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High throughput virtual screening and *in silico* ADMET analysis for rapid and efficient identification of potential $PAP_{248-286}$ aggregation inhibitors as anti-HIV agents

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ABSTRACT

Human semen is principal vehicle for transmission of HIV-1 and other enveloped viruses. Several endogenous peptides present in semen, including a 39-amino acid fragments of prostatic acid phosphatase ($PAP_{248-286}$) assemble into amyloid fibrils named as semen-derived enhancer of viral infection (SEVI) that promote virion attachment to target cells which dramatically enhance HIV virus infection by up to 10^5-fold. Epigallocatechin-3-gallate (EGCG), a polyphenolic compound, is the major catechin found in green tea which disaggregates existing SEVI fibers, and inhibits the formation of SEVI fibers. The aim of this study was to screen a number of relevant polyphenols to develop a rational approach for designing $PAP_{248-286}$ aggregation inhibitors as potential anti-HIV agents. The molecular docking based virtual screening results showed that polyphenolic compounds 2–6 possessed good docking score and interacted well with the active site residues of $PAP_{248-286}$. Amino acid residues of binding site namely; Lys255, Ser256, Leu258 and Asn265 are involved in binding of these compounds. *In silico* ADMET prediction studies on these hits were also found to be promising. Polyphenolic compounds 2–6 identified as hits may act as novel leads for inhibiting aggregation of $PAP_{248-286}$ into SEVI.

1. Introduction

According to United Nations Programme on AIDS (Acquired Immuno Deficiency Syndrome) (UNAIDS) there were approximately 35 million people worldwide living with AIDS. Three decades after its initial identification, HIV (Human Immunodeficiency Virus) emerged as a global epidemic and aggressive public health problem: 33 million adults and children are suffering from HIV worldwide [1]. Semen serves as a protective environment for HIV virions that may act to increase HIV transmission [2]. A cofactor had been recently found in human seminal fluid that promote entry of the virus and cause infection at a higher rate [3], which could result into a crucial component in transmission of the HIV [4]. Due to presence of *in vivo* cofactors HIV is prevalent in the population and transmitted easily *in vivo*. A peptide portion of prostatic acid phosphatase ($PAP_{248-286}$) sequence (GIHKQKEKSRLQGGVLVNEILNHMKRATQIPSYKKLIMY) was found to increase the infection rate of HIV and other enveloped viruses [2,5] by various orders of magnitude when aggregated into amyloid fibrils. $PAP_{248-286}$ only increase HIV infection in the form of amyloid aggregates termed Semen-derived Enhancer of Viral Infection (SEVI) which is a positively charged amyloid fibril that is derived from a self-assembling proteolytic cleavage fragment of $PAP_{248-286}$ [6]. It has been well established that SEVI is an amyloidogenic peptide, and that amyloid fibers of the peptide are more efficacious than the monomeric peptide in assisting HIV cell binding. It is confirmed that electrostatic interactions play a major role in augmenting HIV infectivity [2]. The presence of 8 positively charged amino acid residue (either lysine or arginine) in $PAP_{248-286}$ sequence, are thought to decrease the repulsive charge-charge interactions between HIV virions and its host cells, and therefore it helps in facilitating virion attachment

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List of abbreviations

UNAIDS	United Nations Programme on HIV and AIDS
HIV	human immunodeficiency virus
SEVI	semen-derived enhancer of viral infection
PAP	prostatic acid phosphatase
EGCG	epigallocatechin-3-gallate
ADME	absorption, distribution, metabolism and excretion
OPLS	optimized potentials for liquid simulations-2005
RMSD	root-mean-square deviation
NCBI	National Center for Biotechnology Information
HTVS	high throughput virtual screening
SP	standard precision
XP	extra precision
HTS	high throughput screening
SDF	structural data file
ANN	artificial neural network
MRTD	maximum recommended therapeutic dose
MW	molecular weight
SASA	total solvent accessible surface area
FOSA	hydrophobic SASA
FISA	hydrophilic SASA
PISA	carbon Pi SASA
WPSA	weakly polar SASA
MV	molecular volume (MV)
PSA	Van der Waals Polar SA
ROTATB	no. of rotatable bonds
DONORHB	donor-hydrogen bonds
ACCPTHB	acceptor-hydrogen bonds
GLOB	globularity
Polrz	polarizability
logS	aqueous solubility
CIlogS	logS-conformation independent
BB	brain/blood
Metab	metabolites
PCaco	caco-2 permeability
pHOA	percentage human oral absorption
QmHOA	qualitative model for human oral absorption
CA	chromosomal aberrations
AlkPhos	alkaline phosphatase
GGT	gamma-glutamyltransferase
LDH	lactate dehydrogenase
SGOT	serum glutamate oxaloacetate transaminase
SGPT	serum glutamate pyruvate transaminase

to target cells. Importantly, it has also been shown that semen itself strongly enhances virus infection and that the activity of individual semen samples to boost HIV infectivity correlates with the concentrations of $PAP_{248-286}$ peptide present in the respective [7]. Aminoquinolinesurfen [8], BTA-EG6 [hexa(ethylene glycol) derivative of benzothiazole aniline] [9], WW61 (a hexapeptide, Trp-His-Lys-chAla-Trp-hydroxy Tic) [10] are found to have inhibitory activity against various types of amyloid formation under *in vitro* conditions. In fact, the fibrillar structure formation is a common feature of many degenerative diseases like Alzheimer's, Parkinson's, Type II diabetes, Huntington's and others [11].

Polyphenols might possess the ability to interrupt the aromatic interactions that take place during amyloid formation because they are composed of one or many aromatic rings [12]. Epigallocatechin-3-gallate (EGCG), a polyphenolic compound, is a major catechin found in green tea which disaggregates existing SEVI fibers and inhibits the formation of SEVI fibers [13]. EGCG has been proposed to site specific interaction with the side chain of monomeric $PAP_{248-286}$ [14] and also bind to backbone sites of many amyloid proteins [15,16]. EGCG was successful in demonstrating its inhibitory activity in 41 out of 47 semen samples analyzed [13]. This observation supports the hypothesis that EGCG is a strain-selective inhibitor of SEVI precursor $PAP_{248-286}$. The virtual screening model was prepared by using the SEVI precursor peptide $PAP_{248-286}$. The screened compounds were selected on the basis of docking score and binding energy. Five potential hits for target site in the SEVI Precursor Peptide $PAP_{248-286}$ were obtained through molecular docking based virtual screening technique. In the present work, docking study of EGCG and various polyphenolic compounds has been performed with the SEVI precursor peptide $PAP_{248-286}$. Principal descriptors/ADME (Absorption, Distribution, Metabolism and Excretion) and toxicity values for inhibitors have been predicted.

2. Material and methods

All computational analysis was carried out on a Red Hat 10.2 Linux platform on a HP workstation with an Intel Core i7 processor, 2 GB GDDR5 graphics card and 16 GB RAM.

2.1. Protein structure

The X-ray crystal structure of the SEVI precursor peptide $PAP_{248-286}$ (PDB ID: 2L3H) was taken from Protein Data Bank [17]. Processing of protein structure was carried out by "Protein preparation wizard" of Maestro, version 9.7 [18,19]. Hydrogen bonds assignment tool was implemented for optimizing the network of H-bonds. The minimization of energy was carried out by in-built constraint of RMSD (Root-mean-square deviation): 0.3 Å and force field: OPLS 2005 (Optimized Potentials for Liquid Simulations-2005).

2.2. Receptor grid generation

Generation of grid around active sites done by receptor grid generation panel of Glide version 6.2 [18]. The grid points in the *x*-, *y*-, *z-axes* (2.02 × 6.72 × 21.05) and grid size was kept default 20 Å.

2.3. Compound library selection & preparation

Polyphenolic compound and flavonoid libraries of 5000 and 1000 compounds respectively were downloaded from PubChem database of NCBI (National Center for Biotechnology Information). All the ligand structures were in 2D SDF format which were converted to 3D for docking. Ligprep version 2.9 [18] was used for geometric minimization of all ligands using OPLS force field. Ligprep version 2.9 was used to produce a single, low energy, 3D structure with correct chirality.

2.4. Structure based virtual screening

All the docking and scoring calculations were executed by the Glide module, version 6.2 [18]. Virtual screening is used to recognize and rank potential hits from a database of various compounds against one or more targets. Virtual screening was carried out in docking approach by High Throughput Virtual Screening (HTVS), Standard Precision (SP) and Extra precision (XP). HTVS, SP and XP differ only in number penalties. All the screened compounds from