Echinacea purpurea to treat Novel Coronavirus (2019-nCoV)

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Abstract

Novel Coronavirus (2019-nCoV) or Human Coronavirus (HCoV) could be a new coronavirus that belongs to Betacoronaviruses type Human Coronaviruses, just like the Middle-East Respiratory Syndrome (MERS) coronavirus and Severe Acute Respiratory Syndrome (SARS) coronavirus. Wuhan, the capital city of Hubei province, China recorded the initial cases of this virus in December 2019. Until 2 May 2020, 10:00 CET, near 23,8287 deaths were reported out of 3.34 million confirmed cases recorded across the world. By the tip of January 2020, China confirmed that the COVID-19 transmitted from human to human. This study aims to check a completely unique medicament called "Echinacea purpurea" against the crystal structure of 2019-nCoV Main Protease. This study presents an ideal model for Echinacea purpurea to be tested in silico against 2019-nCoV Main Protease.

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Abstract:

Novel Coronavirus (2019-nCoV) or Human Coronavirus (HCoV) could be a new coronavirus that belongs to Betacoronaviruses type Human Coronaviruses, just like the Middle-East Respiratory Syndrome (MERS) coronavirus and Severe Acute Respiratory Syndrome (SARS) coronavirus. Wuhan, the capital city of Hubei province, China recorded the initial cases of this virus in December 2019. Until 2 May 2020, 10:00 CET, near 23,8287 deaths were reported out of 3.34 million confirmed cases recorded across the world. By the tip of January 2020, China confirmed that the COVID-19 transmitted from human to human. This study aims to check a completely unique medicament called "Echinacea purpurea" against the crystal structure of 2019-nCoV Main Protease. This study presents an ideal model for Echinacea purpurea to be tested in silico against 2019-nCoV Main Protease.

Keywords: Echinacea purpurea, COVID-19, 2019-nC0V, Human Coronavirus.

I. INTRODUCTION:

Wuhan, the sprawling capital city of Hubei province, China recorded the first case of Novel Coronavirus (2019-nCoV) on 31st December 2019 at the WHO Country Office in China. Following that, World Health Organization (WHO) confirmed the Wuhan Epidemic (COVID-19) as a Public Health Emergency of Intercontinental Concern on 30th January 2020 and published a surveillance draft, stating any traveller who visited Wuhan city of Hubei province in China, two weeks before the beginning of the signs (symptoms) to be assumed as a COVID-19 positive [1]. Moreover, the organization circulated interim directions for all the laboratories across the world that carry out the testing for the recently developed outbreak and control guidance prevent infection from samples [1]. The viral pneumonia is associated with an unknown animal sold at the Huanan seafood market for the emergence of the outbreak [1]. Until 27th March 2020, 10:00 CET, 509,164 cases were confirmed to be positive for COVID-19 outbreak, leaving 23,335 patients dead across the world [2]. On 20th January 2020, National Health Commission of the People's Republic of China established that the Wuhan outbreak is also known as COVID-19 outbreak was transmittable from one human to another human [1].

Till date, six strains of Coronavirus (CoVs) have been recorded, excluding the newly emerged 2019-nC0V [1]. COVID-19 belongs to *Betacoronaviruses* type Human Coronaviruses (HCoVs) like MERS, OC43, HKU1, and SARS while 229E and NL63 are members of *Alphacoronaviruses*. According to the World Health Organization, SARS and MERS coronaviruses were the most destructive strains of CoVs until the Wuhan outbreak (COVID-19), leaving about 800 deaths each. According to WHO, MERS has a mortality rate of 36% while SARS has 10% [1].

`Coronaviruses are generally very long, single-stranded RNA viruses (30,000 bp). These viruses are composed of two major protein groups:

- Structural Proteins: M- Matrix, S- Spike, E- Envelope, N- Nucleocapsid.
- Non-Structural Proteins: RdRp- RNA-dependent-RNA-polymerase, and nsp12 Protein.

One most vital enzyme in the lifecycle of the coronaviruses or any other RNA virus is the RNA dependent RNA

polymerase (RdRp). Hence this enzyme is mostly targeted in RNA type viruses, including Zika Virus (ZIKV), and Coronavirus (CoVs) [1]. The active site of RdRp represents two consecutive aspartate remains protruding from a β-turn structure and are highly conserved as they are surface handy, through the nucleotide passage (i.e. open nucleotides can pass through) [1]. The crystal structure of nCoV-2019 main protease in APO form is shown in **Figure 1.**

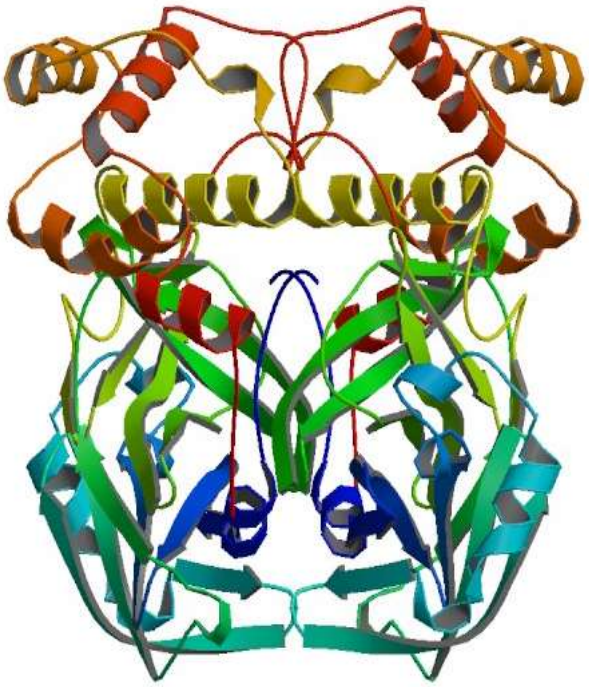


Figure 1: The Crystal structure of nCoV-2019 main protease in APO form (PDB ID: 6M03)

II. ECHINACEA PURPUREA:

Echinacea purpurea is a North American flowering plant from the sunflower family. It is also known as hedgehog coneflower or eastern purple coneflower or purple cone-flower which is inherent to eastern North America. *Echinacea purpurea* is a herbaceous perennial up to 47 inches (120 cm) tall by 10 inches (24 cm) wide at maturity. It blooms during the course of summer into autumn depending on the climate. It is grown as an ornamental plant across temperate regions for curbs, beds, bouquets, walkways etc. [2].

The interesting fact about this North American, Purple Coneflower is that the recent studies have proved the extracts prepared from certain plant parts and species, but all of them, do not possess potent antiviral properties at non-cytotoxic concentrations, mainly in contrast to membrane-containing viruses (RNA type viruses). Moreover, Acute respiratory infections in humans (including 100 rhinoviruses, parainfluenza or influenza viruses A and B, certain adenoviruses, respiratory syncytial virus, including coronaviruses have been proved to be susceptible to Echinacea. Numerous herbal derivatives have recently presented to own a mixture of antiviral activities that could have been suitable to resist severe acute respiratory syndrome (SARS) that emerged in 2002 where Echinacea is one among them and have become very popular besides that fact that not all of them are necessarily beneficial. The extracts are mostly prepared as teas, sprays, tinctures etc. from several parts of more than single species of Enchinacea: *E. angustifolia, E. purpurea, E. pallida.* Reports prove that methanol and aqueous extracts of Echinacea extracted from E. purpurea should inhibit the action of vesicular stomatitis, influenza A virus, herpes simplex virus type 1, etc. [4]. Later Vimalanathan *et al.* [5] evaluated *E. purpurea* aerial parts extracts at different solvent fractions against several viruses and reported that aqueous derivatives were vigorous against influenza virus and herpes simplex virus independent of light exposure. However, more recent studies for a series of ethanol and aqueous extracts of *E. purpurea* aerial parts have shown substantial virucidal action contrary to a wide range of viruses. Though a lot of researches have proven that antiviral activity of *E. purpurea* extracts against a wide spectrum of viruses, there is no affirmation about its mechanism of action. According to a few researches, the antiviral activity of *Echinacea* extracts is because of the multiple bio-activities contained in it. These bio-activities collectively obstruct numerous viruses at different levels. Viruses are evident to contain at least two molecular virion targets (for e.g. Influenza viruses have two target proteins – hemagglutinin and neuraminidase). Hence, ethanol abstracts of aerial parts of *E. purpurea* should be able to bond to polymeric matrix polyvinyl-polypyrrolidone (PVPP) and should consequently be eluted and recovered. [6]. But the fact is that, though Echinacea is a source of powerful antivirals for respiratory virus infections, the actual mechanism behind its antiviral activity is still not clear. Thus, Echinacea is popularly known as a mystical drug of potent antivirals. The 2D structure of Echinacea purpurea (Accession Number: 11528546) is shown in **Figure 2.**

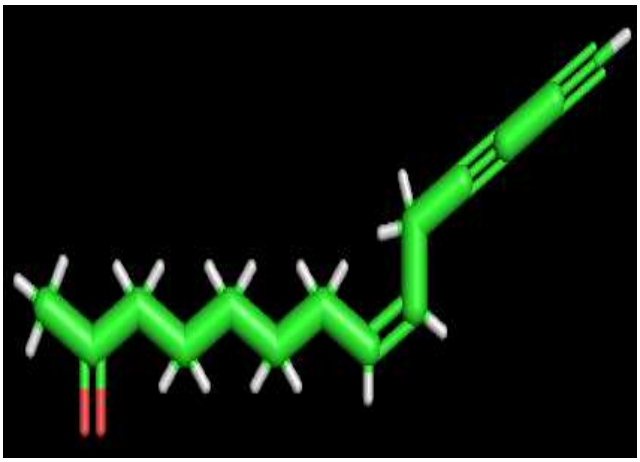


Figure 2: The 2D structure of Echinacea purpurea (Accession Number: 11528546) inspected in PyMoL

III. MOLECULAR DOCKING:

In silico study in medicine is thought to reduce the need for expensive lab work and clinical trials and to increase

the potential to speed the rate of discovery. The term "*In silico*" refers to Pseudo-Latin term for "in silicon". In silicon in "*In silico*" refers to the huge use of silicon in computer chips as an expression meaning "performed via computer simulation or on the computer". This introduced the concept of Molecular Docking [7]. Molecular Docking is a method which predicts the preferred orientation of one molecule to the other when bound to form a stable complex to indeed predict the strength of association or binding affinity between the receptor and the ligand [8].

IV PREPERATION OF LIGAND

For this work, the structure of Echinacea purpurea compound is obtained from PubChem Compounds Repository (PubChem Accession Number: 11528546). The retrieved SDF (Structure Data Format) file is viewed in the AutoDock Tool Kit. Finally, the ligand is prepared by removing water molecules followed by detection of Torsion Tree Root. Finally, the prepared ligand is exported as PDBQT (Protein Data Bank, Partial Charge (Q), & **Atom** Type (T)) file. The 3D structure of prepared ligand is shown in **Figure 3.**

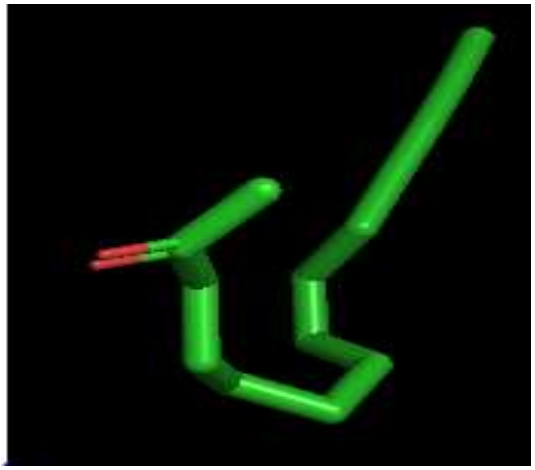


Figure 3: 3D Structure of Prepared Receptor inspected using PyMoL

V PREPERATION OF MACROMOLECULE

For this work, the structure of the crystal structure of Novel Coronavirus Main Protease in APO form is obtained from Protein Data Bank Proteins Repository (PDB-ID: 6M03). The retrieved PDB (Protein Data Bank) file is viewed in the AutoDock Tool Kit. Finally, the macromolecule is prepared by removing water molecules followed by the addition of polar hydrogen's. Finally, the prepared macromolecule is exported as PDBQT (Protein Data Bank, Partial Charge (Q), & **Atom** Type (T)) file.

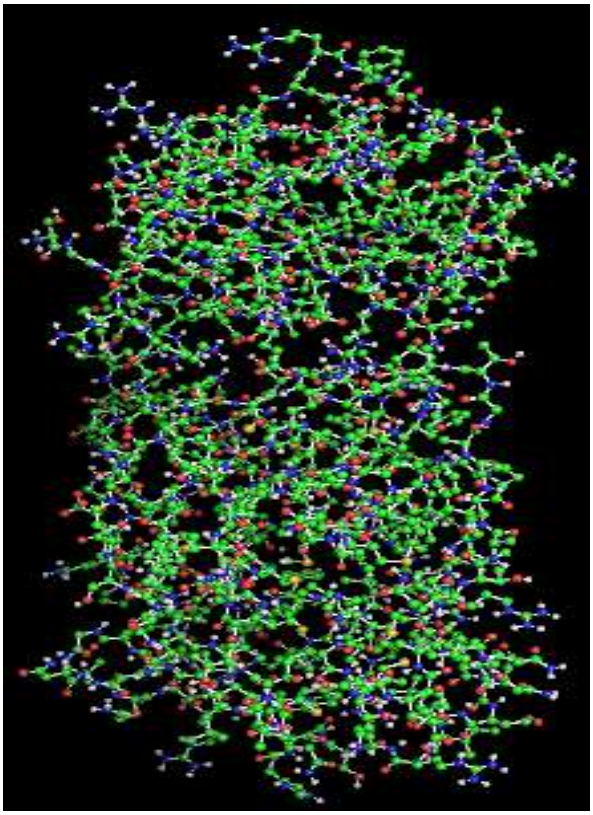


Figure 4: 3D structure of Prepared Receptor Macromolecule inspected using PyMoL

VI. EXPERIMENT:

The Docking experiment is performed using the prepared receptor (macromolecule) with the help of AutoDock Vina software applied in PyRx against the prepared ligand. Vina search space for fitting the ligand in the receptor was maximized to the dimensions of the main protease as follows:

- Exhaustiveness = 8
- center_x = 12.117
- center_y = -11.3843
- center_z = 4.6603
- size_x = 36.8260217381
- size_y = 64.6642951965
- size_z = 62.0708380127

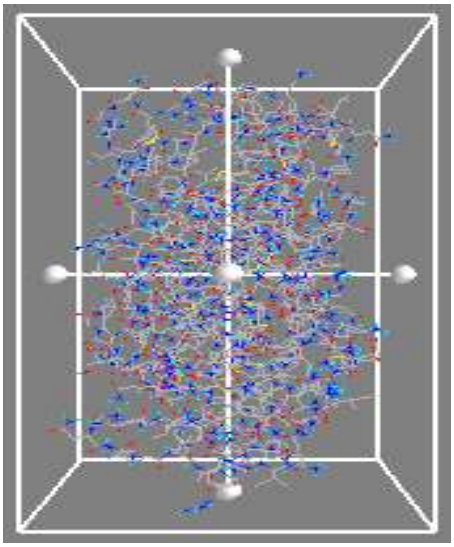


Figure 5: 3D structure of Prepared Receptor Macromolecule and Lig- and fitted in PyRx.

VII. RESULTS:

Results of prepared Ligand (Echinacea purpurea) and Receptor Macromolecule (Main protease of Novel Coronavirus) obtained from AutoDockTools 1.5.6 (ADT) was inspected using PyMoL. Results of Ligand (Echinacea purpurea) and Receptor Macromolecule (COVID-19) obtained after docking using AutoDock Vina Software implemented in PyRx software was inspected using PyMoL. The binding of Ligand to the Receptor was observed in nine different poses at unique binding affinities, RMSD/ub values and RMSD/lb values. Nine different poses of COVID-19 main protease (in Blue ribbon) docked to the novel antiviral drug "Echinacea purpurea" (in Red licorice sticks) with polar contacts/interactions (in green color dotted lines) are shown in **Figure 6**. Further, the binding affinities, RMSD/ub values and RMSD/lb values are tabulated for each pose in **Table 1** and are depicted as the graph in **Graph 1**.

Table 1: Results of Ligand (Echinacea purpurea) and Receptor (COVID-19) obtained after docking using AutoDock Vina Software implemented in PyRx software.

Ligand	Binding Affinity	RMSD/ub	RMSD/lb
POSE 1	-5.6	0	0
POSE 2	-5.4	2.408	1.901
POSE 3	-5.3	2.98	1.627
POSE 4	-5.3	3.306	2.08
POSE 5	-5.1	4.498	2.419
POSE 6	-5.1	3.259	2.32
POSE 7	-5	3.95	2.041
POSE 8	-5	6.811	4.449
POSE 9	-5	5.691	4.364

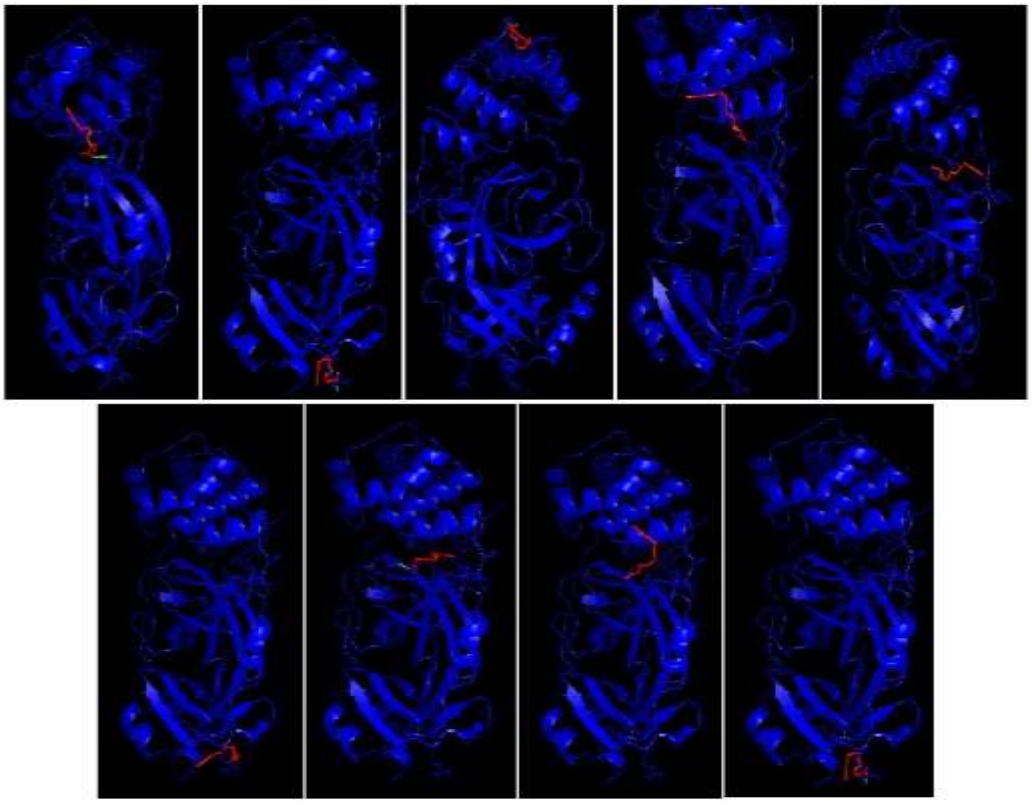
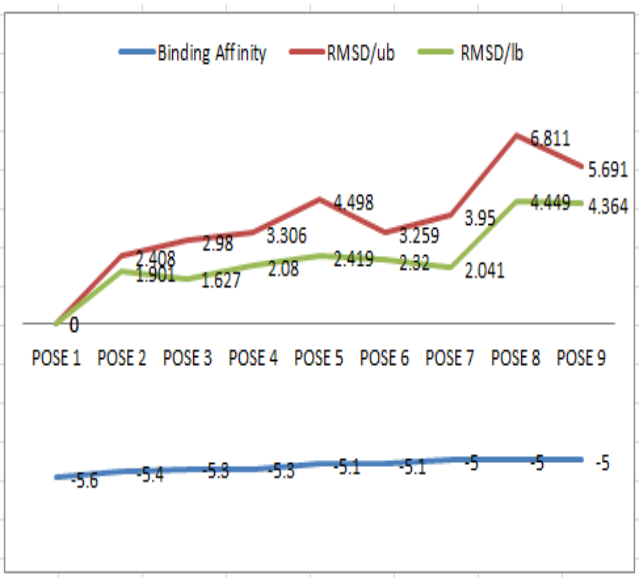


Figure 6: Nine different poses of COVID-19 main protease in APO form (in Blue ribbon) docked to the novel antiviral drug "Echinacea purpurea" (in Red licorice sticks) with polar contacts/interactions (in green color dotted lines) inspected in PyMoL.



Graph 1: Plot between Binding Affinity, RMSD/un, RMSD/lb and different Poses of ligand (Echinacea purpurea) in the Receptor (COVID-19).

The resultant structure (ligand-protein) is virtually screened using PyMoL for the first pose of ligand-receptor bond to perform the following analyses since it had 0 Å rmsd/ub and rmsd/lb values with -5.6 Å Binding Affinity (lower the value of RMSD, higher the accuracy of docking [9]).

Thus, the Atoms (**Figure 7)**, Elements (**Figure 8)**, Nuclear chain (**Figure 9)**, Nuclear sequence (**Figure 10)**, vdw radius (**Figure 11)**, B-factors (**Figure 12)**, occupancy (**Figure 13)** and rank (**Figure 14)** of the Active Residue (R296) that were bound to the ligand, are identified along with the Bond length of the ligand-receptor bonds (**Figure 15)** and binding-pocket of protein crystal structure (**Figure 16)** by analyzing the resultant structure in PyMoL and are shown below:

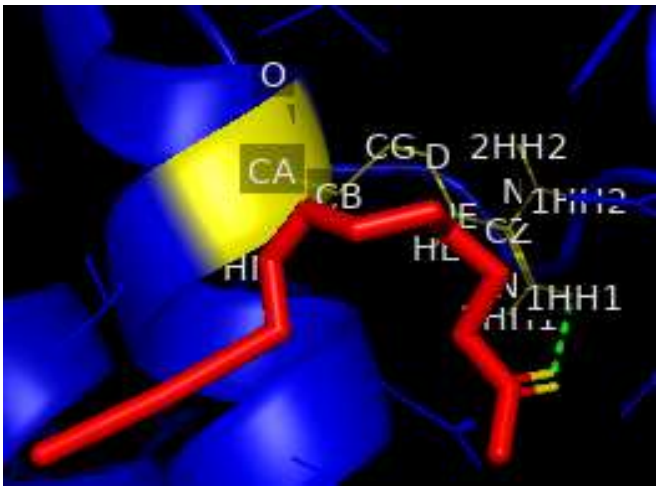


Figure 7: The above picture depicts the atoms in the active-site residues bound to the ligand

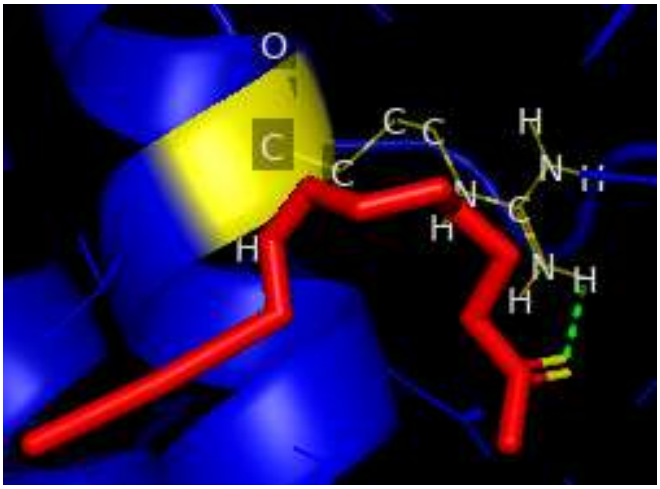


Figure 8: The above picture depicts the Elements in the active-site residues bound to the ligand

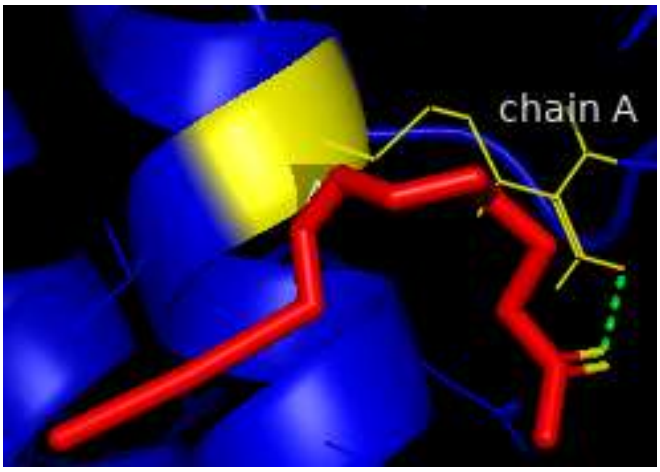


Figure 9: The above picture depicts the Nuclear Chain in the active-site residues bound to the ligand

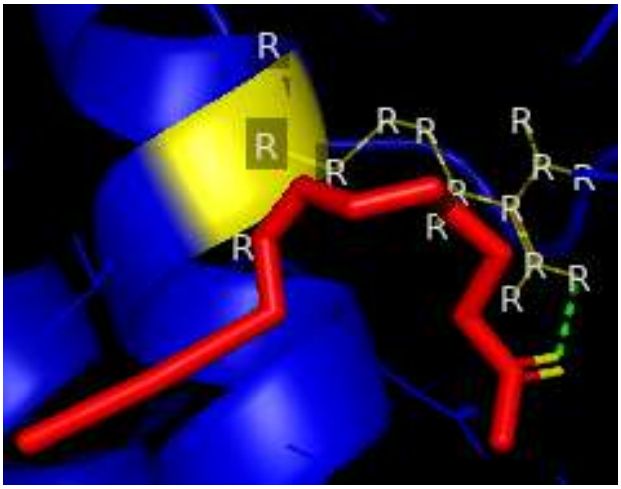


Figure 10: The above picture depicts the Nuclear Sequence in the active-site residues bound to the ligand

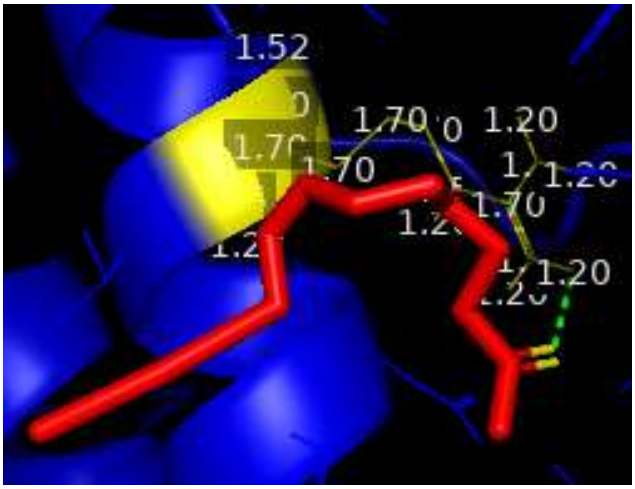


Figure 11: The above picture depicts the vdw radius in the active-site residues bound to the ligand

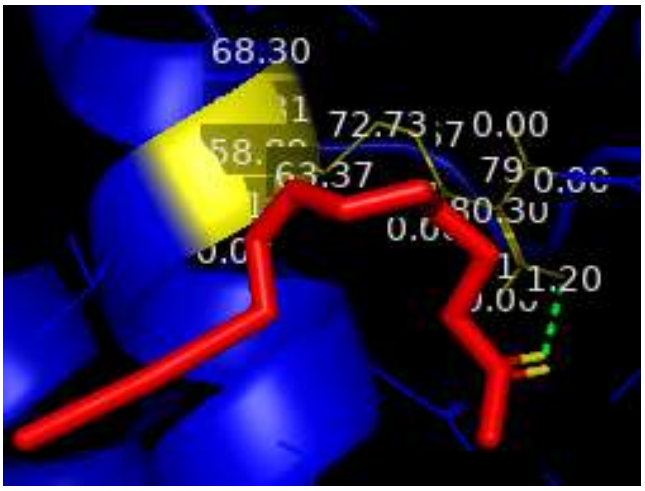


Figure 12: The above picture depicts the B-Factors in the active-site residues bound to the ligand

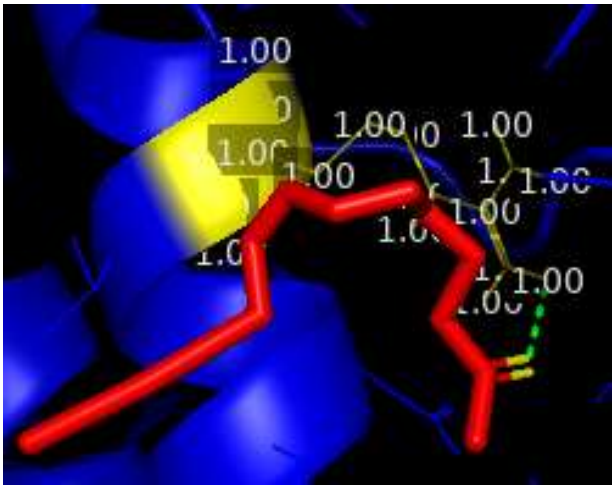


Figure 13: The above picture depicts the Occupancy in the active-site residues bound to the ligand

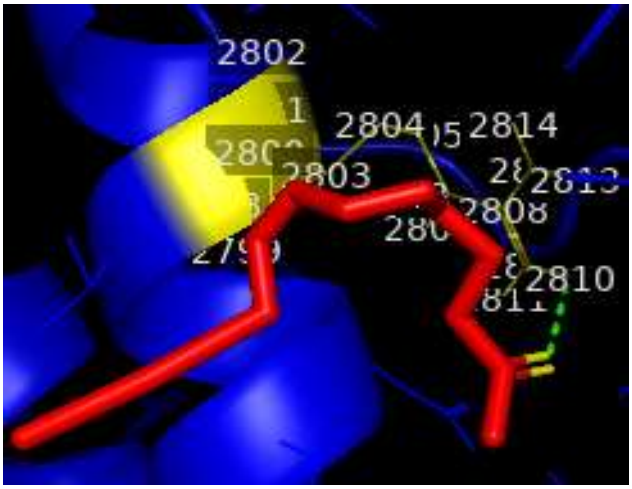


Figure 14: The above picture depicts the Rank in the active-site residues bound to the ligand

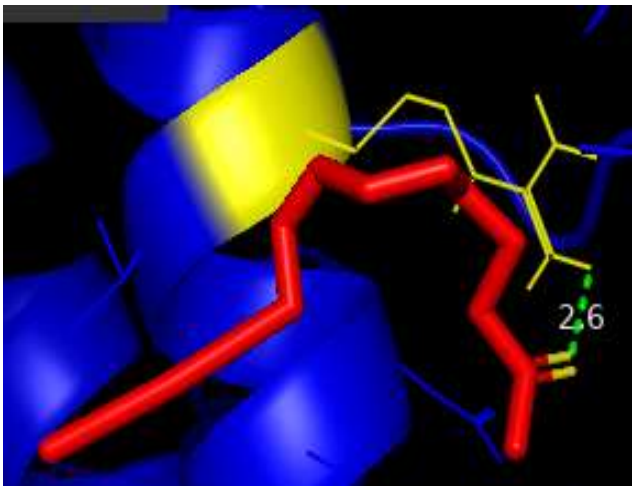


Figure 15: The above picture depicts the Bond length of the ligand-receptor bonds

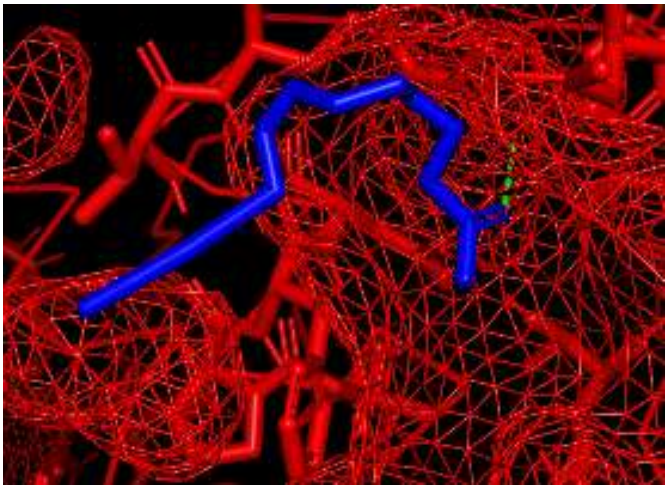


Figure 16: The above picture depicts the view of ligand through the Binding Pocket

CONCLUSION & FUTURE WORK:

The newly emerged novel coronavirus (nCoV-2019) has spread across the world and has registered close to 3.34 million confirmed cases and 238287 deaths by 2nd May 2020, 10:00 CET. Increase in confirmed cases and deaths result in an increase in demand for an antiviral drug. Since it takes a long time to create a new antiviral drug for such a complex virus and for it to pass through *In vito*, *In vivo* and *In sito* tests to qualify to preclinical tests followed by clinical tests, there have been lot researches undertaken to test already available antiviral drugs on COVID-19. The present study is one such work aimed to test Echinacea purpurea as a possible inhibitor, currently in the market to control and decrease the infection as quickly as possible. Thus, with reference to the above results, Echinacea purpurea can be used against the COVID-19 (nCoV-2019). In addition, to that key technologies can help to address the nCoV-2019 [10].

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