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Establishing a Natural Remedy for AIDS

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Abstract

Acquired Immune Deficiency Syndrome is an incurable and terminal disease of the human immune system caused by the Human Immunodeficiency Virus (HIV). The HIV Envelope Glycoprotein (EGP) and Glycoprotein 120 (GP 120) is responsible for AIDS in humans. 3D structures of these two proteins were generated using Homology Modeling. Active compounds of medicinal herbs- *Castanospermum australe* which inhibits HIV replication and synctium formation induced by EGP and of *Ancistrocladus korupensis* which acts on HIV life cycle by inhibiting reverse transcriptase, cellular fusion and synctium formation were selected. Chemical structures of the active component of these herbs were drawn using chemsketch & converted to .pdb. Both the proteins were successfully docked with the *Castanospermum australe* - *Ancistrocladus korupensis*'s active components.

Keywords: AIDS, *Castanospermum austral*, *Ancistrocladus korupensis*, Bioinformatics, Homology Modelling, Drug designing.

Introduction

Acquired Immuno Deficiency Syndrome (AIDS) is a clinical syndrome that is the result of infection with Human Immuno Deficiency Virus (HIV), which causes profound immunosuppression. It has been a serious, life-threatening health problem since the first case was identified in 1981 and is the most quickly spreading disease of the century. Worldwide, it is the fourth biggest killer [1]. HIV emerged later in India

than it did in many other countries [2]. Infection rates soared throughout the 1990s, and today the epidemic affects *all* sectors of Indian society, not just the groups – such as sex workers and truck drivers – with which it was originally associated. In a country where poverty, illiteracy and poor health are rife, the spread of HIV presents a daunting challenge. The spread of HIV in India has been diverse, with much of India having a low rate of infection and the epidemic being most extreme in the southern states [3, 4, 5].

The Envelope glycoprotein (Env) is the sole viral protein present on the surface of Human Immunodeficiency Virus-1 (HIV-1) virions. Env is synthesized as a 160 kDa precursor protein (gp160). It folds and trimerizes in the endoplasmic reticulum (ER) of the host cell, where it obtains ten disulfides and ~30 N-linked glycans depending on the viral isolate. In the Golgi complex, gp160 is cleaved by a cellular protease into a soluble subunit, gp120, and a transmembrane subunit, gp41. They remain non-covalently associated on the surface of infected cells and on virions. Together, the two Env subunits mediate viral entry: gp120 is responsible for binding to the receptor (CD4) and the coreceptor (CCR5 or CXCR4) on the host cell, and gp41 is needed for subsequent fusion of the viral and cellular membranes [6].

Protein-protein interaction surfaces can exhibit structural plasticity, a mechanism whereby an interface adapts to mutations as binding partners coevolve. The HIV-1 envelope glycoprotein gp120-gp41 complex, which is responsible for receptor attachment and membrane fusion, represents an extreme example of a coevolving complex as up to 35% amino acid sequence divergence has been observed in these proteins among HIV-1 isolates. The HIV-envelope glycoprotein (Env) complex comprises a trimer of surface-exposed gp120 subunits that are noncovalently associated with a trimer of gp41 transmembrane subunits. The gp120-gp41 complex is derived from a precursor, gp160, following cleavage by host cell subtilisins in medial- or trans-Golgi compartments. The mature gp120-gp41 complex is incorporated into virions as they bud from the plasma membrane [7].

Several reviews on the natural products for chemotherapy of HIV infection have been published earlier. Matthee *et al.*[8] reviewed naturally occurring HIV reverse transcriptase inhibitors. Jung *et al.*[9] discussed anti-HIV agents according to their chemical classes. Yang *et al.*[10] reviewed natural products-based anti-HIV drug discovery and development facilitated by NCI development programme. Recently, Cos *et al.*[11] reviewed different plant substances as anti-HIV agents according to their mechanism of action.

Michellamine B

Michellamine B is derived from *Ancistrocladus korupensis* (a liana species discovered by NCI in 1987 in Korup National Park in southwestern Cameroon), Michellamine B shows in vitro activity against HIV-1 and HIV-2 by acting "at two distinct stages of the HIV life cycle: inhibiting both viral fusion and reverse transcriptase (RT). Unlike many other non-nucleoside RT inhibitors, Michellamine B inhibits the enzymatic activity of both HIV-1 and HIV-2 reverse transcriptase." [12]

Castanospermine

Castanospermum australe is the only species of the genus *Castanospermum* (the Moreton Bay chestnut or black bean) native to NE Australia. One constituent of the plant, castanospermine, can inhibit the AIDS virus. Castanospermine is an indolizine alkaloid first isolated from the seeds of *Castanospermum australe*.[13]

In this particular work authors wish to establish a remediation for AIDS using computational tools.

Methodology

HIV protein-envelope glycoprotein with accession number-ABH02539.1 and human receptor protein to which HIV protein binds, gp120 with accession number AAF69492.1 was retrieved from NCBI's entrez database. Homology modeling was carried out using Modeller 9v7, for predicting 3 D structures for the above mentioned proteins. Templates were downloaded from RCBS PDB database. The following templates were used:

- Envelope glycoprotein- 3jwdA, 3jwoA and 2bf1A.
- Gp120- 2bf1A, 1yymG and 1g9mG.

Five models of each of the above proteins were generated. The models were analyzed by Rampage Ramchandran plot server and the best model of each was selected.

Chemical structures of active component of *Ancistrocladus korupensis*, Michellamine B (Fig. 1) and active component of *Castanospermum australe*, Castanospermine (Fig. 2) were drawn using ACD chemsketch software individually, converted and saved as *.mol file and was then converted to *.pdb file using Argus lab software.

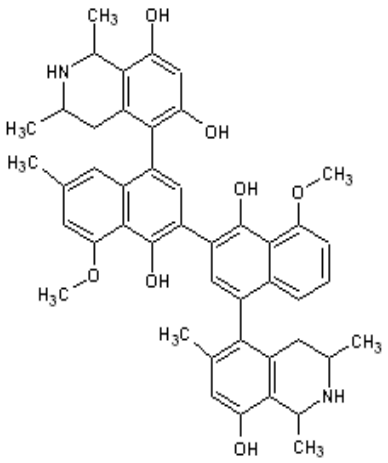

Figure 1: Chemical structure of Michellamine B (drawn using ACD/Chemsketch).

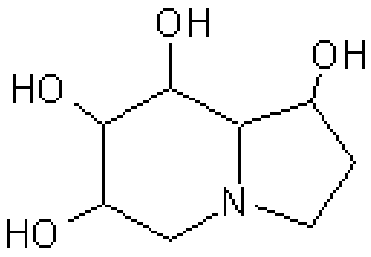

Figure 2: Chemical structure of Castanospermine (drawn using ACD/Chemsketch).

Each of the proteins used for this work, namely HIV envelope glycoprotein and gp120 was docked with active components of *Ancistrocladus korupensis* and *Castanospermum australe* i.e. Michellamine B and Castanospermine.

Results

3D structure of envelope glycoprotein obtained by homology modeling was analyzed by RAMPAGE Ramchandran plot server (Fig 3,4) . The results obtained for best model (#1) are as follows:

Number of residues in favored region (~98.0% expected): 411 (90.7%)
Number of residues in allowed region (~2.0% expected): 37 (8.2%)
Number of residues in outlier region: 5 (1.1%)

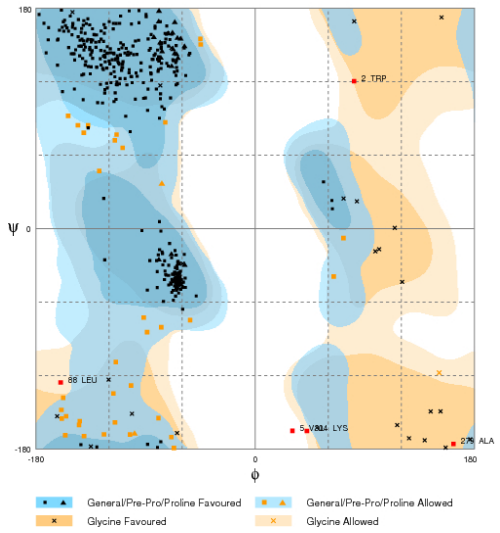

Figure 3: Ramachandran Plot analysis envelope glycoprotein.pdb (model 1).

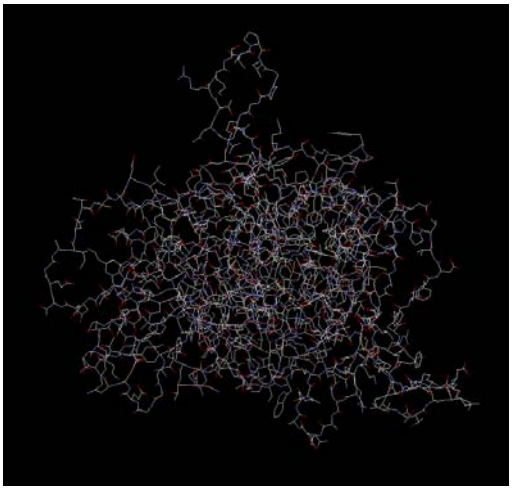

Figure 4: 3d structure of HIV envelope glycoprotein.pdb (visualization in rasmol).

The 3D structure of Gp120 obtained by homology modeling was analyzed by Rampage
Ramchandran plot server (Fig 5, 6). Plot analysis for best model (#3) is:
Number of residues in favored region (~98.0% expected): 394 (87.0%)
Number of residues in allowed region (~2.0% expected): 47 (10.4%)
Number of residues in outlier region: 12 (2.6%)

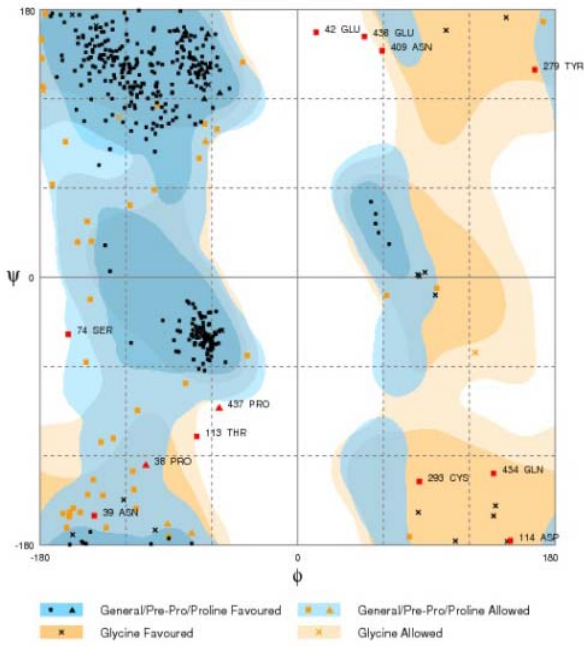

Figure 5: Ramachandran Plot analysis gp120.pdb (Model 3).

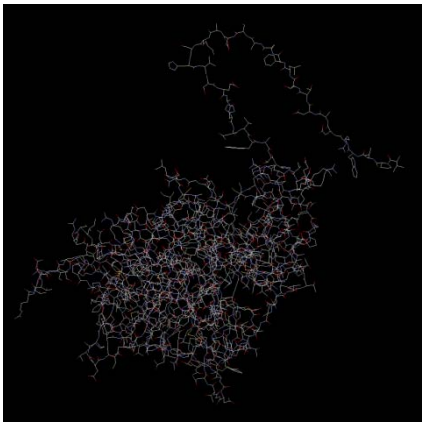

Figure 6: 3d structure of GP.pdb (visualization in rasmol).

The pdb structures of michellamine B and castanospermine (obtained above) are docked with HIV envelope glycoprotein (Fig 7 & 8) and GP120 (fig 9 & 10) using PATCHDOCK server.

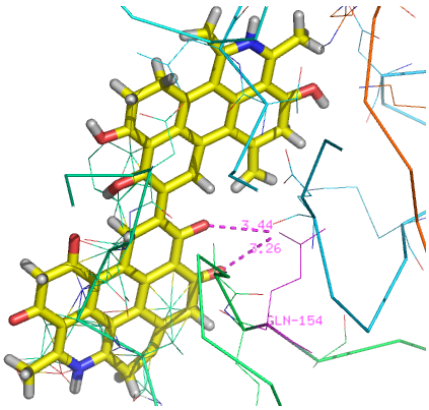

Figure 7: Docked structure glycoprotein.pdb with michellamine B (visualization in PyMOL) Score - 6740.

(ligand interacts with protein at GLN 154, distance between ligand & amino acid 3.44 & 3.26; interaction at two places)

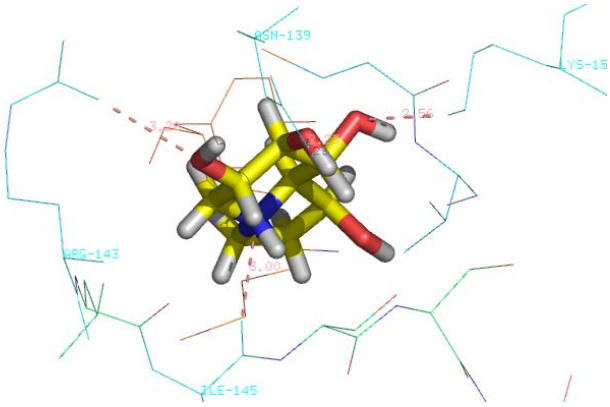

Figure 8: Docked structure glycoprotein.pdb with castanospermine (visualization in PyMOL). Score - 2920
(ligand interacts with protein at LYS153, distance between ligand & amino acid 2.56
ligand interacts with protein at ASN139, distance between ligand & amino acid 2.23
ligand interacts with protein at ARG143, distance between ligand & amino acid 3.26
ligand interacts with protein at ILE145, distance between ligand & amino acid 3.00)

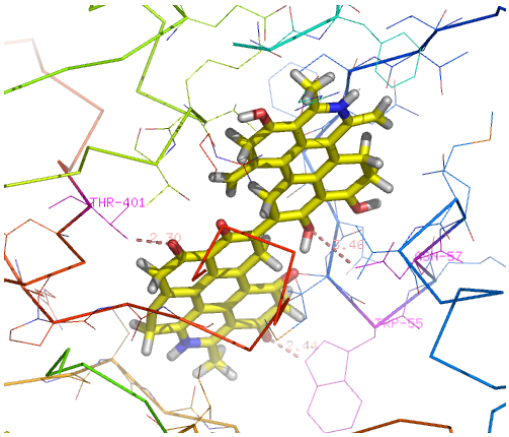

Figure 9: Docked structure GP120.pdb with michellamine B (visualization in PyMOL). Score- 7758
(ligand interacts with protein at THR 401, distance between ligand & amino acid 2.30
ligand interacts with protein at ASN 57, distance between ligand & amino acid 3.46
ligand interacts with protein at ARG143, distance between ligand & amino acid 3.26
ligand interacts with protein at TRP 55, distance between ligand & amino acid 2.44)

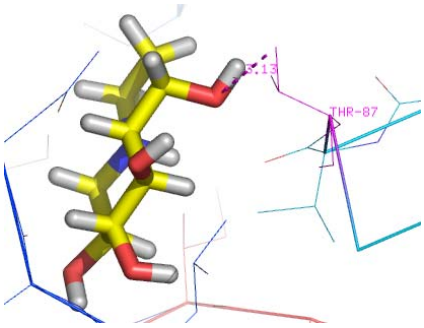

Figure 10: Docked structure GP120.pdb with castanospermine (visualization in PyMOL). Score- 3114
(ligand interacts with protein at THR 87, distance between ligand & amino acid 3.13)

Conclusion

The successful docking of HIV envelope glycoprotein and glycoprotein120 with Michellamine B and Castanospermine suggests that the that the herbs *Ancistrocladus korpensis* and *Castanospermum australe* can be effective in the treatment of AIDS disease. Again, docking scores as per patch dock server are- glycoprotein.pdb with michellamine B- 6740, glycoprotein.pdb with castanospermine-2920, GP120.pdb with michellamine B - 7758 and GP120.pdb with castanospermine – 3114.

Discussion

This *in-silico*-herbal work makes use of ayurvedic herbs in Computer Aided Drug Designing. The principle outlined in Homology Modeling is used to model the 3D structure of the proteins HIV envelope glycoprotein and glycoprotein120. The mention of the herbs *Ancistrocladus korupensis* and *Castanospermum australe* are found in the works of Inder Pal Singh, et. al. [14]. Henceforth, the authors utilize the active components of the herbs *Ancistrocladus korupensis* and *Castanospermum australe* for the docking with the proteins (envelope glycoprotein and gp120). Since the work is done in *in-silico* platform, the active compounds michellamine B and castanospermine needs to go to clinical testing to establish their efficacy.

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