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Research Article

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Insights into Structure, Diagnostics and Available Treatment Strategies for COVID-19 Virus

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was first identified in December 2019 in Wuhan, the capital of China's Hubei province, and has since spread globally, resulting in the on-going 2019–20 coronavirus pandemic. The World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern (PHEIC) and a pandemic on 11 March 2020. Presently, the research on COVID-19 is unprecedented and in initial stages. Based on the literature on COVID-19 virus across Google Scholar, PubMed and Preprint servers, we systematically summarize the content on virus structure, pathogenicity, activity, diagnosis, prevention and treatment strategies of COVID-19 virus. The objective of this review is to support the public to identify and deal with the 2019 novel coronavirus (SARS-CoV-2) and provide an exhaustive literature search for researchers working on COVID-19.

Keywords: COVID-19; Spike protein; Main protease; Transmission; Diagnosis; Anti-virals; Vaccine

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INTRODUCTION

The on-going Coronavirus disease (COVID-19) outbreak across the globe has become the world's leading health headline and is causing major panic and public concerns. On January 30, 2020, the World Health Organization (WHO) declared that the new coronavirus outbreak is a public health emergency of international concern which was originated from Wuhan City in china in December 2019.China isolated this virus on 7 January 2020 which cause severe acute respiratory syndrome (2019-nCoV), where 'n' stands for novel and 'CoV' for coronavirus. This name complies with the WHO Best Practices for Naming of New Human Infectious Diseases.

The virus has already made a direct impact on more than millions of people in the different regions of world and has infected more than 6 million people, posing a health threat of unknown magnitude globally. As of June02, 2020, WHO reported total of 6,287,771confirmed cases (with 379,941 deaths) have been reported in 216 countries including Americas with 29,05,432 confirm cases (including 1,63,248deaths), Europe with 2,175,941 confirm cases(including 182 416 deaths), Japan, Australia, Germany, Iran, India. However, these daily estimates are expected to rise even higher as reports from WHO and other health agencies are gathered and near real-time updates of the Johns Hopkins virus dashboard are made. The outbreak has caused governments of various countries to take

swift and protective measures which includes putting cities on lockdown, implementing travel warnings/bans and cancellations, extending national holidays, and closing schools/universities, etc.

Currently, there is no approved vaccine for the prevention or treatment of the illness caused by the virus whose origin and extent mortalities remain unknown. There have been more than 100 research papers published within the last 60 days that have allowed for the rapid sharing of scientific information about the virus, but serious questions regarding the causes or mechanisms of transmission, incubation period, risk assessments, and options for effective treatment or intervention of the virus remain largely unanswered. There have been reports of significant shortages of medical staff, a lack of clinics that can handle and treat infected patients, and high demands for face masks for protection. Majorly all the central governments are working with extraordinary diligence to mobilize resources, which includes building of new hospitals and developing new coronavirus vaccine, as well as sending medical experts and clinicians to the cities which are most effected by highly transmittable virus outbreak.

With the continuing coronavirus spur, the public has been advised by various health authorities to reduce traveling and stay at home as a basic means of limiting people's exposure to the virus. Health authorities, including the National Health Commission of the People's Republic of China, WHO, and U.S Centres for Disease Control and Prevention, have issued safety recommendations for taking simple precautions to reduce exposure to and transmission of the virus. Unfortunately, the mandated restrictions on travel and directives against participating in outdoor activities, including regular physical activity and exercise, will inevitably disrupt the routine daily activities of tens of millions of people.

While containing the virus as quickly as possible is the urgent health priority, there have been few health guidelines laid down for the public as to what people can or should do in terms of maintaining their daily exercise or physical activity routines. Arguably, staying home, while a safe measure, may have unintended negative consequences since such efforts to avoid human-to-human transmission of the virus may lead to reduced physical activity. It is likely that prolonged home stay may lead to increased sedentary behaviours, such as spending excessive amounts of time sitting, reclining, or lying down for screening activities (playing games, watching television, using mobile devices); reducing regular physical activity (hence lower energy expenditure); or engaging in avoidance activities that, consequently, lead to an increased risk for and potential worsening of chronic health conditions. Therefore, there is a strong health rationale for continuing physical activity in the home to stay healthy and boost immune system to fight the COVID19 virus, where proper diet and intake of polyphenols are primarily essential.

The new COVID-19 is caused by the virus SARS-CoV-2. The most likely ecological reservoirs for SARS-CoV-2 are bats, but it is believed that the virus jumped the species barrier to humans from another intermediate animal host. This intermediate animal host could be a domestic food animal, a wild animal, or a domesticated wild animal which has not been yet identified. (As per WHO).

Materials and Methods

Structural Insights of Virus

COVID-19 is a spherical or pleomorphic enveloped particle containing single-stranded (positive-sense) RNA associated with a nucleoprotein within a capsid comprised of matrix protein. The envelope bears club-shaped glycoprotein projections. Some coronaviruses also contain a hem agglutinin-esterase protein (HE). Coronaviruses possess the largest genomes (26.4–31.7 kb) found among the family of (positive-sense) RNA viruses. Structural components of corona virus is shown in Figure 1. The virus consists of following parts (Figure 1).

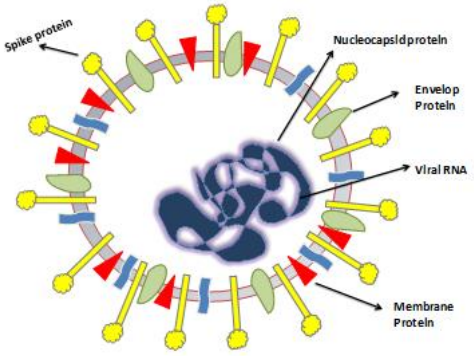

Figure 1: Structural components of corona virus

Spike Protein (S)

It is most important trimeric protein of COVID19 virus as associated with contact with human cell receptor called angiotensin converting enzyme 2 (ACE-2). In fact, the main inducer of neutralizing antibodies is S protein few mutations that form a particularly compact 'ridge' in the spike protein is responsible for speculated virulence. This ridge is more compact than the one in the SARS virus, and this new strain is so adept at infecting humans, causing COVID-19.

Membrane Glycoprotein (M)

It spans the membrane bilayer three times, leaving a short NH2-terminal domain outside the virus and a long COOH terminus (cytoplasmic domain) inside the virion. M plays a predominant role in the intracellular formation of virus particles without requiring S.

Nucleocapsid (N)

Proteins are encoded by ORFs (open reading frames) on the one-third of the genome near the 3′-terminus. Besides these four main structural proteins, different CoVs encode special structural proteins among all known RNA viruses, with G + C contents varying from 32% to 43%.

The Virus Activity

Transmission: COVID-19 can be transmitted through air while sneezing in the form of droplets. As droplets contains huge amounts of viruses, bacteria can also find to stick withit. There are some reports which suggest that the virus might transfer from faecal-oral route. However, it is well established that droplet transmission of this coronavirus leads to community transmission which is the major public health concern.

Spread in Respiratory Tract

As the virus gets inside the human body through nose or mouth, it initially gets stuck in trachea which further spreads to bronchi, bronchioles and alveoli. After entry, this virus transfers its genetical code to the human cells with the help of the protein spikes which help it in attachment with angiotensin converting enzyme 2 (ACE2) receptor. This helps to create a new cell called virions or new virus of the COVID-19. These viruses enter into alveoli inside

lungs where oxygen is absorbed by the cells, these viruses forms a pneumocyte cells. These cells are formed at a similar rate as the growth or multiplication of the virus by its genetical matter inside pneumocyte cell. As due to these cells, a fluid like matter gets accumulated in the alveoli which cause shortness of breath and difficulty in breathing (Figure 2).

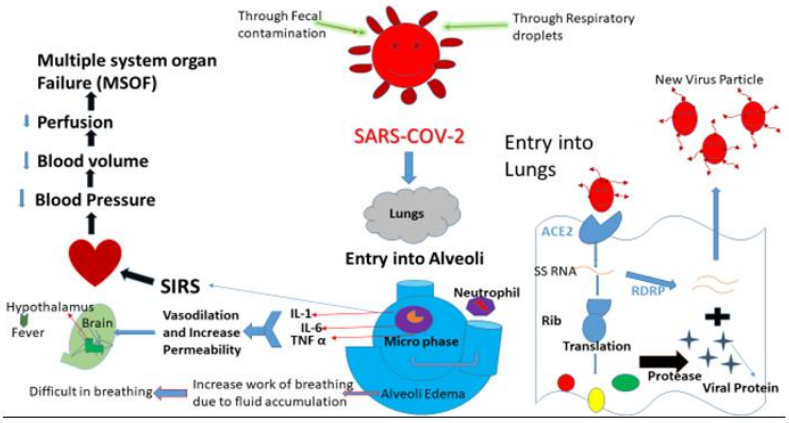

Figure 2: Virus Transmission, replication cycle inside the host cell, and their effect on heart, brain, lungs

Affects Due to Virus Spread

Due to accumulation of fluid, problem in breathing arises and amount of oxygen sucked by the alveolis gradually decreases. Thus, due to this affects hypothalamus and fever starts. As, the normal activity in alveoli's is disturbed, the heartbeat and respiration increase, and level of oxygen gets lower.

Potential Strategies for targeting COVID19 virus

Spike protein or S proteins interacts with host cell receptor, which is angiotensin converting enzyme 2 (ACE-2) receptor. During the first step of receptor binding the spike protein is cleaved in to S1 and S2 by host cell protease known as trans-membrane protease seerin-2 (TMPRSS-2). S1 subunit binds with surface cell receptor of host and S2 subunit (which consists of a fusion peptide, a trans-membrane domain, and cytoplasmic domain which is highly conserved) mediate membrane fusion. The amino acids present in S2 subunit can be the potential drug target. Development of vaccine derived from spike protein can facilitate recognition of virus by immune cell or to develop monoclonal antibodies that bind to covid-19 spike protein and block interaction with human cell. As TMPRSS2 mediate entry of virus into human cell thus can also be potential target as shown (Figure 3).

Spike protein strong binds to ACE-2 and enter to human cell. These receptors are highly expressed in type-2 alveolar cells in lungs. The interaction between ACE-2 receptor and spike protein can be the potential drug target. It has been found that the binding of spike protein with ACE-2 receptor suppress the receptor and contribute to severe lung injury. Administration of excessive soluble ACE-2 may competitively bind to SARS-CoV-2 to neutralize virus and rescue cellular Renin Angiotensin system to protect lung from injury.

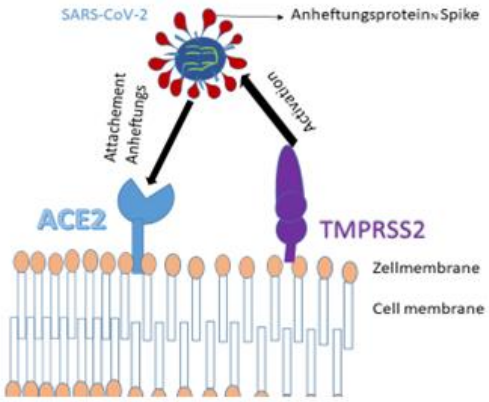

Figure 2: Binding of virus spike protein with cellular ligand of host cell, and activation by protease

SARS-CoV-2 (COVID-19 virus) binds to ACE-2 (the angiotensin-converting enzyme 2) by its Spike and allows COVID-19 to enter and infect cells. For the virus to complete entry into the cell following this initial process, the spike protein must be primed by an enzyme called a main protease (Mpro). Similar, to SARS-CoV, SARS-CoV-2 (COVID-19 virus) uses a protease called TMPRSS2 to complete this process. In order to attach virus spike protein to its cellular ligand (ACE2), activation by TMPRSS2 as a protease is needed.

Many researchers are targeting spike proteins to block this virus-host cell interaction and this category spike protein inhibitors are creating a promising hope for anti- CoV drug discovery.

Targeting Replication of Viral Genome

CoVs has single stranded positive sense RNA (+ss RNA) as their genetic material. The genetic material of CoVs is largest among all known RNA virus i.e. approximately 30kb in length. It possesses 5′-cap structure and 3′-poly-A-tail. The virus uses its genetic material mRNA for translation of replicas polyprotein 1a and 1ab (pp 1a/pp 1ab). Cleavage of these polyprotein produces nonstructural proteins like RNA dependent RNA polymerase, Helicase and nonstructural protein 3, 4, and 6 (nsp3, nsp4 and nsp6). These three nsps are thought to be responsible for ease of corona virus replication transcription complex (RTC) through recruitment of intra cellular endoplasmic reticulum membrane to form double membrane vesicle (DMV).

RNA dependent RNA polymerase (RdRp) and helicase move to DMV and facilitates the production of sub-genomic RNA from which structural and accessory proteins is produced in next phase of translation. Thus, RdRp is the most promising potential target of corona virus disease. Transcription termination occurs at transcription regulatory sequences located between open reading frames (ORFs) that act as templates for production of sub-genomic mRNA.

Virally encoded chymotrypsin like protease (3CLpro), main protease (Mpro) or two papain like protease for production of 16nsp facilitate the frame shift between ORF1 and ORF1b which increase the production of both pp 1a and pp 1ab poly peptide. Once Tans-membrane proteins S, E, M are synthesized they are inserted into endoplasmic reticulum and then transported to endoplasmic reticulum Golgi intermediate compartment. The N protein binds to the viral genomic RNA in cytoplasm and form nuclear capsid. Once the final variant assembly occurs in the intermediate compartment, mature variants are released through smooth wall vesicle by exocytosis.

Preventive Measures adopted to limit the spread of COVID-19 virus

Immune Boosting Measure for Self-care: Elder peoples and person with heart disease, diabetes or the one consuming alcohol or tobacco product are more susceptible to COVID-19 as their immunity is low as compared to normal adult individual. Boosting immunity in infected person is found effective in combating COVID-19 infection.

The immune system depends on the ability of white blood cells to produce antibodies against foreign pathogens like bacteria, virus, and other invaders. Consumption of fruits and vegetables containing nutrients like beta-carotene, vitamin C, and vitamin E can boost immune function. Vitamins C and E are antioxidants that help to destroy free radicals and support the body's natural immune response. Vitamin D supplementation may reduce the risk for viral infections, including respiratory tract infections, by reducing production of pro-inflammatory compounds in the body. Increased vitamin D in the blood has been linked to prevention of other chronic diseases including tuberculosis, hepatitis, and cardiovascular disease. Zinc is a mineral that can help boost white blood cells, which defend against invaders. Research also shows that oil may impair white blood cell function and that high-fat diets may alter the gut micro-biota that aid in immunity. So, consumption of low-fat diet is also effective in boosting immunity. Thus, vegetarians have shown to have more immunity than the non-vegetarians. Maintaining healthy weight is also shown effective in maintaining immune function. Sources of various nutrients that can boost immune system are shown (Table 1).

Table 1: Various nutrients with their sources

Nutrient	Source
Vitamin C	Red peppers, oranges, strawberries, broccoli, mango, lemon, etc.
Vitamin D	Fortified cereals and plant-based milks and supplements.
Vitamin E	Nuts, seeds, spinach, and broccoli
Zinc	Nuts, pumpkin, seeds, sesame seeds, beans and lentils.

Hygienic Habits

The virus spreads through respiratory droplets produced by infected person during coughing or sneezes. When infected person touches a surface by contaminated hand (touch their own mouth, nose, or eyes) of virus particles on it and then it circulates to a healthy person by same mode. Hand hygiene is the important mode to prevent and spread to human for contagious disease. Frequently washing of hand by soap and water for at least 20 seconds or using 68-72 % alcohol-based hand sanitizer is found effective in maintain hand hygiene. Frequently touching of eye, nose, and mouth must be avoided. Best method of coughs and sneezed with the inside of your elbow or upper arm. It prevents to hand become contaminated. Stay home and take rest if you are feeling cold, cough, fever and consultant with doctor.

Various reports suggest that the virus can survive for 5 days on metal surface; 4 days on wood; 2-3 days on plastic and stainless steel; up to 5 days on glass, paper and ceramics; and 24 Hr. on cardboard. So frequently touching surfaces like door handles, light switches, phones, bathroom fixtures and remote controls must be cleaned. For that refer to the CDC's environmental cleaning and disinfection recommendations and this list available of EPA-registered disinfectants. According to the CDC, alcohol solutions with at least 68-72% alcohol, diluted household bleach solutions, and most common EPA-registered household disinfectants should be effective against the COVID-

19 virus. While cleaning a surface the surface must left in contact with the disinfectant for enough period and should not be dried immediately. Different wipes must be used for cleaning different surfaces as use of single wipe can contaminate another surface.

Social Distancing

Keeping a distance from other people is unfamiliar territory for most of us. It feels awkward and unnatural. We're not sure what to do and on top of this, the goal posts appear to shift daily as we grapple with the changing landscape of this coronavirus pandemic. Social distancing, more appropriately called physical distancing, is not always straight forward and if you are sometimes unsure, you are not alone. In order to put the theory into practice, we need to adhere to two principles. Firstly, assume everyone we meet has coronavirus, regardless of how they look or who they are. And secondly, also assume that we have coronavirus, and could give it to other people. It's important we all act as though we are potentially carrying the virus.

The incubation period of the virus ranges from 1 to 12.5 days but can be if 14 days. During this period the infected person may meet many peoples and infect them also. As the virus spreads by meeting sneezes and cough of the infected individual directly or indirectly so proper distancing from peoples must be maintained. This is the only way to break the chain from human to human transmission of the virus. Limiting our contact with people will slow down virus transmission and flatten the epidemic curve so that we can reduce the number of cases occurring at the peak of the epidemic. The aim is to lighten demands on the health system when the epidemic is at its peak, so all of those needing help can get it, and we save lives.

Social distancing reduces the R0. R0 (pronounced "R-naught") is the rate at which a corona virus is transmitted. Also called the basic reproduction number, it indicates the average number of people who will contract the virus from a person who has already been infected, in a population that does not have immunity for the corona virus. R0 is the division of the number of new infections by the number of existing infections, or the average number of new infections over an infectious period (R0= new infections/existing infections). The higher the R0, the more contagious the infection. At its highest, India's R0 was estimated at 4 on 23 March 2020, according to a study by the Indian Council of Medical Research (ICMR).

Regular Physical activity

Exercise at home using various safe, simple, and easily implementable exercises is well suited to avoid the airborne coronavirus and maintain fitness levels. Such forms of exercise may include, but are not limited to, strengthening exercises, activities for balance and control, stretching exercises, or a combination of these. Examples of home exercises include walking in the house and to the store as necessary, lifting and carrying groceries, alternating leg lunges, stair climbing, stand-to-sit and sit-to-stand using a chair and from the floor, chair squats, and sit-ups and pushups. In addition, traditional Tai Ji Quan, Qigong exercises, and yoga should be considered since they require no equipment, little space, and can be practiced at any time. The use of eHealth and exercise videos, which focuses on encouraging and delivering physical activity through the Internet, mobile technologies, and television are other viable avenues for maintaining physical function and mental health during this critical period.

Official measures that restrict people's movements in the presence of the coronavirus crisis do not necessarily mean that physical activity must be limited or that all forms of exercise must be eliminated entirely. Exercise has been shown to have clear health benefits for healthy individuals and for patients with various diseases. In this respect, we strongly echo Dr. Steven Blair's quote from Dr. Ken Powell: "Some activity is better than none, and more is better than less" The aim should be to undertake at least 30 min of moderate physical activity every day and/or at least 20 min of vigorous physical activity every other day. Ideally, a combination of both intensities of physical activities is preferable in addition to practicing strengthening-type activities on a regular basis. Children, the elderly, and those

who have previously experienced symptoms of illness or are susceptible to chronic cardiovascular or pulmonary disease should seek advice from health care providers about when it is safe to exercise (Figure 4).

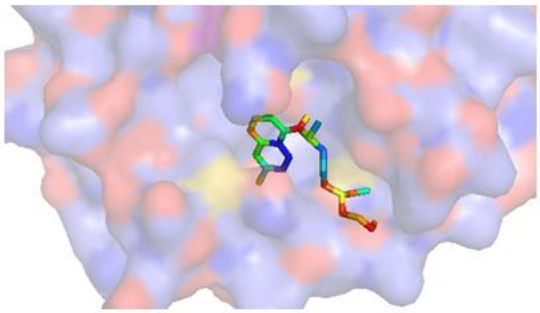

Figure 4: The binding mode of COVID-19 virus Mpro with Hydroxychloroquine (sticks) shows that it forms van der Waal interactions with His41, Met165, Glu166, Leu167, Gln189, Met 49, Arg188 and Thr190. This docking pose is drawn using Pymol software from the output files retrieved from molecular docking using AutoDock Vina

Given the concerns about the increasing spread of COVID-19, it is imperative that infection control and safety precautions be followed. Home stay is a fundamental safety step that can limit infections from spreading widely. But prolonged home stays can increase behaviors that lead to inactivity and contribute to anxiety and depression, which in turn can lead to a sedentary lifestyle known to result in a range of chronic health conditions. Maintaining regular physical activity and routinely exercising in a safe home environment is an important strategy for healthy living during the coronavirus crisis.

Diagnostic Tests for COVID19 Detection as per WHO Recommendations

WHO continues to evaluate available immunodiagnostics tests for COVID-19 and will update their scientific briefing whenever found necessary.

Rapid Diagnostic Tests Based on Antigen Detection

One type of rapid diagnostic test (RDT) detects the presence of viral proteins (antigens) expressed by the COVID-19 virus in a sample from the respiratory tract of a person. If the target antigen is present in enough concentrations in the sample, it will bind to specific antibodies fixed to a paper strip enclosed in a plastic casing and generate a visually detectable signal, typically within 30 minutes. The antigen(s) detected are expressed only when the virus is actively replicating; therefore, such tests are best used to identify acute or early infection. How well the tests work depends on several factors, including the time from onset of illness, the concentration of virus in the specimen, the quality of the specimen collected from a person and how it is processed, and the precise formulation of the reagents in the test kits. Based on experience with antigen-based RDTs for other respiratory diseases such as influenza, in which affected patients have comparable concentrations of influenza virus in respiratory samples as seen in COVID-19, the sensitivity of these tests might be expected to vary from 34% to 80%. Based on this information, half or more of COVID-19 infected patients might be missed by such tests, depending on the group of patients tested. These assumptions urgently require further study to understand whether they are accurate. Additionally, false-positive results – that is, a test showing that a person is infected when they are not – could occur if the antibodies on the test strip also recognize antigens of viruses other than COVID-19, such as from human coronaviruses that cause the

common cold. If any of the antigen detection tests that are under development or commercialized demonstrate adequate performance, they could potentially be used as triage tests to rapidly identify patients who are very likely to have COVID-19, reducing or eliminating the need for expensive molecular confirmatory testing. With the limited data now available, WHO does not currently recommend the use of antigen-detecting rapid diagnostic tests for patient care, although research into their performance and potential diagnostic utility is highly encouraged (Figure 5).

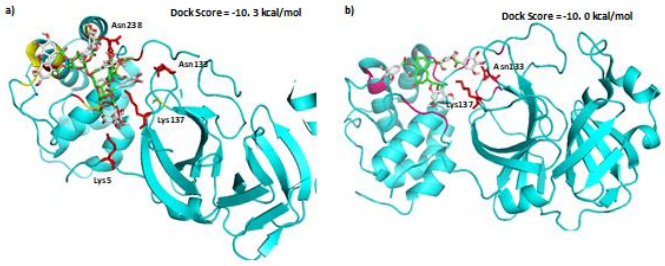

Figure 3: The binding mode of COVID-19 virus M-pro with SH6 (sticks) shows that it forms hydrogen bonding with Asn238, Lys137, Lys5 (shown in sticks red) and van der Waal interactions with Glu288, Met276, Leu267, Gly275, Leu267, Gly275, Leu272, Tyr237, Asn274, Thr199, Asn238, Thr198, Lys137, Val171, Thr169;b) The binding mode of COVID-19 virus M-pro with TDG (sticks) shows that it forms hydrogen bonding withAsn133, Lys 137 (shown in sticks red) and van der Waal interactions with Asp197, Asn238, Ala194, Thr135, Val171, Arg131,Glu290, Asp289, Asn238, Tyr239, Glu288, Leu287, Leu271 and Gly275 residues. These docking poses are drawn using Pymol software from the output files retrieved from molecular docking using AutoDock Vina

There is another, more common type of rapid diagnostic test marketed for COVID-19; a test that detects the presence of antibodies in the blood of people believed to have been infected with COVID-19. Antibodies are produced over days to weeks after infection with the virus. The strength of antibody response depends on several factors, including age, nutritional status, severity of disease, and certain medications or infections like HIV that suppress the immune system. In some people with COVID-19, disease confirmed by molecular testing (e.g. reverse transcription polymerase chain reaction: RT-PCR), weak, late or absent antibody responses have been reported. Studies suggest that the majority of patients develop antibody response only in the second week after onset of symptoms. This means that a diagnosis of COVID-19 infection based on antibody response will often only be possible in the recovery phase, when many of the opportunities for clinical intervention or interruption of disease transmission have already passed.

Antibody detection tests targeting COVID-19 may also cross-react with other pathogens, including other human coronaviruses and give false-positive results. Lastly, there has been discussion about whether RDTs detecting antibodies could predict whether an individual was immune to reinfection with the COVID-19 virus. There is no evidence to date to support this. Tests to detect antibody responses to COVID-19 in the population will be critical to support the development of vaccines, and to add to our understanding of the extent of infection among people who are not identified through active case finding and surveillance efforts, the attack rate in the population, and the infection fatality rate. For clinical diagnosis, however, such tests have limited utility because they cannot quickly diagnose acute infection to inform actions needed to determine the course of treatment.

Some clinicians have used these tests for antibody responses to make a presumptive diagnosis of recent COVID-19 disease in cases where molecular testing was negative but where there was a strong epidemiological link to COVID-

19 infection and paired blood samples (acute and convalescent) showing rising antibody levels. Based on current data, WHO does not recommend the use of antibody-detecting rapid diagnostic tests for patient care but encourages the continuation of work to establish their usefulness in disease surveillance and epidemiologic research.Other than that, many multinational companies from various countries developed the test kits.

PCR Detection Method

PCR detects nucleic acid of covid-19 which is primary method for detecting the virus. Reverse transcription polymerase chain reaction (RT-PCR) kits are developed which genetically diagnose SARS-CoV-2. Basic principle of RT-PCR is reverse transcription of covid-19 RNA into complementary DNA (cDNA) strand followed by amplification of specific regions of cDNA. It was found that the virus conserves its nucleic acid sequences in three regions: the RdRp gene (RNA dependant RNA polymerase gene) in the open reading frame ORF1ab region, the E gene (envelop protein gene), and the N gene (nucleocapsid protein gene). Both RdRp and E genes proteins are highly sensitive for detection whereas N gene provide poor analytical sensitivity. Designing of RT-PCR generally consists of two steps: sequence alignment and primer design, and assay optimization and testing.

The assay can be designed as a two-target system, where one primer universally detects numerous corona viruses including SARS-CoV-2 and a second primer set only detects SARS-CoV-2. RT-PCR can be done in either a one step or a two-step assay. In one step assay reverse transcription and PCR amplification are merged in one reaction. This assay provides rapid reproducible results for high throughput analysis. The challenge is the difficulty in optimizing the reverse transcription and amplification step as they occur simultaneously, which leads to low target amplicon generation. In the two-step assay, the reaction is done sequentially in separate tubes. This assay format is more sensitive than one step assay but it is more time consuming and requires optimizing additional parameters. Lastly, controls needs to ensure the reliability of the assay and to identify experimental errors.

Results and Discussion

Effective Drugs for COVID-19

There are currently no FDA-approved medical countermeasures for COVID-19. FDA stands ready to work with medical product developers to clarify regulatory and data requirements necessary to move products forward in development as quickly as possible. Following drugs have shown some promising effect in the management of infection:

Chloroquine/hydroxychloroquine (CQ/HCQ)

CQ and HCQ is widely used drug for malarial infection. These drugs proved effective in treatment of covid-19 infection. These drugs modulate immune system of infected person. Particularly, HCQ reduces activation of T cell, differentiation and expression of co-stimulatory proteins (e.g. CD154 on CD4+T cells) and cytokines produced by T cells and B cells (e.g. IL-1, IL-6, and TNF) as they rise the intracellular pH which inhibit lysosomal activity in antigen presenting cells (APCs), plasmacytoid dendritic cells (pDCs), and B cells. Which in turn prevent antigen processing and major histocompatibility complex (MHC) class-II mediated autoantigen presentation to T cells. HCQ suppress TLR signaling as it interrupts binding between Toll like receptors (TLR7 and TLR9) and their RNA/DNA ligands.

HQC also interferes with cytosolic DNA and nucleic acid sensor cyclic GMP-AMP (cGAMP) synthase (cGAS). TLR signaling and cGAS stimulation of interferon genes are impaired, also pro-inflammatory signaling activation

and production of cytokines (IL-1, IL-6, and TNF) are suppressed by HCQ. Thus, HCQ is likely to confer an ability to suppress the CRS, which is due to over activation of the immune system triggered by SARS-CoV-2 infection, through which progression of the disease from mild to severe might be reduced.

CQ block the virus entry into the host cell by interfering with glycosylation of angiotensin converting enzyme 2 (ACE-2). Alteration in glycosylation of ACE-2 receptor reduces the binding affinity of SARS-CoV spike protein to bind with the receptor. Figure 4 represents binding mode of COVID-19 M-pro with HCQ which display deep binding inside the active site pocket of M-pro.

Lopinavir-ritonavir

Lopinavir-ritonavir is anti-HIV drug. This combination of drug is used to treat HIV in adults and children over 14 days of age who are infected with HIV-1. In hospitalized adult patients with severe Covid-19, no benefit was observed with lopinavir-ritonavir treatment beyond standard care. Future trials in patients with severe illness may help to confirm or exclude the possibility of a treatment benefit.

Favipiravir

Favipiravir is found effective in treating covid-19 infection. This drug is under clinical trial. Favipiravir is a new type of RNA dependent RNA polymerase inhibitor (RsRp). It is a prodrug which is ribosylated and phosphorylated intracellularly to form active facipiraviribofuranosyl-5′-triphosphate (T-705-RTP) which competes with purine nucleosides and inhibit RdRp of virus. Currently favipiravir is in 3rd phase clinical trial which conducted by Glenmark pharmaceuticals, India.

Remdesivir

Remdesisir (GS-5734) which is previously found effective in treating lethal Ebola and Nipah virus is found most effective for COVID -19 infections. It is a nucleoside analogues drugs that can block the RNA-dependent RNA polymerase (RdRp) during the replication of corona virus in respiratory epithelial cells. The drug is under phase-3 clinical trial. USFDA approved remdesivir as drug for emergencey use to treat corona on 1st May 2020. (USFDA,2020)

Camostat mesylate

Camostat mesylate is found to block the entry of virus into the host cell by inhibiting cellular host TMPRSS-2. Futher study is required for approving this drug in treating corona infection. Camostat mesylate is a protease inhibitor which is approved for treating pancreatic inflammation.

Hesperidin and Rutin

Hespiridin is a natural flavonoid. In various computational study reports hesperidin is found most effective in interfering interaction between spike protein and ACE-2 receptor and best potential inhibitor against protease of COVID-19. According to in silico reports there are 24 other drugs that proved better than Nelfinavir. Our research group also reported recently the potential of theaflavin gallate (TG), theaflavin digallate (TDG) and sanguiin-H-6 (SH6) as potential inhibitors of M-pro of COVID19 virus. Figure 5 shows binding mode of COVID-19 M-pro with SH6 and TDG. The potential of polyphenols for various therapeutic ailments are already established in the literature.

Roche's Actemra (Tocilizumab)

Elevated level of inflammatory cytokine IL-6 in blood of infected person is predicted to be fetal. So, utilization of immune-modulators, Tocilizumab a monoclonal antibody can directly block IL-6 and is recommended in critically ill patient with bilateral lung lesion and conformed level of IL-6. Roche's Actemra is approved by China for treatment of corona virus.

IL-6 can bind to transmembrane IL-6 receptors (mIL6R) and soluble IL-6 receptors (sIL-6R), and the resulting complex can combine with signal transducing component gp130 to activate the inflammatory response. Tocilizumab can bind specifically to sIL-6R and mIL-6R, and block signal transduction.

Novel Corona Virus Vaccines

Listed below are the coronavirus vaccines in various stages of development, across the world.

- Entos Pharmaceuticals is developing Fusogenix DNA vaccine developed using the Fusogenix drug delivery platform to prevent COVID-19 infections. Fusogenix drug delivery platform is a proteo-lipid vehicle that introduces genetic payload directly into the cells. Entos is working on developing an optimized payload containing multiple protein epitopes derived from SARS-COV-2 proteins, which will stimulate an immune response in the body to prevent COVID-19 infection.
- The University of Oxford's ChAdOx1 nCoV-19 is an adenovirus vaccine vector developed by the university's Jenner Institute. The university is testing the vaccine in a clinical trial planned to be conducted in the Thames Valley Region. Approximately 510 volunteers aged between 18 years and 55 years will be enrolled for the study.
- Roivant Sciences is advancing the development of Gimsilumab a clinical-stage, human monoclonal antibody. The drug targets granulocyte-macrophage colony stimulating factor (GM-CSF), which is a pro-inflammatory cytokine found in high levels in the serum of COVID-19 patients. Targeting GM-CSF is expected to reduce lung damage and reduce mortality rate in COVID-19 patients.
- Altimmune has collaborated with the University of Alabama at Birmingham (UAB) to develop a single dose intranasal vaccine for COVID-19 named AdCOVID. The company is currently carrying out immunogenicity studies after, which phase one clinical trial material will be developed. Altimmune and UAB will work with researchers to conduct preclinical animal studies and phase one clinical trial in the third quarter of 2020.
- I-Mab Biopharma is developed TJM2, a neutralizing antibody, as a treatment for cytokine storm in patients suffering from a severe case of coronavirus infection. The drug targets the human granulocyte-macrophage colony-stimulating factor (GM-CSF), which is responsible for acute and chronic inflammation. The company will commence development after receiving approval for the Investigational New Drug (IND) application from the U.S. Food and Drug Administration (FDA).
- Airway Therapeutics is exploring its novel human recombinant protein named AT-100 (rhSP-D) as a treatment for coronavirus. The company has announced a filing with the Respiratory Diseases Branch of the National Institutes of Health to evaluate the drug. AT-100 has shown efficacy in preclinical studies in reducing inflammation and infection in the lungs, while also generating an immune response against various respiratory diseases.
- An intranasal COVID-19 vaccine is being developed by US-based clinical-stage biopharmaceutical company, Altimmune. Design and synthesis of the single-dose vaccine have been completed, while animal testing will follow. The coronavirus vaccine is being developed based on a vaccine technology platform that is similar to NasoVAX, an influenza vaccine developed by Altimmune.
- Moderna and the Vaccine Research Center, a unit of the National Institute of Allergy and Infectious Diseases (NIAID), have collaborated to develop a vaccine for coronavirus. The vaccine targets the Spike (S) protein of the coronavirus. The first vials of the vaccine have been manufactured at Moderna's

Massachusetts manufacturing plant and shipped to NIAID for phase one human clinical trial. The trial began on 16 March at the Kaiser Permanente Washington Health Research Institute in Seattle, Washington. A total of 45 males and females aged between 18 and 45 have been enrolled for the trial.

The participants will be divided into three cohorts who will be administered 25 microgram (mcg), 100mcg or 250mcg dose 28 days apart.

Conclusion

Today the entire human population and world economy is under the major grasping power of COVID19 diseaseand drug discovery against SARS-CoV-2/ COVID19 virus is the utmost requirement. Although, the preventive measures to curb the virus transmission is being followed in every region of world but it's not an ultimate solution. The development of vaccine/anti-CoV drugs against COVID19 virus can bring back the hope and safety compliance among people once gain. The structural details, replication and transmission cycle and available drug design strategies to inhibit COVID19 virus is being addressed in the review. The available treatment like use of hydroxychloroquine, anti-viral drugs (remdesivir, ritonavir, lopinavir, etc.), and use of polyphenols (rutin, theaflavin and analogues) can be used against SARS-CoV-2 pathogenesis.

Finding

No funding has been received for this project from any Government or Non-Government organization.

Authors Contribution

A and AKK have collected the literature and prepare the first draft of manuscript. SS, NG, AS has provided their expert opinion on the manuscript. The content of manuscript was analysed, written and finalized by SB.

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