direct spreading in the form of bats was most likely and was explained the another cause by giving the introduction of food supply chain [Tanu singhal, 2020] [Julieth et al., 2021].

This virus is by a natural and origin of animal which can be caused by spreading infection. There are several theories to be explained but the first case was originated and the researchers are going on. Phylogenetic determines that COVID-19 was born in the month of October or November 2019. A phylogenetic algorithm analysis describes that this virus is spreading

from Guangdong before Wuhan [Grose, 2020]. According to one Italian study it stated that it was present as before as September 2019. By seeing the proofs it describes that it falls downwards from a corona virus that affects the wild bats and it spillover to humans through a primary resource known as animal host. The surety of the virus was by chance missed out and got released from a laboratory is also taken under consideration actively. The initial confirmed case which is human infections was in Wuhan, Hubei, China [Tanu singhal, 2020]. One of the study describes that the first raise of cases was in number of 41 which was posted in January 2020 in the Lancet, mentioned as the before date of showing the symptoms in human as 1 December 2019. On 8 December 2019, the official reports mentioned that the WHO mentioned the before date of symptoms seen in people. Person-to-person spreading was confirmed by the WHO and Chinese authorities by 20 January 2020. Some prints of the virus have been identified in wastewater samples that were collected from Milan and Turin in Italy on December 18, 2019. RT-PCR testing was done on wastewater which has been collected from Milan and Turin and has been taken as consideration for detection of COVID-19 as before as November and December 2019, but in some methods the sewage treatment has not been best applied and it has been not completely studied and some details are still missing, there is a chances of danger of providing wrong statements because the samples of wastewater which has been collected was been polluted. On September 2020 a reviewed article told that the happened case was COVID-19 infection which has already spread to Europe at the end of the 2019 is now identified in large number even in limited conditions the proofs has been provided including in number of pneumonia cases and x-rays of patients in France and Italy in the month of November and December [Plato, Xue and Carafoli, 2020].

Scientists identified its first strain of corona virus in the year of 1965. The main symptom was a common cold. Later on the years passed, the scientists found that the group of same human and animal viruses and named that virus by seeing its structure and is denoted as Crown-like appearance. Seven types of corona viruses can infect humans. SARS has been originated from Southern China in the year 2002 and spreads very fast in and around 28 countries. About more than 8,000 people were affected and 774 died in July 2003. A small spread of disease in the year 2004 affected only for four people. To this disease the symptoms are fever, headache, and some respiration diseases such as cough, cold and shortness of breath. Another strain of corona virus is MERS which is mainly originated from Saudi Arabia in the year 2012. The positive cases were nearly 2,500 and these have been mainly reported in the people who live or travel from Middle East countries [Kenneth McIntosh, Martin and Allyson, 2020], MERS is less harmful than SARS but it is more dreadful disease and had almost killed 858 people. According to respiratory problems it can also cause kidney failure. The predecessor of COVID-19 was named after its genomic modified SARS-CoV which causes a dreadful pandemic in the year of 2002-2003. Before 2019, either its strain or its genetic sequences had been ever known in the family of viruses of humans or animals [Tanu singhal, 2020].

1.2 Origin and Spread of Covid-19

COVID-19 spreads from person to person through close communication. When people with COVID-19 breathe out or cough, they leave their small drops that contains the virus in it.

These drops can enter into the mouth or nose of normal person who is not suffering from virus after passing into the normal person they get caused by infection. The most normal way that this disease spreads is by close communication with the affected person. Close communication is within across 6 feet. This disease is most harmful when a person's symptoms are at high level. However, this disease is possible to someone who has not caused yet and the droplets of virus enter into the body in the any way of our sensory organs. A newer study describes that only 10% of infections are spreading from non-symptomatic people. Drops of our sneeze or cough contains virus in it and can land on nearby objects or surfaces. Infection is caused to the non-symptomatic person by touches that object then to their nose, eyes or mouth. In December 2019, Wuhan, Hubei, a major transportation center for China started visiting local hospitals with serious issue of pneumonia which was an unidentified cause. Many of the starting cases were having a no protection while visiting Huanan wholesale seafood market. The close observation was activated and respiration samples of patients were given to the reference labs for seeing how the development of a disease is occurring in a person. On December 31st 2019, China alerted the spreading of disease all over the world to the WHO and on 1st January 2020, it has officially announced the close of Huanan wholesale seafood market. On 7th January 2020, the virus was known as corona virus that has similarity of >95% homology to bat corona virus and >70% same percentage to SARS-CoV strain. The samples which are collected from Huanan wholesale seafood market also tested positive which mainly expresses that the virus has been originated from that seafood market. The number of positive cases started increasing day by day but some people who has not visited seafood market has also been reported positive and by the fact known that it has been spreaded by transmission. The initial death case was reported on 11th January 2020. The large amount of migrating people of china during the Chinese New year geared to epidemic [Ben Hu et al., 2021]. The cases in other states of china, other countries were reported who were returning from wuhan after Chinese new year. Spreading the disease to health care workers caring for the patients was identified in the month of January 20th, 2020. On 23rd January, the whole country of Wuhan with over 11 million populations was kept under lockdown with some restrictions in entry and exit of that region. After some days these lockdown was extended to some more days and some other cities which lies under Hubei province. Cases of COVID-19 outside the china were reported but didn't found any history that they have visited the china describing that they have caused from human-to-human spreading and the cases has spreaded because of this in other countries too. Airports in other countries including India had implement the screening methods to detect the symptoms in patients who are returning from china and those people are should be kept under isolation and test them for COVID-19. The infection could be spread from symptomatic patients to asymptomatic patients and also before the date the symptoms are expressed. Countries including India who had called their citizens from Wuhan by special flights or having travelers from china placed all symptomatic patients in isolation for 14 days and then tested them. The cases continue increasing day by day and the modeling studies reported against pandemic vs epidemic. According to it is 1.8 days doubling time than epidemic. On 12th February 2020, the molecular tests according to clinical, radiologic, and epidemiologic characteristics of COVID-19 which commonly leads to increase in number of cases by 15,000 in a whole single day [Kenneth McIntosh, Martin and Allyson, 2020]. As of

05/03/2020, 96,000 cases worldwide increased in 87 other countries and 1 international transport had been identified. It is the important note that the number of new cases had been decreased in china after a long time, besides the South Korea, Italy and Iran faces a health crisis and the cases have been increased in a large number. According to the infected cases, 20% cases are critical in condition, 25% cases have been recovered and 3310 people have died. India has reported only 3 cases on March 3, 2020 has also been sudden increase in number of cases. On March 5 2020, 29 new positive cases has been reported in some countries of India such as Delhi, Jaipur and Agra mostly it is a tourist places where the Italian tourists and their guides got affected. One case of Indian who returned from Vienna has been visited to a birthday at city hotel and there were large number of school children. These increases in number of cases are possible to be smaller or less important to be infected and dead because of limitation of observation and testing for virus. The corona virus is mainly originated from bats, the primary resource for this is animal from which is through humans. Pangolins and snakes are the current proofs. This virus belongs to Beta corona virus sub group and by seeing the classification it was named as SARS-CoV. The researchers found that receptor-binding domain (RBD) of the COVID-19 has developed effectively to target a molecular characteristic which is present outside the human cells is called as ACE2 a receptor which is involved in the function of regulating blood pressure. The spike protein function is to bind the human cells. The researcher given the conclusion of result it is a natural action and it is not the substance of genetic engineering. The proof of natural action was to bear the information on SARS-CoV-2's backbone and its total molecular construction. If the researcher is trying to attempt to design, build a new corona virus in the form of pathogen, they would start constructing it from its backbone of a virus to cause a spreading of virus [Tanu singhal, 2020].

Taxonomy

KINGDOM: Riboviria

SUB-KINGDOM: Orthornavirae

PHYLUM: Pisuviricota

CLASS: Pisoniviricetes

ORDER: Nidovirales

FAMILY: Coronaviridae

SUB-FAMILY: Orthocoronavirinae [corona virus, Wikipedia]

1.3 Classification

The study group of corona virus International Committee on Taxonomy of Viruses had classification of viruses comes under the family of coronaviridae and the subfamily of orthocoronavirinae [Franziska et al., 2021]. Based on the genotype and phenotype characteristics, subfamily is divided into four species: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. Before December 2019, only 6 HCoV species that cause human disease and remaining four are caused by common cold symptoms in the low immune system. The four strains are HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1. HCoV-229E and HCoV-OC43 were first identified in the year mid-1960s; HCoV-NL63 is first identified in the year 2004 and HCoV-HKU1 is first identified in the year 2005

[Tieying et al., 2020]. The remaining two strains are very dreadful disease and they are SARS-CoV-2 it has 96% nucleotide sequence identity to the bat corona virus RaTG13, which is similar to the SARS which belongs to the betacoronavirus species. They arranged the closely related genes into 3 ancestors, namely A, B and C which is divided based on its amino acid modification. Lineage A was given the name based on the original bat corona virus which is directly caused from COVID-19, but the shocking point is it was not originated from Wuhan. The A and C types of virus were found in more number in the Americas and Europe, but the B type was mostly from East Asia and has obtained mutations before spillover from outside the East Asia. The lineage C mostly varies from parent lineage B by a mutation process and binds at amino acid position of 26,144 and was mostly spread in France, Italy, Sweden, England, California, Brazil, Singapore, Hongkong, Taiwan and South Korea and it was not spreaded in mainland of Chinese samples [Edison et al., 2020]. From the above all the species, Alphacoronaviruses and Betacoronaviruses affects mammals only, Gammacoronaviruses affects air flying species only, and Deltacoronaviruses affects mammals and air-flying species. The gamma and deltacoronaviruses mainly focuses on avian infectious bronchitis coronavirus (IBV) and a porcine deltacoronavirus (PdCV). They have the largest gene among all the RNA viruses, mainly ranges from 27 to 32 kb [Kenneth McIntosh, Martin and Allyson, 2020].

1.4 Structure of Covid-19

The corona virus contains spike like projections in glycoprotein present on their surface, which looks like a crown and can be visualized under the electron microscope. The virus gene converts the several structural proteins to non-structural proteins. Before the structure the virology concept should be understandable in corona viruses which are present at structural level which is most important because it is linked to health danger. The zoonotic viruses are constant in position and are long-term process. Animal and plant viruses comes under two common classes in which the one class of genetic material is present in long DNA molecules and another class of genetic material is present in RNA molecules. The DNA viruses include Herpes, Adenoviruses and Wart viruses. Corona viruses is named after the shape of sun like appearance when observed in electron microscope by using RNA molecules to convert the genes as the other viruses do like Influenza virus, HIV and Rhinoviruses. The covid is caused by infecting mammals and birds. These viruses are having close relationship with SARS and MERS [Jonathan, Melissa and Eric, 2020]. The virus particles are arranged with long RNA polymers with tightly column in the center of the particle, and are together protected by a protective layer called protective capsid which acts as a fence for repeated protein molecules known as coat or capsid proteins. In the corona virus language it is known as Nucleocapsid protein (N). The corona virus tough particle is together by an outer membrane envelope which is made up of lipids inserted inside with proteins in it. These membranes are obtained from the cells in which the virus was at last assembled and had changes to contain some important virus proteins such as spike protein, membrane protein, and envelope protein [Kenneth McIntosh, Martin and Allyson, 2020].

A set of proteins in the outer membrane layer mainly focuses out of the particle and that protein is known as spike protein. These proteins are identified by receptor proteins present

on the host cells which will then get infected. Corona viruses mainly damages human lung cells through a receptor called as ACE2 (Angiotensin-converting enzyme 2). ACE2 belongs to the family of angiotensin converting enzymes which then includes ACE and this is the main source of taking blood pressure medicines for Americans. These tablets composition are adding chemicals which acts by stopping the ACE and perform its specific function. The first step to virus infection, the virus spike protein identifies and attaches to ACE2 receptor [Anshumali et al., 2021]. The virus is taken into the lung cells and the viral RNA is leaved freely into the cytoplasm. The viral RNA molecules make a list of cellular equipment to make thousands of nucleocapsid, membrane, and envelope and spike proteins. These unite to form the new virus particles which born and comes out of the cell membrane. The cells leaved freely to form new viral particles which spread the infection and at the end leads to death of the cell. Envelope protein bears club-shaped glycoprotein projections. Some corona viruses also contain a hemagglutininesterase protein (HE)⁴. At their core, corona virus contains a genetic map called RNA which is similar to DNA. The single stranded RNA function is a molecular message that gives the production of proteins requires other components of the virus. The fat, round or bulging projections seen outside the corona virus which are in the form of spike proteins [Yuan et al., 2021]. The edges of proteins give the appearance like crown under the microscope and in the Latin it is named as corona [Leila and Sorayya, 2021]. The spike protein gives example of well which is dragging water from inside the well using the pulley which fastens to drags water same as like that of it is used in proteins to drag and allows the virus to fasten the process and place it onto the host cells, break it and open the cells for infection. Like other viruses the corona viruses are not able to grow or develop properly and not able to produce more copies outside the live host [Scripps research].

1.5 Structural and Functional Genes of Covid-19

The spike protein is having several functions molecular machine that acts as a major role in the pre-matured stages of virus infection by communicating with host affecting factors such as receptors and proteases. These communications particular happened when they infect human cells, which mainly contains a receptor called hACE2 trans-membrane protein. The spike protein is a transmembrane glycoprotein created by S1 regions containing the two terminal domains such as N-terminal domain (NTD) and C-terminal domain (CTD) and in S2 regions it contains a transmembrane region and a short cytoplasmic domain. The two methods have been determined i.e., Cryo-EM and crystallographic method determines the multi structural complex alone in the spike protein. The more structures of spike protein were seen in many states with combining of receptor binding domain either in an “up” or “down” conformation. To interrupt the hACE2 receptor, the receptor binding domain present in S1 protein undergoes a movable mechanism which either make visible or cover the receptor binding domains and there changes [Anshumali et al., 2021]. The total of spike protein present in ectodomain having similar appearance with closely related spike protein structure with an RMSD value of 3.8 Angstroms with 959 C α atoms with a high in number degree of homology structure when single domains of spike protein and SARS-CoV-2-S were arranged in the manner. The protein which is present on the surface of the virus plays a key role in the infection. By comparing with other viruses the spike protein resolves receptor recognition,

cell attachment of virus infection during fusion. The protein trimer which is located on the viral envelope surface a basic part which ties to the receptor. COVID-19 has 8 accessory proteins which obtain from sub-genomic RNA: 3a, 3b, 6, 7a, 7b, 8b, 9b and orf14 and they are equally supplied among the structural genes [Huseyin et al., 2020]. SARS-CoV-2 Wuhan-Hu-1 is the first successfully completed gene was isolated with virus strains to be sequenced and constituted to form 29,903 bp long RNA. It is a 5' and 3' polyadenylated, which consists of 2 on each one side in untranslated regions (UTR's) and contains many ORF's which converts many proteins [Chittaranjan and Satyanarayana, 2020]. The gene makeup itself to get divided into 13-15 ORF's which approx. contains 30,000 nucleotides. The gene contains 38% of the GC content and 11 protein coded genes, containing 12 expressing proteins. These gene substances play a main role in virus entrance, fusion and chances of surviving in host cells [Ben Hu et al., 2021].

1.6 Epidemiology of Covid-19

Around the globe, over 150 million positive cases of COVID-19 have been mentioned. The updated case counts according to the WHO and European centre for disease prevention and control website. The first reported case was from Wuhan a city of Hubei province of china, the cases have been reported by the end of the month in December in all the countries. The positive case counts regards the total pressure of the virus, only in the fraction of acute infections are treated and mentioned. The level of pathogen in a population campaign in the United States and Europe have determined after process of work for providing wrong statements, the rate of prior subjection to SARS-CoV-2, as focused by giving a positive result which crossed its limits to the occurrence of confirmed cases by approximately 10 folds or more folds. Human-to-human spreading is the main purpose of SARS-CoV-2 spreading. Direct human-to-human respiratory spreading is the preliminary step of spreading the corona virus. It is mainly occurs through close communication via respiration particles ie., virus leaved freely in the respiratory discharged when a human suffering from infection via cough, sneeze or by talks can get infected by the another person if he/she is inhaled or makes direct communication by these discharge or by touching the contaminated surfaces they touch their nose, eyes and mouth but contaminated surfaces are not ever think to be a main cause of spreading. Corona virus can be spread through longer distances through the air, but the area which is covered through is the mode of spreading has give away to the pandemic is uncertain. The exact time period when passing from person to person is uncertain. The possibility of passing the virus starts prior to the development of symptoms and is high in starting stages of the virus when infected the danger of spreading slows reduces before the process has started. Transmission before 7 to 10 days of causing is unlikely, particularly in having normal immune response patients with non-severe infected patients. Infection caused in single person are high likely to be dangerous in the starting stages of causing disease when viral RNA levels moves from upper respiratory samples are more. One modeling study, in which the mean time period between the dates of symptoms among 77 spreading pairs in china was 5.8 days, estimated the level of infection between two days before and one day after the symptoms has been decreased within seven days. In another study, that assess across 2500 close communication with 100 patients with covid-19 in Taiwan, after all the secondary

confirmed cases it had a first subjection to the last case within six days of showing symptoms before date and there was no infection reported in the 850 close communication whose subjection was after the time period. The duration of viral RNA parking is variable and may inclined with the age and the seriousness of causing the disease. In 28 reviewed articles, the pooled median time period of viral RNA showing in respiratory samples was 18 days following with the before the date of symptoms in some single persons, viral RNA was identified from the respiratory tract in many months after the first infection. As an example, nine patients study was conducted with the mild COVID-19 the infectious virus was not identified from respiratory samples when the viral RNA level was $<10^6$ copies/mL. Transmission of corona virus which is caused in individuals but no symptoms has been well reported. As an example, the analysis of 628 positive cases and 3790 close contacts in Singapore, the risk of secondary infection was 3.85 times higher among contacts of a symptomatic individual compared with the contacts of an asymptomatic individual [Sayampanathan et al., 2021]. Virus present on the contaminated surfaces is the another cause of infection if detected in individuals by touching the surfaces and then transfer virus infection to mucous membranes in the mouth, eyes or nose [Kenneth McIntosh, Martin and Allyson, 2020].

1.7 Pathogenesis of Covid-19

Following the viral spreading, covid-19 gets attached to the surface of epithelial tissue membrane of the oral cavity whereas the mucous membrane of the octia canal. ACE 2 protein which is highly expressable on many human cells which includes type 2 alveolar cells, oral epithelial cells myocardial cells and in kidneys the proximal tubule cells are present whereas in the bladder the urothelial cells are accepted to resolve the internal process of SARS-CoV-2. The SARS-CoV-2 is spitted in the form of cellular enzyme named as furin at the S1 or S2 site. These splitting are important for the lung cells in the viral entry. The activation process of S2 protein is primarily by the TMPRSS2 and at last gets attached on ACE2 receptors for the entry of host cells SARS-CoV-2 first aims the epithelial cells of lungs and the intestinal and other epithelial cells can also be affected with the alive replication and de-novo production of virus infection. Three stages of pathogenesis occurs in this virus- asymptomatic state, upper airway and performing airway response and hypoxia, ground glass infiltrates and development of ARDS (Acute respiratory distress syndrome) [Tofael et al., 2020].

Active replication and leaved freely the virus in the lung cells may leads to not like exact symptoms but like such as fever, myalgia, headache and respiratory symptoms. In an exploratory hamster model, the virus causes temporary damage in the cells in the olfactory epithelium which leads to olfactory impairment, which may describe the short-term loss of taste and smell commonly observed in this virus. The supply of ACE2 receptor in many tissues may describe the site of infection and patient symptoms. The molecular phenomenon of spike proteins is identified in the insertion of S1 or S2 sites and these sites are absent in SARS-CoV but the importance of insertion is still missing it assumes that the special insertion -in spreading the human host all over the process. The viral RNA seizes the host cell's machinery to initiate the viral gene replication and polypeptides chain synthesis and forms the RCT (replication-transcription complex) which is important to be synthesized by

the sub genomic RNAs as well as structure proteins. Despite of all these values, the blood C-reactive protein value is 16.16 mg/L has been mentioned which is more than expected in a normal range [Ben Hu et al., 2021].

1.8 Mechanism of Infection of Covid-19

SARS-CoV-2 is highly dreadful and can be directly passed when an individual comes in communication with the respiratory drops of an affected person or it can be indirectly passed by coming in communication with objects which is used or touched by affected person. The virus entry into the body is by nose, mouth or eyes. The protein holds together particularly to ACE2 receptors which are present on type 2 pneumocytes which is produced from surfactants and decreases in damage pressure and also declines the alveoli in surface tension. The hold together of the ACE2 receptor permits the entry of the virus in the host cell. Due to the proteases in the host cell it splits the protein into the corona virus. The virus enters into the host cell either by the direct method ie. Direct cell entry method by membrane fusion or by endocytosis method. Same like a common flu method which starts its journey by entering into nucleus once in a while it starts the action in the host cell but in COVID-19 its leaves freely in positive sense RNA and enters in the cytoplasm in the host cell [Suman et al., 2021]. This RNA is translated into polyproteins which comprises of two types i.e., pp1a and pp1ab. This helps in the process of replication and transcription of the viral RNA [Chittaranjan and Satyanarayana]. The process of replication starts from positive-sense RNA by using an enzyme called RNA-dependent RNA polymerase enzyme which gives a negative-sense RNA. The negative-sense RNA function which is neither can be replicated or transcribed but if it is replicated it gives positive-sense RNAs which is involved in the viral genes [Vinay et al., 2021]. The transcribed mRNAs function is too translated to produce viral proteins like the corona virus structure proteins present in it. In host cell the ER transports the proteins into the Golgi apparatus, where they are filling up in the form of vesicles and join together near the cell membrane of the host. The newly types of viruses that will get out of the host cell by the exocytosis method to destroy the other cells present in the host as the first cell gets infected. This method finally concluded that the death of the host cell [Suman et al., 2021]. From all the above observations which have been recently studied it indicates that a person-to-person by transmitting the virus, which was later, reported more than 100 countries in the overall the world. The person-to-person transmitting of the virus occurs due to close communication with an affected person is unshielded to coughing, sneezing, respiratory drops or water particles. These water particles can infiltrate in human body which occurs from lungs through breathing via nose or mouth [Meredith and Aaron, 2020]. The hACE2 receptor has a high expressing in small intestine, testis, kidneys, heart, thyroid and adipose tissue; the medium expressing in lungs and liver, whereas low-to-no expressing is in most of the cells and organs of the immune system whereas immune system covers the parts like blood cells, spleen, bone marrow and blood vessels. Even when the similar replication of SARS-CoV and SARS-CoV-2 has been found in the lower respiratory tract. The respiratory drops are $>5-10 \mu\text{m}$ in diameter whereas drops $\leq 5\mu\text{m}$ in diameter are mentioned as droplet nuclei or water particles [Buddisha et al., 2020]. Fomite aerosols can be identified by the testing method RT-PCR from which we found the surfaces for time period ranging from hours to days, based on the

suitable environment and the type of the surface present in particular position at high concentration in health care facilities where COVID-19 patients were being given a treatment [Edison et al., 2020].

1.9 Role of Bioinformatics in Drug Designing Of Covid-19

In the current trend of COVID-19 pandemic, the main applications of bioinformatics methods used in applicable genomic sequences which is deposited in online data warehouse could hugely support the search for a powerful vaccine and drug that will fight against the spread of virus. This has been produced unequally in the levels of interaction between governments, academia and private organizations that have overcome to bind fastly to develop vaccines and antibody counter measures aims against the structure and non-structure proteins of the gene in the virus. The partnerships on available softwares, including bioinformatics to speed up the response to the ongoing disease. Reverse vaccinology is low in cost and decrease the time spending in the traditional drug designing approach. Immune-informatics i.e., bioinformatics approach with immunology, includes the approaches for the complete data on an organism's immunomics, and using computer generated data to make assumptions for immune responses against some molecules [Onyeka et al., 2021]. A bioinformatics application in drug designing uses the computer-aided drug designing (CADD) method that combines the other methods of lead compound Quantitative structure activity relationship (QSAR) optimization, sequence, homology structure, stereo chemical validation, molecular docking and 2-dimensionl (2D) molecular interaction checking. Using the molecular docking method, the top most candidates that arrived as a particular answer for lopinavir and remdesivir [Onyeka et al., 2021]. With the experienced reuse of the drugs, they can recheck by clinical trials for the manufacture of more powerful types and a COVID-19 vaccine [Koichi, Miho and Sophia, 2020]. Another method for drug reuse is the building of preresumed disease-related molecular networks ie., interconnection between gene products includes in the cause and symptoms of the virus [Garrett M.Morris et al., 2009] [Onyeka et al., 2021].

Table 1. Basic Bioinformatics Databases/ Tools Useful in Covid-19

DATABASES/TOOLS	APPLICATIONS	REFEREN CES
Sequence Read Archive (SRA) database (https://www.ncbi.nlm.nih.gov/sra)	It is the largest publicly available repository of high throughput sequencing data, stores raw sequencing data and aligning information.	Leinonen R., Sugawara R. and Shumway M., 2011.
European Nucleotide Archive (ENA) (https://www.ebi.ac.uk/ena/browser/)	Provides a comprehensive record on DNA and RNA raw sequencing and assembly data.	Leinonen R. et al., 2011.

Metagenomics and Whole genomic sequencing FastQC (https://www.bioinformatics.babraham.ac.uk/projects/fastqc/)	Used to check quality control on raw sequences generated from high throughput sequencing pipelines.	Brown J., Pirrung M. and McCue L.A., 2017.
Cutadapt (https://cutadapt.readthedocs.io/en/stable/)	Used to clean the sequences. It finds and removes adapter sequences, primers, poly-A tails and other types of unwanted sequence from the high-throughput sequencing read.	Martin M., 2011.
Qiime (http://qiime.org/)	An open-source bioinformatics pipeline for performing microbiome analysis for raw DNA sequencing data. It interprets demultiplexing and quality filtering, OTU picking, taxonomic assignment, and phylogenetic reconstruction, and diversity analyses and visualizations through command lines.	Kuczynski et al., 2011.
MaSuRCA (https://github.com/alekseyzimin/masurca)	Genome assembler	Zimin A.C. et al., 2013.
Ragout (https://github.com/fenderglass/Ragout)	A reference assisted assembly tool. Records contigs to create high quality scaffolds by using a genome rearrangement approach and multiple closely related genome references as a guide.	Kolmogorov et al., 2014.
Prokka (https://kbase.us/applist/apps/ProkkaAnnotation/an)	Rapid annotation of prokaryotic genomes.	Seemann T., 2014.

notate Contigs/release?gclid=Cj0KCQiAzZL- BRDnARIsAPCJs729c42yhdcRV0tbPIaJ5NVefV zYHwx5kDILF1ndoV- P5_UelqstiYaAgWrEALw_wcB)		
AUGUSTUS (http://augustus.gobics.de/)	A tool to predict genes in eukaryote genome sequences.	Stanke and Morgenstern, 2005.

1.10 Mechanism of Action of Drugs against Covid-19

The anti-malarial drugs used are chloroquine and hydroxychloroquine which is showing a promising possibility in clinical startups to fight against COVID-19. Looking at the potential the chloroquine and hydroxychloroquine of in silico studies which has been equipped with molecules having similar to chloroquine and reuse of chloroquine for cross checking of its success. These anti-malarial drugs have expressed its importance in the endocytic pathway, blockage of sialic acid receptors, and restriction of pH intervening spike protein splits at the ACE2 binding site and stop the cytokine storm. Sarma et al., (2020) identified the two main classes of components, such as theophylline and pyrimidone drugs as potential inhibitors of RNA binding to the N-terminal domain of nucleocapsid protein of corona virus, the opening of new challenges for in vitro checking. Now-a-days, the drugs reuse has been used to know the possibility of drugs which act against corona virus. The huge amount of efforts had been made and paid for the ability to validate the FDA approved or preclinical trial drugs for this disease. The many promising drug candidate aims too many virus protein. In the point of view the urgent and current use is to decrease the cost, time and danger of the drug development process, scientists are included in revalidating the already approving drugs again used for testing in COVID-19 patients. For example, chloroquine and hydroxychloroquine are past drugs which had been used to cure malarial, rheumatoid arthritis, lupus and sun allergies for past more than sixty years [James, Marguerite and Tomasz, 2020]. More than hundreds of patients expressed the advantage of chloroquine while compared with the treatment of standard care in terms of reducing the exacerbation of pneumonia, viral load and symptoms [Koichi, Riho and Sophia, 2020]. The first patient case was reported in washington on the eleventh day he had been hospitalized and had high fever with 39.4⁰C with cough and on the same day evening the treatment had been started giving the tablet remdesivir, the next day his condition has been improved. Cao et al., (2020) had experimented the trial test by using the two doses of lopinavir-ritonavir these are anti-viral drugs for COVID-19 patients. It cannot be recommended to take ribavirin and interferon drug because of the high danger chances of side effects but these drugs can be considered if the treatment was done with lopinavir, ritonavir, chloroquine and hydroxychloroquine then we can consider it [Elahe et al., 2020]. Up to this the trial test results have been confirmed from FDA-approved therapeutics or drugs but these had not been helpful in the treatment, curing or stopping the COVID-19 [Koichi, Miho and Sophia, 2020].

1.11 Proposed Drugs and Their Binding Energies of Covid-19

Table 2. The binding energies and function of proposed drugs

DRUGBANK ID	NAME OF THE DRUG	ΔG_{bind} (kcal/mol)	DESCRIPTION	REFERENCES
DB00284	Acarbosa	-99.51	Treatment and management of type II diabetes	Lance K.Campbell, John R.White and R Keith Campbell, 1996.
DB01698	Rutin	-92.44	Decrease capillary fragility	Aditya Ganeshpurkar and Ajay K. Saluja, 2017.
eDB06708	Lumefantrine	-88.91	Antimalarial agent	Sarah D'Alessandro et al., 2020.
DB06695	Dabigatran etexilate	-88.60	An anticoagulant that prevent blood clots forming	Claudia dimatteo et al., 2016.
DB00320	Dihydroergotamine	-88.36	A vasoconstrictor	Abimeal Gonzalez-Hernandez et al., 2018.
DB00183	Pentagastrin	-88.33	A synthetic polypeptide that stimulates gastric acid secretion	M.C.Mason, G.R.Giles and C.G.Clark, 1969.
DB00385	Valrubicin	-85.96	Treatment of the bladder cancer	Michael S.Cookson et al., 2014.
DB06772	Cabazitaxel	-85.57	Treatment of the prostate cancer	Channing J.Paller and Emmaneul S. Antonarakis, 2011.
DB12615	Plazomicin	-85.01	Antibacterial activity	Georgina Cox et al., 2018.
DB01229	Paclitaxel	-84.06	A chemotherapeutic agent	K.singla Anil, Alka garg and Deepika Agarwal, 2002.

From the above 10 drugs, acarbose and rutin has shown the more effective binding energies as compared with other drugs. For the comparison of using 2D-ligand-protein interactions of two highest binding energies, I found that rutin interconnect with ASN142, GLU166 and GLN189 by getting hydrogen bonds, which is same as saquinavir drug. But in case, acarbose interconnect with other amino acids in binding pockets using CASTp binds at THR24 and THR26. It mentions that the rutin drug shows the same inhibitory effect as saquinavir drug [Yifei, Lei and Zhong, 2020].

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