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Comparative Docking Analysis on Natural Compounds Versus a Synthetic Drug as a Therapeutic for Acquired Immuno Deficiency Syndrome

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Abstract: Problem statement: Acquired Immune Deficiency Syndrome (AIDS) is one of the worst pandemics affecting and spreading quickly all over the world with a high mortality rate. AIDS has been able to kill so many people due to the unique property of Human Immunodeficiency Virus (HIV) virus. It attacks the immune system of the victim there by not allowing the immune system to fight against the infection. Till today there has been no vaccine or medicine invented against AIDS and thus the syndrome remains incurable. **Approach:** In the present study, automated docking was performed by comparing two natural compounds namely ellagic acid, quercitine against a synthetic drug namely nevirapine on Cluster of Differentiation 4 (CD4), which serves as the high-affinity receptor for cellular attachment and entry of the HIV which is responsible for AIDS. Using the available Bioinformatics tools and techniques a comparative study between the natural and the synthetic drug was done. **Results:** From the results, it was found that the natural compounds showed more inhibiting activity towards CD4 than the already available drug. Perhaps the quercitine could be used as a potential lead compound that has an activity on the target and could be modified to improve its pharmaceutical features in the drug discovery process for AIDS. **Conclusion:** However the results from clinical studies were always the limiting step to the entrance of the novel drugs into the market. This research was an attempt to take a good step towards the drug discovery against AIDS.

Key words: HIV, CD4, ellagic acid, quercitin, nevirapine, automated docking

INTRODUCTION

Acquired Immuno Deficiency Syndrome (AIDS) is a condition in humans in which the immune system begins to fail, leading to life-threatening opportunistic infections. Human Immunodeficiency Virus (HIV) is the causative agent of AIDS. HIV infection in humans is now pandemic. HIV on invading the body specifically attacks the T-cells which is the core part of human defense system. CD4 is the primary receptor present on the T-cells which get attached to the viral envelope known as gp120 on HIV (Gilbert *et al*., 1993; Vermeire *et al*., 2006; Yang *et al*., 2005). Compounds used for docking analysis were ellagic acid (Cozzi *et al*., 1995) from pomegranate (*Punica granatum*), quercitine from apple (*Malus domestica*) against a synthetic drug namely nevirapine on CD4 protein which is responsible for the syndrome.

MATERIALS AND METHODS

Various tools, software and databases that were used are:

- PDB, the protein data bank (http://www.pdb.org/pdb/home/home.do) contains information about experimentally determined structures of proteins, nucleic acids and complex assemblies.
- PubChem (http://pubchem.ncbi.nlm.nih.gov/) is a small molecule database which gives information on the physical, chemical, structural and biological activity of the small molecule
- ChemSketch, chemically intelligent drawing interface freeware developed by Advanced Chemistry Development, Inc., (http://www.acdlabs.com/download/). This can be used for 2D structure cleaning, 3D optimization and viewing, InChl generation and conversion, drawing of polymers, organometalics and Markush structures. It could also create IUPAC systematic naming for molecules with fewer than 50 atoms and three rings.
- PRODRG2 Server (http://davapc1.bioch.dundee.ac.uk/prodrg/) is an online tool to convert coordinates for small

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molecules in PDB format to other necessary formats

- AutoDock4 (http://autodock.scripps.edu/) is a suite of automated docking tools
- PyMol (http://www.pymol.org/) is an open-source molecular visualization program for visualizing the interaction between the receptor and the ligand

The 3D structure of the CD4 protein (1WI0) was downloaded from PDB. Using the small molecule database PubChem, structure of ellagic acid (Fig. 1), quercitin (Fig. 2) and nevirapine (Fig. 3) were retrieved. With the help of ChemSketch, the structures were drawn and saved in .mol format. The format of the retrieved structures to AutoDock acceptable format was done using PRODRG server and all the structures were changed in to pdbq format. Docking was done using automated Gnetic Algorithm method AutoDock4 and the interactions were studied using PyMol.

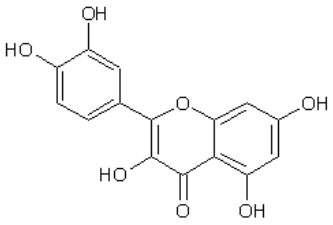

Fig. 1: Structure of ellagic acid

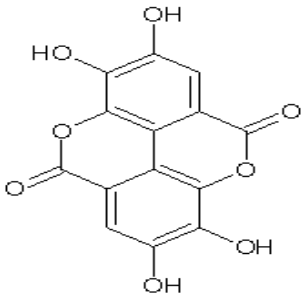

Fig. 2: Structure of quercitin

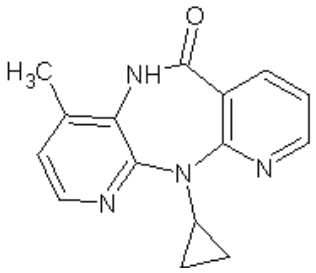

Fig. 3: Structure of nevirapine

RESULTS

Results show that ellagic acid and quercitine with the least docking score of -5.58 and -6.48 formed well and more number of hydrogen bond interactions at a distance of 2-3 Å. The interactions of natural compounds are better with CD4 protein when compared to the already existing drug, nevirapine found using PyMol (Table 1).

DISCUSSION

The objective of this study is to compare the efficiency of the two natural compounds against the already existing drug in market with the help of docking analysis. The docking scores show that ellagic acid and quercitin interacts more strongly with CD4 than nevirapine (Table 1). The interactions study shows that nevirapine formed two hydrogen bonds with CD4 (Fig. 6) while ellagic acid and quercitin formed three and two hydrogen bonds (Fig. 4 and 5) that measures the intermolecular interaction between the protein and ligands. Eventhough most of the studies show that the effect of quercitin against HIV by acting upon HIV integrase enzyme, this study proves its action upon CD4 protein also (http://www.life-nthusiast.com/index/Education/Ellagic, http://www.pnas.org/conten-/90/6/2399.short). These compounds could be taken into account for *in vitro*, *in vivo* and clinical studies.

Table 1: Interaction between the receptor and compounds

Target receptor ID	Compounds	Docking score	H-bond interactions	Bond length (A^o)
	Ellagic acid	-5.58*	O-----HO	2.7
			N-----HO	3.3
			O-----HO	3.4
1WI0	Quercitin	-6.48*	N-----HO	3.4
			N-----HO	3.4
	Nevirapine	-4.34	N-----HO	3.3
			N-----HO	2.8

*: Indicates the least docking score

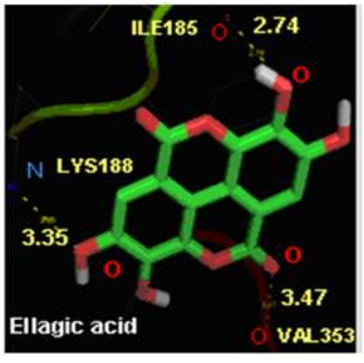

Fig. 4: H-bond interactions between CD4 and ellagic acid

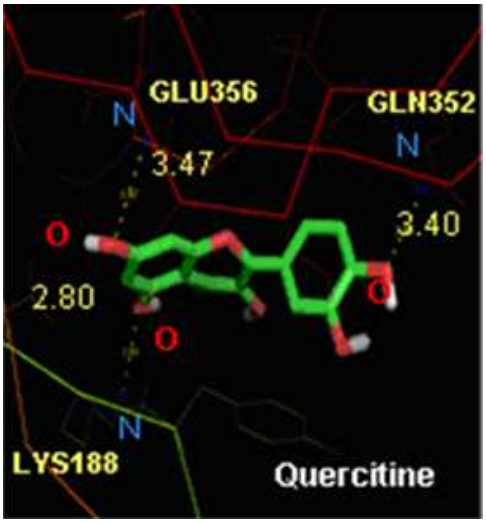

Fig. 5: H-bond interactions between CD4 and quercitin

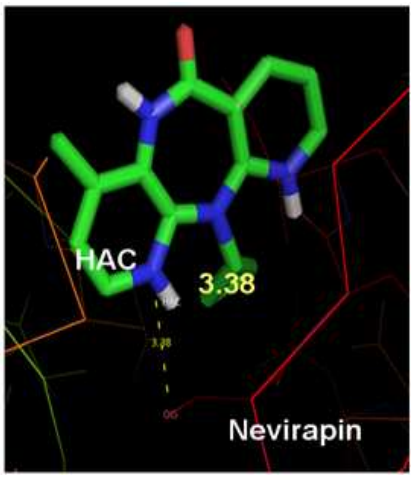

Fig. 6: H-bond interactions between CD4 and nevirapine

CONCLUSION

In the light of the good docking score and number of hydrogen bonds shown by docking analysis in the comparison of two natural compounds against nevirapine, the earlier two showing the better efficiency could be used as potential leads in drug designing against HIV infection.

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