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Original Article

Molecular modelling and Docking studies on shrimp vitellogenin receptor and ligand target mediated delivery system

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Abstract

Viral pathogens of shrimp such as the white spot syndrome virus (WSSV), Yellow head virus (YHV), Taura syndrome virus (TSV), Hepatopancreatic parvovirus (HPV), and Monodon Baculovirus (MBV), which are geographically widespread, are major concern in shrimp aquaculture due to the associated huge economic loss . The control of such diseases is a challenging task for the shrimp aquaculture industry. Drug delivery mediated by specific receptor and ligand interaction plays an important role in effective control of diseases. In the present study focus on vitellogenin receptor and ligand interaction for targeted drug delivery for control of MBV infection in black tiger shrimp (*Penaeus monodon*) was explored by insilico studies. Vitellogenin protein receptor of shrimp *P. monodon* and ligand molecules sequences were retrieved from public domain. Molecular modeling and docking studies were explored by using online bioinformatics tools. The results suggested that 20-hydroxy ecdysone might be a potential target of vitellogenin receptor for effective targeted drug delivery system for control of monodon baculovirus.

Key words: Monodon bavulovirus**,** Black Tiger Shrimp, Vitellogenin, 20-hydroxyecdysone, Molecular modeling and docking.

INTRODUCTION

Viral diseases are a major threat to the shrimp aquaculture industry as many viral infections remain undetected till they result in massive disease outbreaks. Several viral diseases have been reported from cultured penaeid shrimp [1]. There are nearly 20 viral pathogens that are known to cause diseases in farmed shrimp [2]. Monodon baculovirus (MBV) is an economically important and one of the major viruses included in the diagnostic screening, for fry quality assessment in the hatchery phase in shrimp larval production [3]. The family Baculoviridae, encompasses a group of arthropodspecific viruses found ubiquitously in the environment and have been isolated from more than 600 host insect species predominantly from the Lepidoptera, Hymenoptera and Diptera. Based on their occlusion body morphology baculoviruses are divided into two genera, Nucleopolyhedrovirus (NPV) and Granulovirus (GV). The baculovirus life cycle typically involves the production of two virion phenotypes, budded virions (BVs) and occlusion-derived virions (ODVs) [4]. MBV was one of the earliest viruses found in shrimp, but its economic impact on shrimp farming has not yet been determined. However, it is considered to be a potentially serious pathogen in larvae, post larvae (PL) and early juvenile stages of cultivated shrimp. Acute MBV causes loss of hepatopancreatic tubule and midgut epithelia and, consequently, dysfunction of these organs may be followed by secondary bacterial infections. MBV transmission occurs exclusively by the oral route, principally by cannibalism and faecal-oral contamination [5]. Basic studies on vitellogenin structure are important for elucidating reproductive mechanisms in prawns and shrimp, particularly for important commercial species such as the

giant freshwater prawn (*Macrobrachium rosenbergii*), kuruma prawn (*Penaeus japonicus*) and black tiger prawn (*Penaeus monodon*).

The hepatopancreas is the site of synthesis for vitellogenin (Vg) in the freshwater giant prawn, *M. rosenbergii* [6]. For molecular modeling, docking is a method which predicts the preferred orientation of one molecule to another, when bound to each other to form a stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules. Docking is frequently used to predict the binding orientation of small molecules, drug candidates to their protein targets in order to predict the affinity and activity of the small molecule [7].

MATERIALS AND METHODS

In the present study we used biological databases like NCBI, Drug Bank, PRODRG, PROCHECK, 3D verify and software's like Hex, Rasmol, Qmol and Swiss pdb viewer [8] for molecular modelling , prediction and insilico structural and functional analysis. The protein sequences were retrieved from the biological database NCBI which was accessed using the (URL: http://www.ncbi.nlm.nih.gov/). Using the protein name as query, the sequence data was collected e (accession number: ABW79798.1). The chemical structures of the compounds to be docked were obtained from pubchem database. The quality of protein geometry was checked by employing PROCHECK. The output of PROCHECK evaluated the various aspects of the model's quality. One of the most important outputs (evaluations) is the Ramachandran plot, which allows pointing out those residues with anomalous combinations of φ and ψ angles. Other model evaluation method used were Verify-3D (http://www.doe-mbi.ucla.edu/Verify3d.html) [9]. The Ligand molecules energy minimization was calculated by PRODRG online server (http://davapc1.bioch.dundee.ac.uk/programs/prodrg/prodrg.html). Hex is an Interactive Molecular Graphics Program for calculating and displaying feasible acids and small bimolecular. The program reads in molecular coordinate files and interactively displays the molecule on the screen in variety of representations and color schemes [10]. RASMOL [Raster Display of Molecules] is a molecular graphics program intended for the structural visualization of proteins, nucleic acids and small biomolecules. The program reads in molecular coordinate files and interactively displays the molecule on the screen in variety of representations and color schemes [11]. Qmol—a program designed for viewing the output of simulations and theoretical calculations of protein, peptides and small molecules [12]. The target receptor sequence which was retrieved from NCBI (Accession No: ABW79798.1) was found to be too large for conducting homology modeling. Hence, the molecule was split into 4 chains and each of the four chains was used one at a time for homology modeling. The Molecular modeling of vitellogenin 3D structure was predicted by T-08 SAM SERVER, based on the HMM. The quality of the refined

Figure 1-Modelled 3D structure of shrimp vitellogenin receptor.

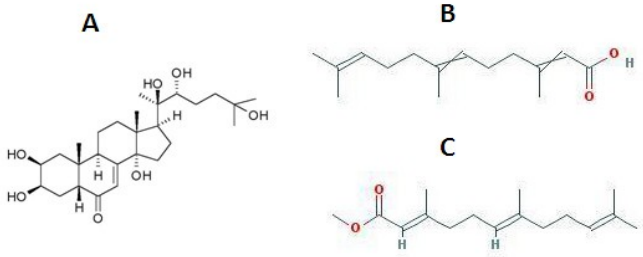

Figure 2-Structure of Ligand molecules, A-20-hydroxy ecdysone, B- Methyl farnesoate, C- Farnesoic acid.

model is assessed using PROCHECK and 3D verify. The 3D structure was visualized by RASMOL. Ligand's molecule was obtained from drug bank. The 3D structure and energy minimization was studied by PRODRG online server. There were three ligand molecules tested in this study. When the receptor was docked with the 20-hydroxy ecdysone, the energy value was obtained using Hex docking software. Docking structure was visualized by Qmol software. H-bond interaction and length was visualized by SWISS PDB VIEWER.

RESULTS

The 3D structure was visualized for Vitellogenin receptor of shrimp *P. monodon* protein sequence (Fig.1). Ligand's molecule was obtained from drug bank (Fig.2). Three ligands molecules were tested in this study. When the receptor was docked with the 20-hydroxy ecdysone the energy value obtained was -174.54 Kcal/mol using Hex software (Table 1). Docked structure was visualized by Qmol software (Fig.3A).

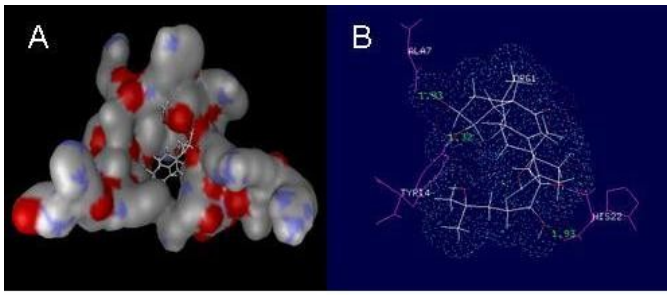

Figure 3- interaction between 20-hydroxy ecdysone and the modelled Shrimp vitellogenin receptor molecule using hex software. A-docking result Surface model, B-docking result wireframe model.

Table-1: Energy value Docking results of shrimp vitellogenin receptor with ligand molecules using hex software.

COMPOUND	E VALUE (Kcal/mol)
Methyl farnesoate	-98.56
Farnesoic acid	-132.72
20-hydroxy ecdysone	-174.54

Three H-bond interaction between receptor and ligand molecule and the bond length is 1.93, 1.93 and 1.32Å was observed by H-bond interaction and length visualized by swiss pdb viewer (Fig.3B). The docking result suggested that 20-hydroxy ecdysone might be a potential target of vitellogenin receptor for drug delivery system against shrimp monodon baculovirus.

DISCUSSION:

Computer modelling allows chemists to build dynamic models of compounds which in turn allow them to visualize molecular geometry and demonstrate chemical principles. Molecular structures can be generated using a variety of software. The complexity arises due to the fact that various interactions are involved in the intermolecular bonding like hydrophobic, dispersion, or van der Waals force, electrostatic and hydrogen bonding. The major force of binding appears to be hydrophobic interactions, but the specificity of the binding appears to be controlled by hydrogen bonding and electrostatic interactions [13]. Designing the ligand for drug delivery is a complicated process because though the 3D structures of many ligands (drug molecules) that interact with the receptors are known, the structure of most receptors are unknown. The modelling of the ligand in the present study was performed using T-08 SAM, a server that has its principles based on Hidden Markov Modelling (HMM). This kind of docking study using the T-08 Sam server has been used limitedly in studies for drug designing. Molecular docking is used for structural based drug designing to various diseases. As important therapeutic drug targets, matrix metalloproteinases (MMPs) have recently attracted great interest in the search of potent and selective inhibitors using computer-aided molecular modeling and docking techniques [14]. The new inhibitors of the ErbB2 tyrosine kinase domain are potential lead compounds against the most aggressive forms of breast cancer [15]. The retinoic acid receptor (RAR) and retinoid X receptor (RXR) are members of the nuclear receptor super family pharmacological targets for various cancers and skin diseases [16]. Docking is performed by energy minimization in rotational and translational degrees of freedom [17]. The interaction between the ligand and the receptor are usually examined in terms of the pocket shape as well as chemical nature of the residues lining the ligand-binding cavity [18]. A combined electrostatics-hydrogen bonding potential is developed during docking [19]. Binding energies calculation and complementarity scores are used for evaluation of docking [20]. Another factor to be taken into consideration is the bond energy in the interaction. A negative bond/ dock energy is considered a good sign of strong binding. Hence the more negative the energy, the higher is considered to be the interaction, hence making the docking study more valid. The docking values of most of the studies seem to be in the units to tens range in the negative scale. To site a few examples the docking values of Dectin-1 (PAMP) receptor of *Bubalus bubalis* is −1.25 Kcal/mol [21], that of HIV-1 receptor with nevirapine is -80.4485 Kcal/mol [22], and that of homochiral (3S, 30S)-astaxanthin to matrix metalloproteinase-13 (MMP-13) was -15.15 Kcal/mol [23]. The molecular docking energy in the present study is -180.3 Kcal/mol, a value that has not been obtained till date. The low energy in this interaction goes to prove that the docked model can be of valid use to effectively delivered for endocytosis mechanism of black tiger shrimp against MBV.

CONCLUSION

The Receptor-Ligand interaction plays a significant role in organ specific receptor mediated drug delivery system. In the present work we have taken the receptor vitellogenin and identified the ligands that were used against drug delivery system. When the receptor was docked with the ligand 20-hydroxy ecdysone the energy value obtained was (-174.54 Kcal/mol) using hex software. There are three H-bond interaction between receptor and ligand molecule and the bond length is 1.93, 1.93 and 1.32 Å. From this we concluded that 20-hydroxy ecdysone can be used for the receptor cell mediated drug delivery system against MBV in black tiger shrimp.

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