2022 8th International Conference on Advanced Computing and Communication Systems (ICACCS)

Quantum Chemical Studies on SARS-CoV-2 - a Review

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2022 8th International Conference on Advanced Computing and Communication Systems (ICACCS) | 978-1-6654-0816-5/22/$31.00 ©2022 IEEE | DOI: 10.1109/ICACCS54159.2022.9785163

***Abstract*—As soon as foreign substances like bacteria, fungi, chemicals and viruses (antigens) enter a human body, a protective protein (mostly Y-shaped), known as an antibody (immunoglobulin G - IgG) is produced by our immune system. But antibodies are not that much effective against viruses. Because viruses tend to mutate that leads to change in their shape which disturbs the necessitation of shape complementarity which limits the effectiveness of the antibody. Coronaviridae is a family of viruses that are responsible for SARS-CoV-2 (COVID-19) infection which is a contagious and serious viral infection. These spreads breathing of viral drops coming out of coughing and sneezing of infected persons. Touching of infected surface is also a prime cause of infection. Vaccines tend to train and prepare our body's immune system to recognize and fight off the infectious foreign bodies when they enter. After vaccination, if the antigens enter our body later, our immune system will be immediately ready to destroy them to prevent sickness. Lot of factors like vaccine inefficiency to different variants of existing viruses, age factor, denial of vaccination and previously existing illness make the issue still critical. To face this deadly, alarming global challenge and to prevent the future coronavirus outbreaks, various scientific communities have been toiling in multiple diverse studies about this newly emerged virus. In this review, we underline and summarize the recent research findings involving the SARS-CoV-2's structure, character, lifecycle, its target, finding out antivirus drugs (mainly S-protein of SARS-CoV-2 is targeted), inhibitors, a protocol to identify anti-COVID-19 candidates, detection of efficient and approved vaccines etc.**

Keywords: SARS-CoV-2, S-protein, ACE2, RT-PCR

I. INTRODUCTION

Out of several viral respiratory infections and illness such as influenza A (H1N1), MERS and Tuberculosis (TB), Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV-2) [1] becomes a key epidemic and qualified as severe pandemic and turns out to be a major intimidation to the public wellbeing. SARS-CoV-2 has been identified in Wuhan city, China in 2019 and spread right through the entire world. It has been considered to be a strain of corona virus that is responsible for Corona virus disease 2019 (COVID - 19). This viral outbreak is still existing as a threat and shattering the lives of human fraternity. SARS-Cov-2 is considered as a non-segmented RNA virus with an envelope.

On 11th February 2020, World Health Organization (WHO) has recognized SARS-Cov-2 and announced it as an international community health emergency. On 30th January 2020, it has been announced as a pandemic. Coronaviruses are large particles having unique surface projections and they are enveloped by many protein molecules like a cover including the spike glycoprotein (S-protein) [2] as shown in Fig.1. The COVID-19 virus is RNA-pocketed through a strand. The S-protein of COVID-19 virus has a sugar coat of glycans which serves a challenge against the immunity of a human body (Fig.2). The coronavirus is wrapped by large number of glycosylated S-proteins at its surface which helps them to attach with the host cell receptor Angiotensin Converting Enzyme 2 (ACE2). This mediates SARS-CoV-2 to go inside the human body.

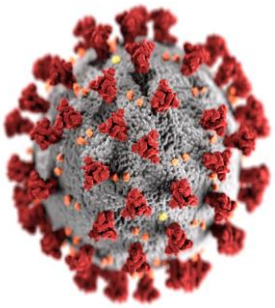

Fig.1. Structural Morphology of Coronavirus (Source: CDC/ Alissa Eckert, MSMI; Dan Higgins, MAMS)

While the S-protein attaches to the receptor, its activation encourages the entry of virus inside the cell. Immediately after the virus entry, the release of viral RNA occurs which leads to RNA replication. This duplication leads to the synthesization of structural proteins which helps them to be assembled and packaged in the host cell which gives the way to the release of viral particles. (Fig. 3) [3].

When a coronavirus enters a human body, it becomes as an invader and multiplies in the body. It fastens its spiky glycosylated surface proteins to receptors on healthy cells in our body especially in lungs and takes over the healthy cells and kills them also. These S-proteins play a significant role

in deciding the life cycle of a virus and also considered to be suitable target for drug therapies. Within 2 to 14 days, our immune system responds to SARS-CoV-2 with fever, cold, cough, intolerable body pain, inhalation problems, smell and taste disorders. COVID-19 is believed to be a fatal and contagious disease. This causes respiratory infection which may lead to pneumonia. This virus is generally transmitted when infected people cough, sneeze, and through their saliva droplets and nasal secretions. The mechanism of SARS-CoV-2 entry inside the cell which leads to the immune dodging and cell contagion are studied.

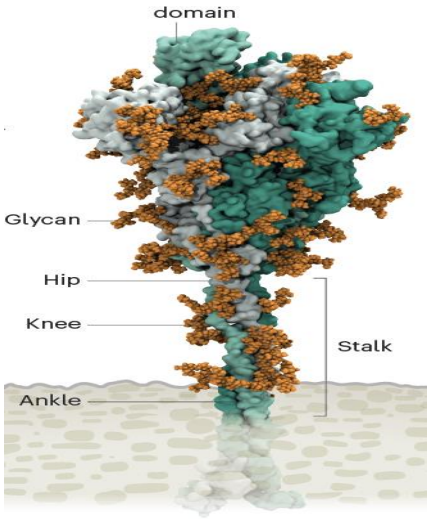

Fig.2. The hidden spike of Coronavirus (Source: Lorenzo Casalino, Univ. California, San Diego).

II. ANTIVIRUS DRUGS DEVELOPMENTS

The original hot spots between the SARS-CoV-2 S-protein and ACE2/B38 antibody was studied which will give helpful information for antibody design in future. Centaurea jacea is a herb used for skin related problems and medicine for fever also. Inhibitors are the substances that suppress the activity of another substance. The activity against SARS-CoV-2 of the bio active element of Centaurea jacea has been studied by using a threefold approach and found that it can be used as a preventive measure and found to be a potential inhibitor against COVID-19 infections [4].

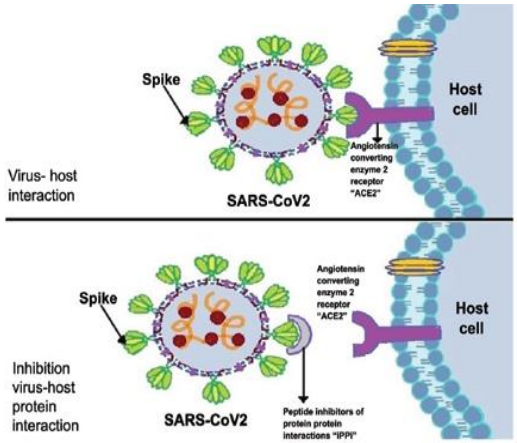

Fig.3. Cell entry mechanism of coronavirus

Carrageenans are linear sulfated polysaccharides. Kappa, iota- and lambda-carrageenans are ionic carrageenan polysaccharides. They are obtained from red seaweeds and widely used in nasal and mouth sprays. With their effective antiviral property, they are found to be efficient against SARS-CoV-2 treatment [5]. Apart from identification of efficient vaccines and antiviral treatments, identifying the way by which the infectious virus enters into cells is also important. This will be useful for targeted treatment of diseases due to viruses such as SARS-CoV-2 through vitro-vivo investigations.

The fact is that the spike protein in COVID-19 virus exploits ACE2 to kick off contagion. SARS-CoV-2 spike-interfering elements act as entry inhibitors. Molecular docking and SPR screening are used to identify the action of inhibitors and also the effective drugs for SARS-CoV-2. It was demonstrated that ACE2 mediates The S-proteins of SARS-CoV-2 allow cell entry which was shown to be a key receptor for coronavirus [6]. Among several methods used for identification of SARS-CoV-2, Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and Computed tomography (CT) scan are playing vital role. CT results of affected patients resembles with few symptoms of pneumonia caused by other viruses with some dissimilarities. Hydroxychloroquine (HCQ) is utilized mainly in malaria and rheumatoid arthritis treatments [7]. Even though WHO does not recommend the hydroxychloroquine for preventing COVID-19, a previous study shows that the structure of hydroxychloroquine and its derivatives helps them to act against COVID-19 related pneumonia and also it is identified that the Covid-19 incidence does not appear to be related to chronic use of hydroxychloroquine [7]. Neutralizing antibodies have useful antiviral properties against the COVID-19. This was by isolating of 4 human-origin monoclonal antibodies from a recovery patient. The biologically active compounds exist in Azadirachta indica and Aloe barbadensis is suitable for COVID-19 drug discovery [8].

Since the mild symptoms are being identified even after the vaccination against SARS-CoV-2, an antiviral therapy in combination with vaccination is hypothesized to control the disease which was explored by using molecular docking and simulation methods. In human body, defensins (α and β) play a vital role as the cationic antimicrobial peptides. These peptides are capable of killing bacteria, fungi, and even viruses by disrupting their microbial covering. In the above study, in addition to the binding affinity of these α and β defensins, it was identified that the plant defensins act as neutralizing antiviral agents to be used as a potential medicine for COVID-19. The molecular docking was employed to study the 4-Acetamido-3-nitrobenzoic acid's (ANBA) chemical reactivity with S-proteins of coronavirus and its structural characteristics.

Neutrophil is a kind of a white blood cell which is considered to be a vital part of the immune system of a human body. This is one of the first fighter cells which give boost to the immune system to facilitate the body to fight against disease caused by antigens like bacteria or viruses. Neutrophils seem to be a moderator for COVID-19-associated inflammatory problems. An efficient therapeutic

method was explored to lessen neutrophil-associated inflammatory lung diseases. In this study, the effectiveness and therapeutic properties of roflumilast, a phosphodiesterase inhibitor, that effort to decrease the swelling of lungs with great potential in curing COVID-19 was investigated. Apart from cross infection among the humans, as the zoonotic origin, bats and camels are acting as COVID-19 intermediate hosts. Since the transmutation modifications taking place in middle host is usual, SARS-like bat COVID do not directly affect humans [9]. Multiple organ failure is a major condition that can lead to deadly outcomes in COVID-19 patients. It has been investigated and believed that the Salicyl-carnosine is a manageable and promising medicine for the COVID-19 treatment [10]. In this work, the synthesis procedure of salicyl-carnosine was highlighted and it was showed that it has antioxidant and anti-inflammatory properties which helps it to treat inflammation, oxidative stress and thrombosis.

Apart from severe lung contagion, it is identified that COVID-19 affects female reproductive system through mitochondrial hijacking. This is because female reproductivity and mitochondrial function are closely related. And also this demands a proper preventive steps and finding out therapeutic targets for women with the viral infection. As already mentioned the S-protein of SARS-CoV-2 is a key component which takes part in attaching it the host body. Molecular dynamics studies are used to identify some molecules interacting favorably with spike protein (S1) and Receptor Binding Domain (RBD) with important properties including anti diabetic, anti platelet properties. Molecular modeling and docking are considered to be appropriate methods to explore and exhibit the newly formulated medications and natural elements against viral infectivity. These methods have been used to investigate several HIV protease inhibitors including some natural complexes. It is interesting to note that the natural complexes show a better binding affinity.

It has been already illustrated that HCQ is suitable to be used against malaria and rheumatoid arthritis [7]. A recent study [11] shows that HCQ explores a considerable response against SARS-CoV-2 by inhibiting its cell entry [7]. In addition to the other mentioned organ damages, SARS-CoV-2 affects the kidney also. A low dosage of acetazolamide, a carbonic anhydrase inhibitor has been recognized to prevent the kidney damage due to the SARS-CoV-2. The Mpro is the important protease of COVID-19. Targeting the Mpro is considered to be a better approach in the development of drugs because this enzyme is found to take part in viral replication and transcription [12] and a study [13] reiterates the role of Mpro as a potential target for drug development for SARS-CoV-2 infections. Quantitative Structure-Activity Relationships method based virtual screening and molecular docking was employed to find internal molecules which might be effectual against SARS-CoV-2 PLpro enzyme [14] and found that the internal molecules are likely to be used as a start for COVID-19 drugs.

Apart from drug discovery, diagnosis of COVID-19 is also equally important for its remedy and control. Bio and nano technologies are being widely used in the detection of pathogens like viruses. Since the current technology, quantitative Real-Time polymerase Chain Reaction (qRT-PCR) has many disadvantages like intensive need of labor, time consumption and cost effectiveness etc., machine learning-based signal processes using nano and biosensors which are sensitive and affordable can be considered as suitable diagnostic systems for SARS-CoV-2 detection.

III. CONCLUSION

The COVID-19 epidemic remains to increase and spread around the entire globe and being a major community threat. Identifying an appropriate inhibitor for SARS-CoV-2 virus is a fundamental requirement to safeguard the human race from the deadly infectious ailment. Consequently, the entire scientific community is searching for etiquettes first to identify the existence of COVID-19 virus, its pathway of spreading and anti-COVID-19 drugs through various experimental and computer aided theoretical methods.In addition to the approved drugs, lot of medications in the clinical trial is also present. Compared to the experimental procedures, computer simulation and quantum chemical methods are considered to be an essential and suitable tool to explore the changes in the conformations at the molecular level which are related to inhibition process of the SARS-CoV-2 [15]. In this mini-review, we summarize various quantum chemical and other related studies which tried to investigate the structure, function, new drug design and vaccines which can fight the COVID-19 virus.

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