ISSN No:-2456-2165

Exploring the Horizons of Ephrin B2 Receptor for Combating *Paramoxyviridae* Infection

Yuktha.S.Shreenivasan, Praveena. A*
Department of Biotechnology, Prathyusha Engineering College
Chennai-602025, TamilNadu, India

Abstract:- Nipah virus belongs to the family of Paramyxoviridae. It is a deadly virus which needs to be treated using a drug of increased efficacy and reduced toxicity. The main objective of this research is to identify the suitable drug molecule which could inhibit the escalation of this infection within the biological system susceptible to the infection. For this, bioinformatics tools were being exploited over the due course. Through literature survey, it was identified that the Nipah virus invades the susceptible human cell by adhering to the Ephrine B2 receptor through the viral phosphoprotein and glycoprotein moieties respectively. The novel approach of blocking the Ephrine B2 receptor using an organic compound is proposed in this paper to be effective in preventing the emerging Nipah virus. Further the docking studies of alkaloid Berberine with the Ephrine B2 receptor B and D chains in particular gave the docking energy as -5.65 kcal/mol which reveals a significant interaction between the target protein and the ligand molecule. The ligand further obeys Lipinski's rule of 5, which provides Berberine therapeutic advantages in treatment of this deadly disease.

Keywords:- *Berberine, Increased Efficacy, Molecular Docking, Lipinski's Rule.*

I. INTRODUCTION

Ephrine B2 which is a transmembrane receptor which is approximately of 40kda of size, belongs to the class of Eph receptors. The participation of Ephrin-B2 in a range of physiological systems, including vascular, lymphatic, neuronal, and renal development, neurotransmission, synaptic plasticity, and tumor metastasis respectively amongst the several inevitable existing functions. Ephrin-B2 along with its cognate receptors B3 and B4 are expressed in complementary fashion on adjacent cells. The combination of forward and reverse signaling is central to the tissue development and remodeling functions of Ephrin and Eph associated proteins.

The *Hendra* and *Nipah* viruses (HeV and NiV) are prominant members of the *Paramyxoviridae* family [1]. The initial cases were detected in Australia in 1994-95 and Malaysia in 1998-99. *Henipa* viruses have been transmitted to humans through several sources [2]. *Henipa* virus interactions with target cells are mediated by its 75 kDa glycoprotein moiety attachment and 70 kDa fusion proteins attachment respectively, where both of them are evident prospects for membrane fusion. Recently Ephrin-B2 has been identified as a functional cellular receptor for Hendra and *Nipah* viruses [3].

Though several other moieties could perhaps contribute towards HeV and NiV fusion permissiveness there exists a strong correlation between Ephrin-B2 expression patterns and the tropism of *Henipa* viruses. Further, the Ephrin-B2 receptor is observed to establish conservative paradigm in advancement of the infection amidst other prone individuals.

Berberine being phytochemical of interest in the present study is a quaternary ammonium salt from the protoberberine group of benzylisoquinoline alkaloids found in plants including Berberis (e.g. Berberis vulgaris – barberry, Berberis aristata – tree turmeric, etc) [4]. Berberine is prominently found in the roots, rhizomes, stems, and barks in those plants reported to contain the phytochemical. Berberine was anciently used in China as a folk medicine. In accordance with the collaborative analysis of the existing mechanism and our novelty, the receptor moiety was selected as the Ephrin B2 and the compatible ligand molecule as Berberine for the *in-silico* studies.

II. MATERIALS AND METHODS

A. Sequence Analysis

The method of deciphering the treatment of *Nipah* virus in this case is seen to be target based drug discovery approach. This was concluded after thorough study of the mechanism of evasion of the pathogen into the host cell. To study the infection caused by it, the sequence has been retrieved from the NCBI database [5]**.** The accession number of the *Nipah* virus genome is AF212302.2. BLAST [6] is used to identify similar library sequences for sequence analysis.

B. Receptor Localisation

The position of the Ephrin B2 receptor in the host cell was analyzed by the exploitation of the tool-CELLO [7] (http://cello.life.nctu.edu.tw/). This tool enables in predicting the position of receptor in various parts of the cell. This tool is very vital in determining the route of administration of the drug moiety.

C. Receptor Analysis

The structure of the receptor, EphrinB2 was retrieved from the PDB database [8]. The Protein Data Bank (PDB) is a database for the three-dimensional structural data of large biological molecules, such as proteins and nucleic

acids. The SOPMA [9] tool has been used to predict the secondary structures of the receptor.

D. Ligand Selection

The examination of the Berberine phytochemical with the desired attributes was shortlisted from a range of molecules possessing drug likeliness property from the drug bank [10]. It was choosen based on the Lipinski's rule five of pharmacopeia standards respectively [11].

E. Molecular Docking

The identified molecule was analysed for its strength of binding by performing docking studies. Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand-protein docking is to predict the predominant binding modes of a ligand with a protein of known three-dimensional structure. SWISS dock automated docking tool was used for the molecular interaction study of the EphrinB2 receptor and the Berberine [12].

III. RESULTS

A. Sequence Analysis

The sequence analysis revealed that *Nipah* virus and *Hendra* virus possessed high sequence similarity. The aim of this result is to propose that, due to extensive genetic similarity between these two species, the treatment proposed for the *Nipah* virus infection can also be applicable for the infection caused by *Hendra* virus. The hypothesis aims to propose this as the genetic similarity may lead to common modes of pathogenesis leading to a common pathway of combating the infection. The sequence identity obtained from BLAST search between the *Hendra* virus and the *Nipah* virus has been 80.3% which manifests a close relationship between the eminent members of *Paramoxyviridae* family.

B. Receptor Localisation

The highest reliability factor of 2.544 for extracellular cytoplasmic positioning was obtained which reinforces the receptor to presumably be suitable for oral route of administration (Fig 1). This is proposed to support the high efficacy and decreased toxicity attribute of the phytochemical Berberine in the presence of assured binding of the ligand with the EprineB2 receptor respectively.

C. Receptor Analysis

The EprineB2 receptor structure (PDB ID: 2VSM) was retrieved from the PDB database (Fig 2). The secondary structure details of the receptor was understood from the secondary structure prediction tool, SOPMA. The receptor mainly comprises of extended strands 31.12%, alpha helix 7.19% and beta turns 7.37% respectively.

F. Ligand Selection

As a part of the receptor based drug discovery process, following the localization of the Ephrin B2 receptor, the ligand molecule capable of specifically binding to the regions of the receptor which was anticipated for resulting in the apoptosis of infected cell in order to prevent the proliferation of the pathogen possessing minimal toxicity was investigated. The examination of the ligand (Fig 3) with the desired attributes was shortlisted from a range of molecules possessing drug likeliness property from the Drug bank (Table 1). The primary reason for selecting a photochemical is because the plant based molecule can have increased efficacy and decreased toxicity. In addition to this, the residual stores of the phytochemical has to offer minimal menace to the affected individual.

D. Molecular Docking

Upon finalizing the ligand (Berberine) and the receptor (Ephrin B2), the subsequent step in combating the infection would be by predicting the binding energies between the receptor and the ligand. To speculate this, the docking studies were perfomed. The results of the docking studies revealed a binding energy of -5.65 kilo joules/mole which is hypothesized as s substantial energy level capable of offering therapeutic advantage (Fig 4). The docking studies were specifically conducted with the B and D chains of Ephrin B2 receptor which is known to play a crucial role in encouragement of the pathogenicity in the host. The receptor upon strong binding with the ligand would not allow the viral progeny to be released from the host cell thereby causing apoptosis of the virus infected cell. In this way the phytochemical aims in halting the cancerous production of the virus infected cell which stands as a vital reason for the expansion of the viral progeny.

IV. DISCUSSION

The present study is to understand that the deadly pathogen of the Paramyxoviridae family is a normal homo-flora in the flying mammals, the *Chiroptera* family respectively [13]. Nowadays, computer-aided drug design helps to reduce time and cost of drug discovery process [14]. Adding to this hypothesis, the effects of the Berberine moiety to the *Chiroptera* family needs much attention. Similar findings was reported by many researchers using the *in silico* methods such as the novel bioisosteres of favipiravir have promising potential to target NiV-G/ephrin interactions to disrupt viral entry and provide the foundation for structure-based antiviral drug design [15]. Choosing between further analysis and immediate cure for the drastically widespread disease, there is an increased pressure being felt over all the responsible and concerned citizens of the world to find a cure for it. Hence animal culture testing of the proposed ligand and receptor activity in combating the disease stands as a vital step in conceptualization of the effectiveness of the drug moiety.

V. CONCLUSION

Nipah virus is an emerging virus which is known to affect individuals and result in mental trauma due to social stigma apart the physical tortures and tremors one has to deal with. Empathetically, the possible solution is an appropriate cure for the disease to destroy the dynasty of the *Paramoxyviridae* family. This research proposes a possible cure obtained through *in-silico* studies. The

proposed treatment is the use of Berberine phytochemical to block the EphrinB2 receptor which is the receptor in assistance to the emergence of the viral progeny into the host (*Homo sapiens sp.*). In this way the infected cell would be evacuated from the biological system by apoptosis and the further entry of the *Nipah* virus progeny would be restricted.

REFERENCES

[1]. Vincent P. Hsu, Mohammed Jahangir Hossain, Umesh. Parashar, Mohammed Monsur Ali,Thomas. Ksiazek, Ivan Kuzmin, Michael Niezgoda,Charles Rupprecht, Joseph Bresee, and Robert F. Breiman, "Nipah Virus Encephalitis Reemergence, Bangladesh". 2004, 10(12): 2082–2087.

[2]. K.B. Chua, K.J. Goh, K. T. Wong, A. Kamarulzaman, P.S.K. Tan, T.G. Ksiazek, et al. "Fatal encephalitis due to Nipah virus among pig-farmers in Malaysia". Lancet, 1999. 9; 354(9186):1257-9.

[3]. Oscar A. Negrete, Ernest L. Levroney Hector C. "Aguilar EphrinB2 is the entry receptor for Nipah virus, an emergent deadly paramyxovirus" *Nature*, 2005, 436, 401–405.

[4]. J.F. Pan, C. Yu, D.Y. Zhu, H. Zhang, J.F. Zeng, S.H. Jiang, J.Y. Ren, "Identification of three sulfate-conjugated metabolites of berberine chloride in healthy volunteers' urine after oral administration". Acta Pharmacol Sin. 2002, 23(1):77-82.

[5]. E.W. Sayers, T. Barrett, D.A. Benson, S.H. Bryant, K. Canese, V. Chetvernin, D.M. Church, M. DiCuccio, R. Edgar, S. Federhen, M. Feolo, L.Y. Geer, W. Helmberg, Y. Kapustin, D. Landsman, D.J. Lipman, T.L. Madden, V. Maglott DR,Miller, I. Mizrachi I et.al., "Database resources of the National Center for Biotechnology Information". Nucleic Acids Res. 2009 ;37(Database issue):D5-15.

[6]. S.F. Altschul, W. Gish, W. Miller, E.W. Myers & D.J. Lipman. "Basic local alignment search tool." J. Mol. Biol. 1990, 215:403-410.

[7]. S. Wacharapluesadee, K. Boongird, S. Wanghongsa, N. Ratanasetyuth, P. Supavonwong, D. Saengsen, G.N. Gongal, T. Hemachudha. "A longitudinal study of the prevalence of Nipah virus in *Pteropus lylei* bats in Thailand: Evidence for seasonal preference in disease transmission". Vector Borne Zoonotic Dis. 2010; 10: 183–190.

[8]. H.M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T.N. Bhat, H. Weissig, I.N. Shindyalov, P.E. Bourne." The Protein Data Bank". *Nucleic Acids Research*, 2000, 28: 235-242.

[9]. Geourjon, Christophe and Gilbert Deléage. "SOPMA: significant improvements in protein secondary structure prediction by consensus prediction from multiple alignments." *Computer applications in the biosciences: 1995, CABIOS* 11 6: 681-4.

[10]. D.S. Wishart, C. Knox, A.C. Guo, S. Shrivastava, M. Hassanali, P. Stothard, Z. Chang, J. Woolsey. "DrugBank: a comprehensive resource for in silico drug discovery and exploration". Nucleic Acids Res. 2006, 1;34(Database issue):D668-72.

[11]. C.A. Lipinski, F. Lombardo, B.W. Dominy, P.J. Feeney. "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings". Adv. Drug Deliv. Rev. 2001, 46 (1–3): 3–26.

[12]. Grosdidier, V. Zoete, and O. Michielin, "SwissDock, a protein-small molecule docking web service based on EADock DSS," Nucleic Acids Research, 2011, vol. 39, no. suppl, pp. W270–W277.

[13]. E.W. Sayers, T. Barrett, D.A. Benson, S.H. Bryant, K. Canese, V. Chetvernin, D.M. Church, M. DiCuccio, R. Edgar et.al., "Database resources of the National Center for Biotechnology Information". Nucleic Acids Res. 2009;37 (Database issue):D5-15.

[14]. Neema Bisht and B. K. Singh, "Role of computer aided drug design in drug development and drug discovery", Int J Pharm Sci Res 2018; 9(4): 1405-15.

[15]. Ashish P Shah, Bhumika M Parmar, Mubasarin A Ghodawala, Avinashkumar Seth, "*In silico* drug discovery of novel small lead compounds targeting nipah virus attachment glycoprotein", J Integr Health Sci 2018;6:60-3.

PROPERTY	VALUE
Molecular weight	336.123
Hydrogen bond donor	0
Hydrogen bond acceptor	4
logp	-0.18

Table 1:- Predicted properties of Berberine moiety obeying the lipinski's rule of 5

ISSN No:-2456-2165

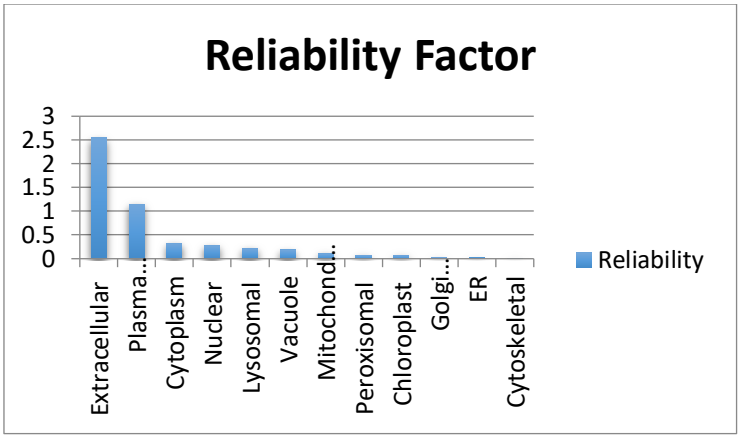

Fig 1:- The localized Ephrin B2 receptor using CELLO tool

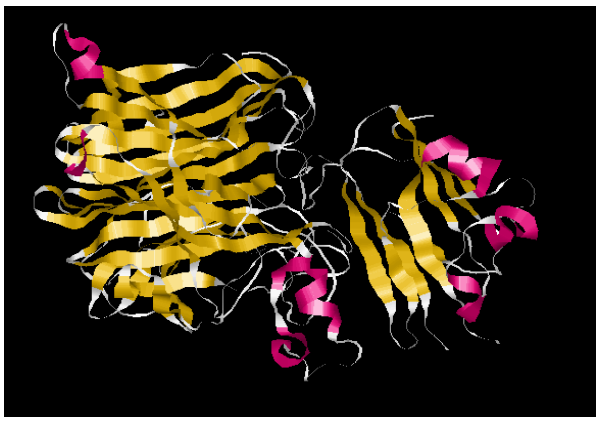
Fig 2:- 3D structure of the Ephrine B2 receptor procured from PDB

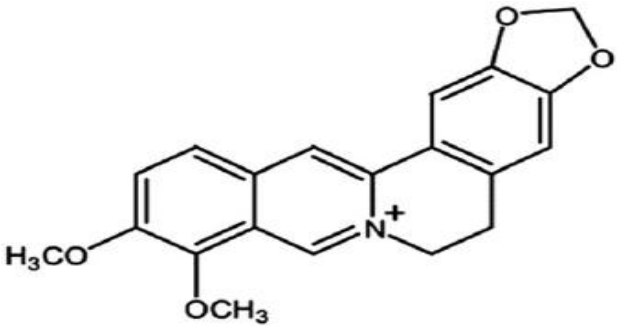

Fig 3:- Skeleton structure of Berberine derived from Berberis vulgaris – barberry

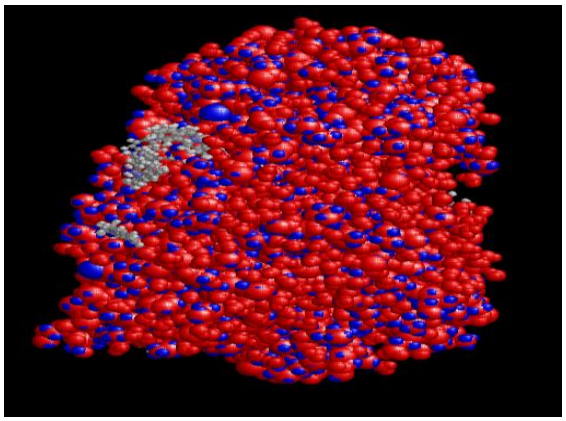
Fig 4:- Molecular docking results of the Ephrin B 2 and the ligand Berberine