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IDENTIFICATION OF POSSIBLE INHIBITORS OF CORONAVIRUS HEMAGGLUTININ-ESTERASE THROUGH MOLECULAR DOCKING, MOLECULAR DYNAMICS SIMULATION AND BINDING FREE ENERGY CALCULATION

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AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Vaccines are urgently needed to control the 2019 novel coronavirus disease (COVID-19) and help restore normal conditions before the pandemic. The hemagglutinin-esterase belongs to viral envelope glycoproteins family that facilitates reversible binding to *O*-acetylated sialic acids as a result of acting as lectins as well as receptor-destroying enzymes. Associated hemagglutinin-esterase take place in influenza C, toro-, besides coronaviruses. At this point, we initiate the crystal assembly of a coronavirus hemagglutinin-esterase in composite with its receptor through RCSB-PDB (id 5n11). We prepared this protein for docking more inhibitors with Autodock 4.0 by adding polar hydrogen and Kollman charges. We described its active site through Dog Site Scorer server and found Bovine corona virus is very near to our target protein with the help of phylogenetic analysis through MEGA-X software and proposed that we can do drug designing on Bovine coronavirus too for clinical trial on animal.

Keywords: Coronavirus; potential inhibitors; molecular docking; molecular dynamics.

1. INTRODUCTION

The SARS-CoV-2 infection arose in December 2019 and afterward spread quickly around the world, especially to China, Japan, and South Korea. Researchers are trying to discover antivirals explicit to the infection. A few medications like chloroquine, arbidol, remdesivir, and favipiravir are at present going through clinical research to test their adequacy and security in the treatment of Corona infection 2019 in China; few promising results have been proficient so far. This paper summaries experts with apparent possibility against Indian strain of SARS-CoV-2.

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The RNA molecule is a grouping of synthetic units. Every one of these units can be named with one of the four letters A, U, C or G, addressing a special particle. A line of these single-letter characters, organized in a particular arrangement, portrays the whole RNA molecule. The RNA molecule at the center of SARS-CoV-2 is depicted by a succession of near 30,000 such letters.

More often than not, very little happens when the grouping of the Covid RNA changes. Anyway few changes do have an effect. A few transformations in the receptor-restricting locale of the infection's spike protein, which structures some portion of its jacket, may permit the infection to tie better to cells. This expands the opportunity of an individual getting a contamination when they experience the virus.

With this foundation, here's a supposition for the first flood of corona virus in quite a while. This was basically driven by the significant Indian urban communities, Mumbai and Delhi among them, and less significantly fairly more modest metropolitan territories. Contaminations during this wave were overwhelmed by few variations that carried on generally a similar way, characterizing what is known as a strain of the infection. The conditions encompassing the lockdown guaranteed that the sickness spread moderately gradually outside these spaces. This can be ascribed to the moderately lethargic opening up of the country after about August, 2020 and some healthy degree of consistence with limitations on open social events and concealing in the months after that.

For what reason did cases start to ascend across India since the center of February? Absolutely, expanded laxity assumed a part. No matter how you look at it, weariness with hostile to corona virus measures appears to have reached a crucial stage by January, when the celebration season in November and December didn't prompt a spike in cases. (To trust that the New Year would introduce regularity, particularly behind the scenes of consistently diminishing case numbers, was maybe common).

Another variation, as of late named B.1.617, figures unmistakably in the abrupt increment of cases in Maharashtra. This variation contains two explicit transformations, called E484Q and L452R. Both these changes modify the spike area, permitting it to tie all the more effectively to cells. This variation seems to spread all the more effectively between individuals.

Here are some epidemiological inquiries to which we don't have the foggiest idea about the appropriate responses: Has the B.1.617 variation spread all the more adequately in Maharashtra among February and now, supplanting the more established strain? How much is this variation answerable for the spray in cases outside that state? Is the B.1.36 variation, common in south India, likewise more contagious than the first strain? Assuming this is the case, by what amount? At long last, what is the contamination casualty proportion, related with the new strains? Are there huge changes in the manner fatalities emerging from contamination are circulated across ages?

For this we need information made accessible in a convenient way. We likewise need – particularly – straightforwardness. Which job will antibodies play in the many months to come? Antibodies, essentially every one of them, ensure against sickness yet not against disease. However, how is the harmony among extreme and gentle illness moved when somebody previously inoculated is contaminated with the new variations? Which of the two immunizations presently accessible in India may work better against the new strain or do they perform similarly well? Of the new immunization applicants that anticipate endorsement, how well may they neutralize the new strains? These inquiries anticipate answers.

1.1 Objective

As the scourge spreads, researchers all throughout the planet are effectively investigating drugs that would be conceivably successful in battling corona virus. For the most part, there are no at long last checked antivirals explicit to corona virus as of now. The viability and wellbeing of these up-and-comer drugs in the treatment of corona virus should be affirmed in additional preclinical and clinical preliminaries.

Our objectives are:

1. To find or homology model the target protein of corona virus hemagglutinin-esterase.
2. To find the alternative of our target protein of corona virus hemagglutinin-esterase (*Homo sapiens*) in other organisms through help of phylogenetic analysis.
3. To prepare active site of our target protein for inhibitor docking and adding polar hydrogen with Kollman charges.

2. REVIEW OF LITERATURE

Despite some serious exploration, presently there is no effective antibody for this extremely severe respiratory disease (SARS-CoV-2). This tempting as well as transferable infection of pandemic has become one of the most significant universal health challenges. The clinical management of corona virus is restricted to control of pandemic in addition to fight processes associated to regular contemplation like supplemental oxygen as well as mechanical ventilation. Then, efforts are being made to find

convincing treatments to prevent the replication of infections, reduce performance, increase resistance and reduce mortality. Certain classes of drugs are being evaluated, many of which are effective for different diseases, depending on various clinical information about the conventional history and development of the disease obtained from contaminated patients. Here we will recap the common history and current information on proven drugs and repair experts for the anticipation and handling of corona virus. These comprise several medications as well as auspicious study on immunity. Given the controversy and the unreasonable number of mixtures tested and disclosed in the brief, we believe this audit can provide useful and up-to-date comprehensive data for potential drugs for the prevention, control, and treatment of corona virus patients across the world.

Infections are delivered mainly through individuals and contaminated individual positions of individuals closely in close contact with each other, and are delivered through respiratory drops delivered when they are turned or talking. The most ideal approach to Forklel is not presented to the infection. During cell contact, the viral infection can cross the cell with the joining of endosomal or plasma layers. The SARS-COV-2 SPIKE (S1E S2) protein is interjected on the plasms membrane through restraining ACE2 as the section receiver. The spike protein sensitivities just after the cerulein 2 transmembrane protease (TMPRSS2), which is adjacent to ACE2 receptor and initiates combination with the viral film, the tip protein, which is close to the ACE2 receptor that initiates a combination with the Viral film, it is cathepsin l or the other. The last system causes an antiviral safety reaction and is more effective for viral replication [1]. The viral RNA is delivered once in cells and the polyprotein is interpreted. The Genomic RNA encodes the non-structural proteins (NS) that takes a basic rest in combination of viral RNA, and significant primary proteins are collected for new virions. The first protein 1a of NS 1A and 1AB is cleaved with papain-shaped protease (pipro) as well as 3C protease (3clpro) in addition to 3C protease (3Clpro) to a NS protein, like Helicase or RNA: polymerase complex RNA (RDRP) is detached. The basal protein S1, S2 and the envelope (E), with layer (M) are construed with the ribosomes interconnected with endoplasmic reticulum (ER), and are presented on the exterior of the virion. Nucleocapside (N) remnants in the cytoplasm, collected with RNA molecule. Finally, virions are directed from ER to the cell surface with the help of Golgi vesicles. Thus the virion is transported through exocytosis, and another replication cycle of virus starts [2].

Appearances and symptoms linked to viral pneumonia are communal in patients throughout the inception of COVID-19 [3,4,5,6,7,8]. Contaminated patients can also feel loss of taste or smell as well as some gastrointestinal symptoms such as nausea, vomiting or laxity of the bowel [9,10,11]. In the final analysis, from all angles, the severity of the disease is closely related to the hidden conditions of the host, including age, gender, and general health issues. When examining patients, hypertension, diabetes, circulatory as well as kidney diseases increase the risk of disease, and there is some overlap [12]. Identify useful treatments for corona virus through onset of infection and pathophysiology.

A better understanding of transmission methods, incubation periods and sub molecular instruments are the basis of infections and pathophysiology in addition to genetic factors, which are critical to the advancement of infectious diseases. Corona virus treatment procedures. Almost all corona virus patients have pulmonary contributions, as shown on the chest X-ray, although serious difficulties have only been detected in some patients. Though it has been observed that older age in addition to the occurrence of comorbidities are possible reasons for the harshness of infection, it was further observed that high illnesses can also occur in younger generations with no prior complaints [13]. Ferritin, C-reactive protein in addition to D-dimer levels are higher, as is the ratio of neutrophils to lymphocytes and increased serum levels of some fierce cytokines and chemokines and excessive inflammation are closely related [14,15,16].

In hospitalized patients, corona virus tangles such as pneumonia, respiratory failure, as well as severe respiratory distress (ARD) are found as frequently as possible [17]. The acute respiratory infection affected by SARS-CoV-2 is close to mountains in other effluence instigated by viruses plus microorganisms [18,19]. The stimulating cytokines affected by SARS-CoV-2 (called cytokine storm) can increase the risk of vascular pores and organ failure. If not controlled, it can lead to death [20,21]. Encoding the class of interleukins, chemokines as well as interferons, it was abnormally reported in patients 24 hours after the onset of SARS-CoV-2 disease, which was linked to the higher perception of T cells, Natural Killer cells as well as monocytes [22,23]. This interpretation is like some other causes of Corona, for instance, the Middle East Respiratory Disease (MERS) produced by MERS-CoV, in which interleukins as well as interferons increase significantly within 24 hours after the disease [24]. The distended IL-15, IL-17 in addition to TNF-α clusters have also been construed as MERS-CoV infection [25].

The National Center for Biotechnology Information (NCBI) dynasties a sequence of databases applicable to biotechnology as well as biomedicine including Gen Bank for DNA sequences in addition to PubMed for the biomedical literature.

PubMed is a database advanced at the National Library of Medicine (NLM). The database was intended to offer access to citations from various biomedical journals.

The Protein Data Bank (PDB) is a repository for the 3-D structural data of biomolecules, obtained by X-ray crystallography or NMR spectroscopy and are freely accessible via the websites. The PDB is supervised by an organization called the Worldwide Protein Data Bank, PDB.

3. MATERIALS (SOFTWARES)

3.1 DoG Site Scorer

DoG Site Scorer is a grid-based technique which practices a Difference of Gaussian filter to identify possible binding pockets - solely based on the 3D structure of the protein - and splitting them into sub pockets.

3.2 Autodock

Auto Dock is a group of automated docking tools, designed to predict how lesser molecules bind to a receptor of known 3D structure.

3.3 MEGA Software

The Molecular Evolutionary Genetics Analysis (MEGA) programming executes numerous scientific strategies and tools for phylogenomics and phylomedicine. Here, we report a change of MEGA to empower cross-stage use on Microsoft Windows and Linux working frameworks. MEGA X doesn't need virtualization or imitating programming and gives a uniform client experience across stages. MEGA X has also been moved up to utilize various registering centers for some sub-atomic transformative investigations. MEGA X is accessible in two interfaces (graphical and order line) and can be downloaded from www.megasoftware.net for nothing.

4. METHODOLOGY

1. Found the target protein Hemagglutinin-esterase (Corona Virus) from literature database PubMed (NCBI) and to download from RCSB-PDB.
2. Analysed the active site (functional site) of our target protein by Dog Site Scorer designed by Hamburg University.
3. Found the alternative of our target protein of corona virus hemagglutinin-esterase (*Homo sapiens*) in other organisms through help of phylogenetic analysis with MEGA X.
4. Prepared active site of our target protein for inhibitor docking and adding polar hydrogen with Kollman charges with Autodock 4.0.

5. RESULTS AND DISCUSSION

Target Protein (5N11):

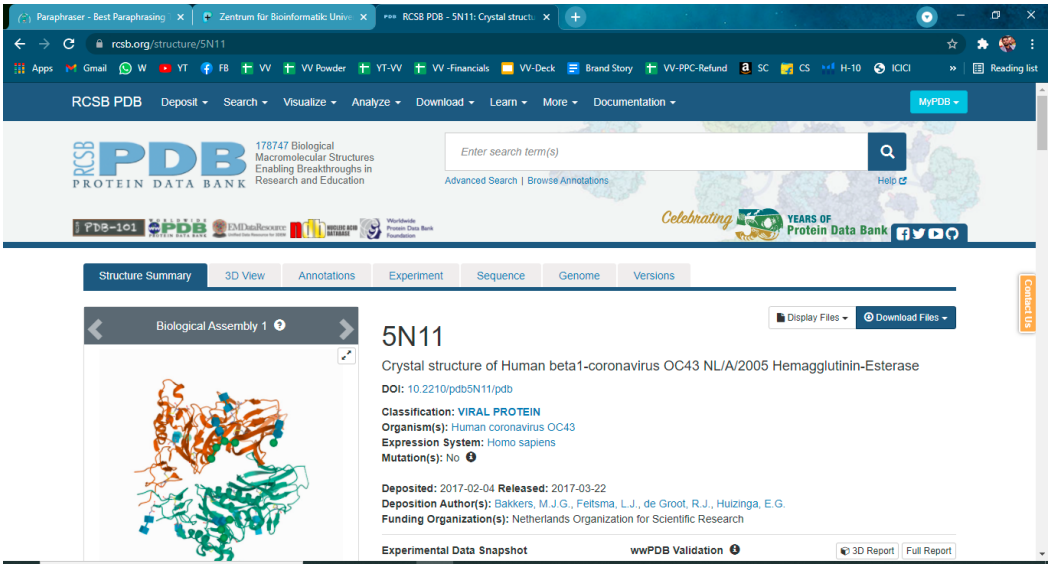

Fig. 1. Target protein Hemagglutinin-esterase (Corona Virus) from RCSB-PDB

Preparation of Protein:

Analysed the active site of protein (5n11)

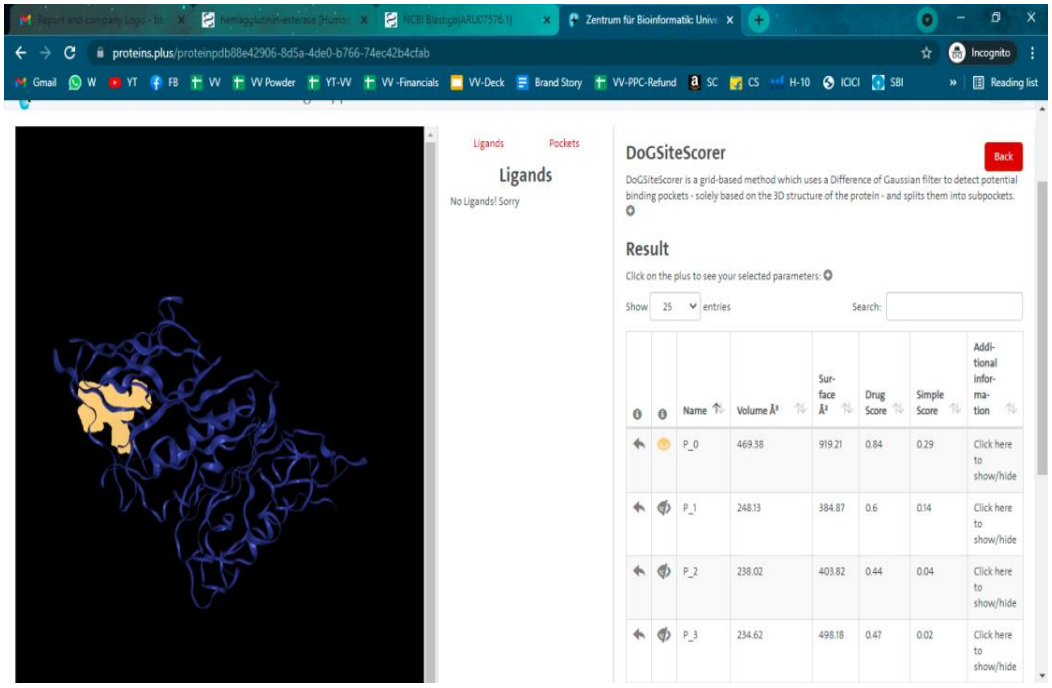

Fig. 2. Functional site of protein 5n11 through Dog Site Scorer

Opened protein (5n11) in Auto dock – Deleted all unnecessary chains but chain A – deleted all water molecules – deleted all already present ligands – added all polar hydrogen – added kollman charges on protein chain A – through grid box prepared configuration file and saved the final prepared protein in protein.pdbqt.

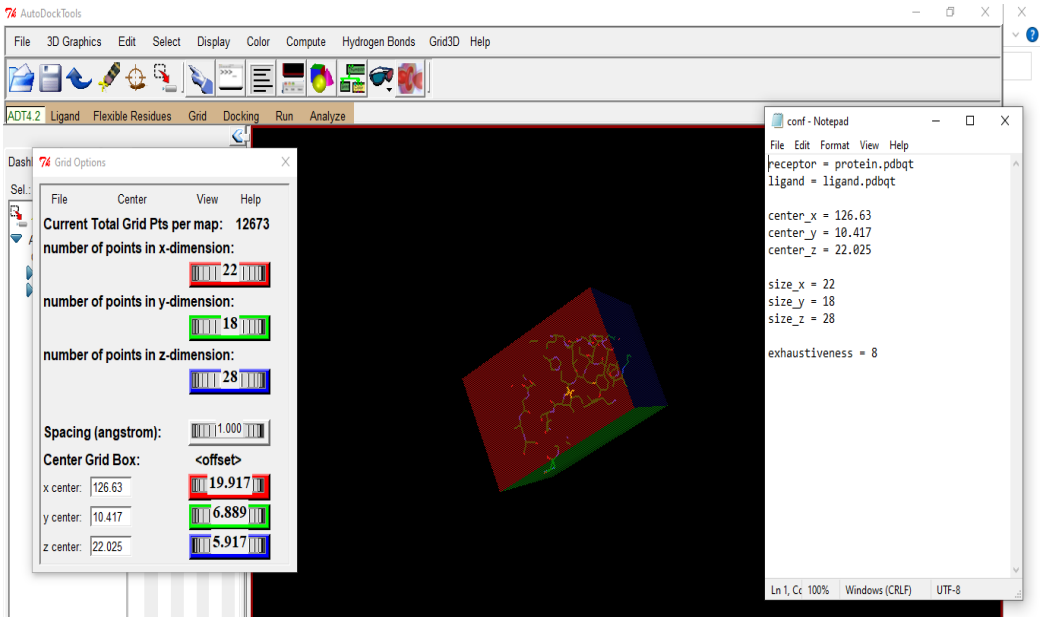

Fig. 3. Protein.pdb molecule and all ligand pdb format docking through Auto dock software

Phylogenetic Analysis:

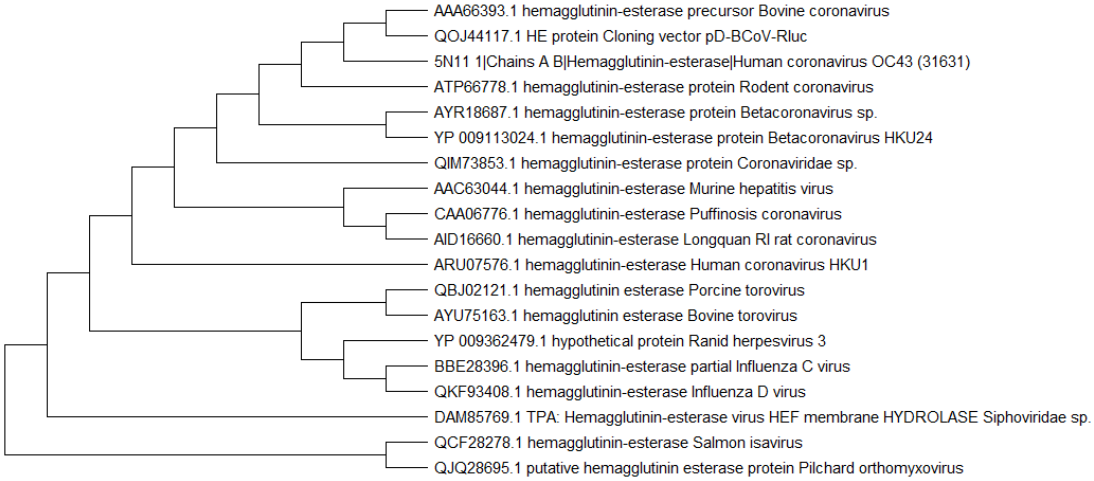

Fig. 4. Phylogenetic analysis with MEGA X

6. CONCLUSION

Here, we establish the crystal assembly of corona virus hemagglutinin-esterase in composite with its receptor through RCSB-PDB (id 5n11). We prepared this protein for docking more inhibitors with Auto dock 4.0 by adding polar hydrogen and Kollman charges. We described its active site through Dog Site Scorer server and found Bovine corona virus HE is very near to our target protein with the help of phylogenetic analysis through MEGA-X software and proposed that we can do drug designing on Bovine corona virus too for clinical trial on animal.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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