Ayurvedic-Informatics Establishing an In-silico Ayurvedic Medication for Influenza a Virus (Swine Flu)

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Abstract- Swine flu disease is an incurable degenerative and terminal disease. It is associated with Neuraminidase (NA), Hemoagglutinin (HA), and Matrix (M2) protein .3D structure of the one protein neuraminidase was generated using Homology modeling. Active compound of medicinal natural compound – EPICATECHIN GALLATE, MARCHANTIN, XYLOPINE were selected as these three natural compound of chemical structure of the active component of these natural compound were drawn docked with Epicatechin gallate, Marchantin , Xylopine Active component combinations. Known inhibitor taken from the literature docked, and docked at the binding site. Obtain molecule Epicatechin gallate, Xylopine, Marchantin have been given score of -174.3 kcal/mol, -148.5 kcal/mol, -131.4 kcal/mol. This is greater than known inhibitor. Zanamivir and Oseltamivir have been given score of -155.9 kcal/mol, and -132.7 kcal/mol molecules were employed for similarity search from zinc database. To the candidate molecules with drug likeness property can be considered for the test in vitro. And finally it can act as lead compound for the future development and optimization.

Index Terms- Swine flu disease, Drug designing, Homology modeling, Natural compound.

I. Introduction

Influenza A virus has caused seasonal influenza epidemics and influenza pandemics which resulted in serious threat to public health and socioeconomic impact main influenza A virus cause acute respiratory disease in human , birds and other mammal , representing one of the major threats to public's health. Influenza A viruses mutates frequently because of their segmented RNA genome, making it almost impossible to produce a timely and sufficiently effectives [3]. Two neuraminidase inhibitors ZANAMIVIR and OSELTAMIVIR were both approved in 1999 for treatment cause and prevention for acute uncomplicated flu caused by influenza A virus and B. Neuraminidase inhibitors interfere with the enzymatic activity of the NA protein, which is critical for the efficient release of newly synthesized virus from infected cells. However, resistant virus strains are constantly emerging, especially to Oseltamivir. [4]. Different from the oral administration Oseltamivir , Zanamivir can only be inhaled due to its low bioavailability , which makes the limited use of this drug. The currently available drug such as Oseltamivir and Zanamivir was considered as reference drug in this work .one thousand natural compound showing the antiviral, antioxidant, and immunostimulatory properties were selected from various scientific articles . The initial screenings of the molecule was based on the bases on the lipinski's rule of five and compound having structured similarity to the study drug Oseltamivir and Zanamivir [27]. Molecule which were satisfying this rule were taken docking study using docking software molegro virtual docker . Out of the three natural molecules evaluated Epicatechin gallate was found to have better ligand binding affinity than the commercial drugs. Epicatechin gallate the bioavailability studied of ECG also showed that bioavailability is less than 30%. Also the blood and the cardiovascular toxic health effects of ECG was predicted to be lesser than the study drug Oseltamivir adverse effects than the commercial drugs taken in the study.

The research proposes that intake of Epicatechin gallate which is abundant in green tea can be potent anti-viral therapy against H1N1 swine flu influenza A virus. Drug discovery has evolved through various stages in to more rational and evidence based drug designing has made tremendous contributions in the field of viral chemotherapy, drug resistant infections and viral disease to mention a few new drug discovery method are furthered by development in the technology especially computers, bioassays techniques and calibrated instruments computational structure based drug designing opens the door to novel treatments in modern medicines [3].

II. METHODOLOGY- SOFTWARES/ WEB SERVER

- PHYRE SERVER
- SWISS PDB VIEWER
- RASMOL
- SAVES SERVER
- Q SITE FINDER
  (http://www.modelling.leeds.ac.uk/qsitefinder/)
- CHEMSKETCH (http://www.acdlabs.com/resources/freeware/chemsketch)

- DISCOVERYSTUDIO
- MOLEGRO VIRTUAL DOCKER

Influenza A virus disease causing protein neuraminidase (NA) were taken for this work. NA protein sequence was taken from NCBI database.Homology modeling was carried out using phyre server, for the predicting 3D structure for the above mentioned proteins. Homology modeling was done using phyre server template pdb id $3CL_2$ A CHAIN protein from RCSB PDB database.

3 models of protein were generated the models, were analyzed by saves server (ramachandran plot) [14] and the best model was selected. Chemical structures of active components of Epicatechin gallate , Marchantin , Xylopine were drawn chemsketch softwares . This combinations structures was saved as *.mol file and was later converted to *.pdb file using online tool chemspider.

III. RESULT

3 D Structure of neuraminidase PDB ID $3Cl_2$ A chain protein obtained by homology modeling was analyzed by Saves server. The result obtained for best model are as follows :-

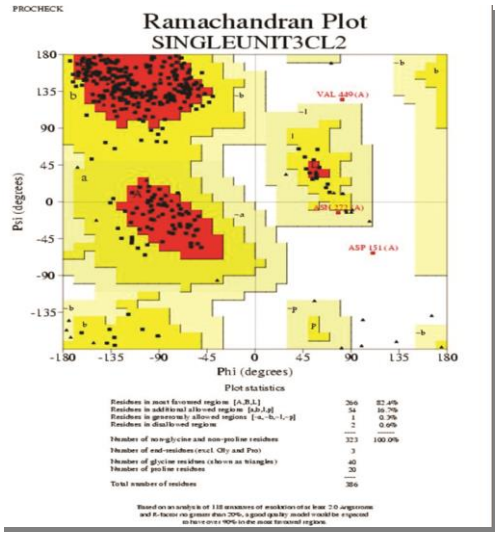
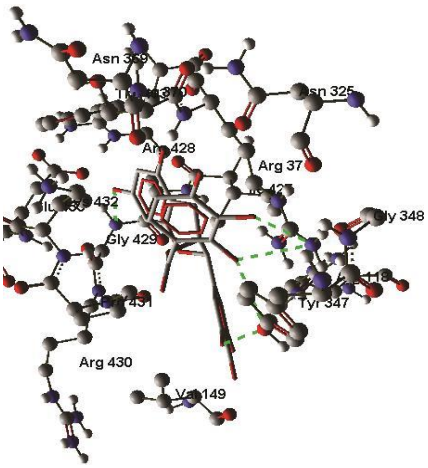
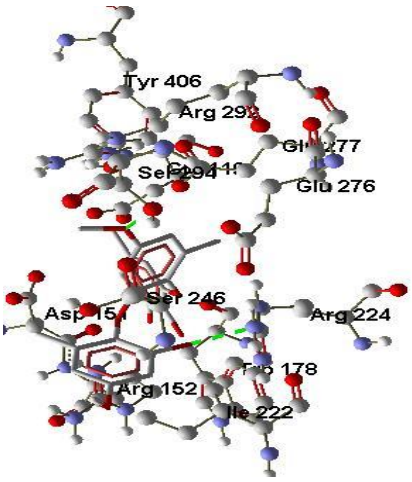
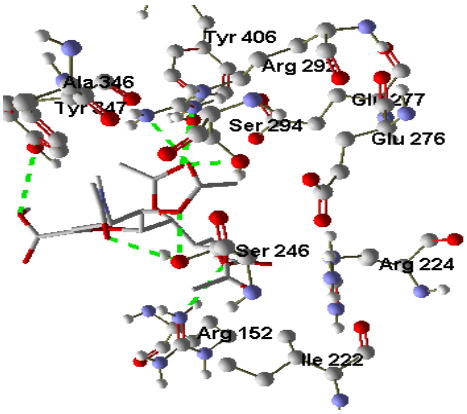


Fig 1:RAMACHANDRAN PLOT DIAGRAM

- Number of residue in favored region (82.4%)
- Number of residue in additional allowed region (16.7%).
- Number of residue in generously allowed region (0.3%).
- Number of residue in disallowed region (0.6%).
- Very-3D 100.00% of the residue an averaged 3 D score >0.2.

IV. DOCKING RESULT

Docking result of the inhibitor molecule. The NA and zanamivir interaction has observed with minimal dock score -155.968 kcal/mol. And oseltamivir has been docked with -132.72 kcal/mol. on the other hand we search the other inhibitor molecules [6] like Marchantin [8], Xylopine , Epicatechin gallate , by the research paper. The docked energy of NA into each of the inhibitor molecules such as Epicatechin gallate, Xylopine, Marchantin. acid have been -174.3 kcal/mol , -148.5 kcal/mol , -131.4 kcal/mol [11].

Sr. No.	Docking interaction	Predicted binding site on protein	No of hydrogen bond	Moldock score
1.	**Docking study of Epicatechin gallate** 	gly – (429), pro – (431), cys – (432), arg – (428).	Tyr-(347), gly – (429).	-174.3 kcal/mol
2.	**Docking study of marchantin** 	ser – (294), ser – (246), asp – (151).	arg – (152), ser – (294).	-131.4 kcal/mol
3.	**Docking study of Xylopine** 	Tyr– (406), ser– (294)	ser - (246) , arg –(152) , tyr –(347).	-148.5 kcal/mol

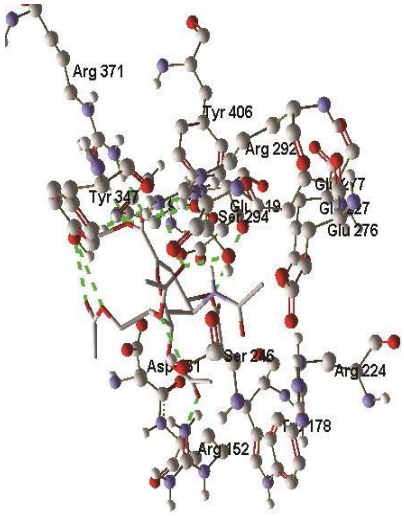
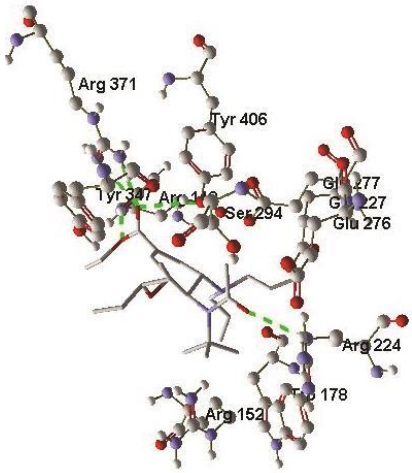
4.	**Docking study of Zanamivir** 	**ser** – (246), gly – (429), Tyr – (406), arg – (292)	Tyr – (347), ser – (294), asp – (151).	-155.9 kcal/mol
5.	**Docking study of oseltamivir** 	Tyr – (406), ser – (294), arg – (224)	arg – (152), Tyr – (347).	-132.7 kcal/mol

Table 1: List of natural compound which shows docking score .

V. CONCLUSION

The successfully docking of Neuraminidase protein with Epicatechin gallate (ECG) , Marchantin , Xylopine that combination proves that the combination can be effective in the treatments of swine flu influenza A virus diseases. Present drugs are not much more effective to cure this disease and have many side effects also. Present work targets neuraminidase protein of influenza virus. It consists of six, four stranded beta sheets, 3 helix and loops .When the different natural ligands docked with protein. It checks all possible orientations and conformation for all set of ligands. Those docking results are included which showed best interaction with neuraminidase protein. After docking we find the binding energy of main drug zanamivir is -155.9 kcal/mol and the Oseltamivir is -132.7 kcal/mol. We have search many inhibitor molecule of H1N1. After docking we select one inhibitor molecule in the basis of binding energy. The binding energy of Epicatechin gallate is -174.3 kcal/mol.

VI. DISCUSSION

This In - silico herbal work makes use of Ayurvedic herbs in computers aided drug designing. The principles outlined in homology modeling is used to modeled the 3D structure of the protein neuraminidase since suitable template was not found by searching across PDB and BLAST search , so the author have used phyre server to model the proteins. The mentions of natural compound Epicatechin gallate , Marchantin , and Xylopine is found in the work of drug designing. Author utilized the combination of

the active components of the natural compound with protein of influenza A virus. Again, since the work is done in In-silico platform. The combination Epicatechin gallate, Marchantin, Xylopine. Combination needs to go to clinical testing to establish its efficacy.

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