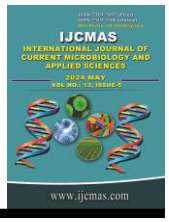
Int.J.Curr.Microbiol.App.Sci (2024) *13*(05): 51-63

International Journal of Current Microbiology and Applied Sciences
ISSN: 2319-7706 **Volume 13 Number 5 (2024)**
Journal homepage: http://www.ijcmas.com



Original Research Article https://doi.org/10.20546/ijcmas.2024.1305.008

Therapeutic Implications of Neurological Drugs For Prions Disease

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Keywords

Prion disease, Uniprot, Docking, Virtual screening, Potential ligands, medicinal chemistry

Article Info

Received:
20 March 2024
Accepted:
22 April 2024
Available Online:
10 May 2024

A B S T R A C T

Prion diseases is a neurodegenerative disorder that effects the brain and nervous system. This disease alters the normal functioning of nervous system and have same molecular mechanism and proteins involved both in humans and animals. Prion disease is caused by the deposition of abnormally folded proteins in the brain, that causes changes in memory, behavior, and movement. Prion diseases causes a progressive decline in the brain function due to misfolding of proteins called prion proteins (PrP). Misfolded PrP begins to accumulate and form clumps within the brain, damaging and killing nerve cells. Current research was done to screen and study the neurological drugs against prion disease. To predict potential drug that can be used for drug development and discovery. In this research two prion proteins i.e., PrPLP /Prion Protein 2(PDB ID: 1I4M) and ERI1 Exoribonuclease 3protein (PDB ID: 2XRI) were selected as drug target. These proteins were docked against 20 ligands screened from PubChem database. These 20 ligands were selected based on reference research papers, extensive literature search and these ligands have function in neurological diseases and act as drug. Twenty selected ligands were docked against target protein using CB dock server. Docking result shows that Prion protein 2 shows best interaction with Celastrol with a Vina Score of -8.2 and in ERI1 Exoribonuclease 3 shows best interaction with Celastrol and Amisulpride with a Vina score of -9.7 and -8.8 respectively. This study gives insight into the potential ligand for prion disease and can be used for drug designing process.

Introduction

Prion's disease is a fatal, rare group of neurodegenerative disorders caused by abnormal folding of prion protein (PrP). It consists of several conditions (Sigurdson *et al*., 2019). It is a neurological disease cased due to misfunctioning of prion protein. A prion protein may trigger normal proteins to fold abnormally in brain. It can spread in both humans and animals and sometimes may transmit from infected meat products to humans (Houston *et al*., 2019). Creutzfeldt – Jacob disease is the most common type of prions disease (Minikel *et al*., 2020).

Prion disease occurs when the normal prion protein which is found on normal cells behaves abnormally and forms clump in the brain resulting in brain damage (Baiardi *et al*., 2019). Memory impairment, personality changes and difficulties with movement are seen due to abnormal accumulation of protein in the brain. Risk

factors include genetic transmission, older age, intake of infected meat or by contaminated equipment's. Symptoms include rapid development of dementia, hallucinations, difficulty in walking, muscle stiffness, fatigue, ataxia, insomnia, not having control over one's body (Rhoads *et al*., 2020).

The prion protein can be present in two distinct structural states. The "cellular" prion protein (PrPc) is a predominant alpha-helical neuronal glycoprotein which is tethered to outer surface of plasma membrane (Ayers *et al*., 2020). In prion disease condition the PrPc undergoes conformational conversion into beta sheet rich termed as "PrP scrapie" (PrPsc) (Liberski *et al*., 2019).

PrPsc can be differentiated biochemically from PrPc by its partial resistance to degradation by deposited aggregates and spread within the brain leading to prions disease (Kushwaha *et al*., 2021). PrPsc is autocatalytic means it can catalyze its own formation by acting as template for conversion of PrPc into PrPsc. The self-propagating nature underlies the ability of disease to spread within brain and transmit between organisms (Porter *et al*., 2022).

Prion diseases comprises multiple conditions, prion is a sort of protein which triggers normal proteins to fold abnormally within the brain (Krance *et al.,* 2020). It may occur in both animals and humans and are spread at times to humans by tainted meat products. The chief kind of prion illness that influences people is Creutzfeldt Jakob sickness (CJD) (Carroll and Chesebro, 2019).

An individual can inherit this condition, during which case it's called familial CJD. Sporadic CJD, on the opposite hand, develops immediately with none known risk factors (Minikel *et al.,* 2019). Mostly cases of CJD are sporadic and tend to hit people around age sixty. Acquired CJD is caused by exposed infected tissue during a procedure, like a cornea transplant. Symptoms of CJD mentioned below cause severe disability and death (Vallabh *et al.,* 2020).

Human Prion Diseases Creutzfeldt-Jakob disease (CJD) it can be Sporadic, Inherited or Acquired. It was first described in 1920 and most identified cases of CJD are Sporadic (Connor *et al.,* 2019). Fatal Familial insomnia (FFI)- One of the major symptoms of this condition is the worsening insomnia (Amano *et al.,* 2021). It affects the thalamus region, which is the part of brain that manages waking and sleeping cycles. The mutation is inherited in a dominant manner, meaning an affected person has a 50 percent chance of transmitting it to their children (Lahiri *et al.,* 2020).

Risk factors for prion disease include Family history of prion disease, eating infected meat because of mad cow disease, by contaminated medical equipment (Singh, 2020). Indications of prion infections include a) Rapidly developing dementia, Difficulty in walking, Hallucinations, Muscle stiffness, Confusion, Fatigue, Difficulty speaking. Diagnosis Prion diseases are affirmed after death or by taking a sample of cerebrum during a biopsy (Jelsma *et al.,* 2020).

Prion's disease can be difficult to diagnose as it resembles symptoms to other neurodegenerative disorders. The only way to confirm the disorder is to undergo a brain biopsy after death, but healthcare professionals can predict it also by going through the symptoms, medical history, and some medical tests (Zheng *et al.,* 2018). Currently there is no cure instead the treatment focuses on providing ease of symptoms and supportive care (Abdelaziz *et al.,* 2019).

In current research virtual screening and docking studies has been done to identify potential ligands against target protein. Two function proteins that is PrPLP /Prion Protein 2 and ERI1 Exoribonuclease 3 were selected as target protein that have function in prion's disease. Neurological drugs were selected and docked against target protein to identify potential and effective ligand. Identified ligand can act as potential drug against prion's disease.

Materials and Methods

Protein related to prion disease was thoroughly studied using extensive literature survey and protein databases. Total five proteins PrPLP /Prion Protein 2, ERI1 Exoribonuclease 3, Shadoo/ SPRN and Alternative Prion Protein, PRND/ Prion like protein doppel, were identified that have function in prion diseases (Pritzkow *et al.,* 2018).

Functional and structural details of these five proteins was done using different databases like UniProt database, KEGG Pathway database, PDB database etc. Universal Protein Resource:https://www.uniprot.org/taxonomy/was used to select protein specific structure and that have function in prion disease and PDB Ids were selected. 3D structures of selected proteins were retrieved from the

PDB databasehttps://www.rcsb.org/#Category-searchand shown in Table 1. Drugs related to Neurological diseases were selected from chemical and drug database that is PubChemhttps://pubchem.ncbi.nlm.nih.gov/ database. It is an open chemistry database at the National Institute of Health (NIH).

Total Twenty ligands were retrieved from PubChem database these ligands have function in diseases related to neurological disorders. List of selected ligands along with their properties has been shown in table 2.

To study the binding efficiency of selected target proteins PrPLP /Prion Protein 2 and ERI1 Exoribonuclease 3with the identified ligands as mentioned in table 2, docking was performed. CB dock server http://clab.labshare.cn/cb-dock/php/blinddock.php that automatically predicts binding sites was used for docking (Liu *et al.,* 2020). It predicts the binding efficiency between target proteins and ligands without any pre information about binding sites.

CB Dock server is a user-friendly blind docking web server which predicts binding sites of a given protein and calculates binding site and docking score (Blaszczyk *et al.,* 2019). This server was used for the docking of the Potential ligands used in prions disease which were retrieved by PubChem database

Results and Discussion

Prion target proteins that are, PrPLP /Prion Protein 2 (PDB Id:1I4M) and ERI1 Exoribonuclease 3 (PDB Id: 2XRI) were studied using protein visualization software Pymol and protein structures were analyzed. PrPLP /Prion Protein 2 as shown in figure 1(a) shows that it includes mostly alpha helices and only one beta-sheets protein structures. Whereas, and ERI1 Exoribonuclease 3 protein as shown in figure 1(b) shows that it is complex protein that have alpha helices and beta- sheets secondary structures. These proteins were further used for docking with selected ligands and binding efficiency was predicted.

The Virtual Screening of twenty potential ligands against two target proteins- Prion Protein 2 &ER1 Exoribonuclease 3 was done using CB Dock server. These target proteins that have function in prions disease were used for screening of potential ligands and docking scores were analyzed and compared. Table 3 shows the comparison between Vina scores of two target proteins Prion Protein 2 (PDB ID: 1I4M) and ERI1 Exoribonuclease 3 (PDB ID: 2XRI) with all twenty ligands. Further detailed analysis of top five ligands was done these ligands were selected based on docking score that is Vina scores and comparison was done between both the target proteins.

Celastrol is a chemical compound which is separated from the root extracts of *Tripterygium wilfordii* and *Tripterygium regelii*. Celastrol is a pentacyclic nortriterpenoid quinone and belongs to the family of quinone methides." For the Prions Protein 2 the Vina score is -8.2 and for ERI1 Exoribonuclease 3 Vina score is -9.7. "Celastrol modulates intricate cellular pathways and networks associated with disease pathology, and it interrupts or redirects the aberrant cellular and molecular events to limit. Disease progression and facilitate recovery, where feasible (Xu *et al.,* 2021)."

Docking of Prion Protein 2 and ERI1 Exoribonuclease 3 with Ligand Loratidine ligand was shown in figure 3(a) and (b) respectively.

Loratadine, sold under brand name 'Claritin' among others, is a medication used for treating allergies. This includes allergic rhinitis (hay fever) and hives (Hunto *et al.,* 2020). For the Prions Protein 2 the Vina score is -7.8 and for ERI1 Exoribonuclease 3 Vina score is -7.4.

This medicine is an antihistamine which treats symptoms such as runny nose, itching, watery eyes, and sneezing from "hay fever" and other allergies. It is also used to relieve itching from hives.

Docking of both the target proteins with the Amisulpride ligand shows that Prions Protein 2 shows the binding efficiency with the Vina score of -7.4 (figure 4(a)) and for ERI1 Exoribonuclease 3 with the Vina score is -8.8 (figure 4(b)). Amisulpride is a dopamine receptor and benzamide derivative antagonist that selectively works on dopamine receptors. "As an antipsychotic agent, amisulpride alleviates both positive and negative symptoms of schizophrenia, and it exhibits antidepressant properties in patients with psychiatric disorders, dysthymia, and major depression (Li *et al.,* 2020)."

Amisulpride is a dopamine D2 receptor antagonist used for treating acute and chronic schizophrenia, and in the prevention and treatment of postoperative nausea and vomiting in adults."

Table.1 List of protein with PDB structure ID and UniProt ID that are retrieved from literatures. Two proteins PrPLP /Prion Protein 2 and ERI1 Exoribonuclease 3 were used for Docking study

S. No	Protein Name	PDBID	UNIPROT ID
1	**PrPLP /Prion Protein 2**	**1I4M**	**P04156**
2	**ERI1 Exoribonuclease 3**	**2XRI**	**O43414**
3	Shadoo/ SPRN	N.A.	Q5BIV9
4	Alternative Prion Protein	N.A.	F7VJQ1
5	PRND/ Prion like protein doppel	1LG4	Q9UKY0

Table.2 List of ligands along with their properties that were used for docking with target protein

S. No.	Ligand	PubChem Id	Mol wt.	Mol. Formula
1	Agomelatin	387179827	243.3g/mol	C15H17NO2
2	Amisulphide	2159	369.5g/mol	C17H27N3O4S
3	Ginkoglide B	65243	424.4g/mol	C20H24O10
4	Aniracetam	2196	219.24g/mol	C12H13NO3
5	Etodolac	3308	287.35g/mol	C17H21NO3
6	Cilomilast	151170	343.4g/mol	C20H25NO4
7	Nepafenac	151075	254.28g/mol	C15H14N2O2
8	Etomidate	667484	244.29g/mol	C14H16N2O2
9	Lidocaine	3676	234.34g/mol	C14H22N2O
10	Tamsulosine	129211	408.5g/mol	C20H28N2O5S
11	Aprepitant	135413536	534.4g/mol	C23H21F7N4O3
12	Rufinamide	129228	238.19g/mol	C10H8F2N4O
13	Celastrol	122724	450.6g/mol	C29H38O4
14	Felbamate	3331	238.24g/mol	C11H14N2O4
15	Loratidine	3957	382.9g/mol	C22H23ClN2O2
16	Mepacrine	237	400g/mol	C23H30ClN3O
17	Pentosan polysulfate	37720	602.5g/mol	C10H18O21S4
18	Guanidinium	32838	60.08g/mol	CH6N3+
19	Aminothiazole	2155	100.14g/mol	C3H4N2S
20	Dysideamine	44188455	343.5g/mol	C21H29NO3

Table.3 The Vina scores comparison of ligands for both proteins

S.No.	LIGAND	Prion Protein 2 (PDB ID: 1I4M)	ERI1 Exoribonuclease 3 (PDB ID: 2XRI)
1	Celastrol	-8.2	-9.7
2	Loratidine	-7.8	-7.4
3	Amisulpride	-7.4	-8.8
4	Aprepitant	-7.3	-7.9
5	Dysideamine	-7.3	-7.5
6	Tamsulosine	-6.9	-6.6
7	Cilomilast	-6.9	-7
8	Nepafenac	-6.7	-6.6
9	Agomelatin	-6.7	-6.5
10	Rufinamide	-6.6	-6.1
11	Mepacrine	-6.5	-6.1
12	Pentosan polysulfate	-6.4	-7.3
13	Etodolac	-6.3	-6.7
14	Ginkoglide B	-6.2	-6.4
15	Aniracetam	-6.1	-5.5
16	Felbamate	-5.9	-6.1
17	Etomidate	-5.7	-5.9
18	Lidocaine	-5.3	-5.2
19	Aminothiazole	-3.5	-3.4
20	Guanidinium	-2.9	-3.3

Figure.1 (a) structural analysis of PrPLP /Prion Protein 2 (PDB Id: I4MI) (b) Structural analysis of ERI1 Exoribonuclease 3 protein (PDB Id: 2xrii)

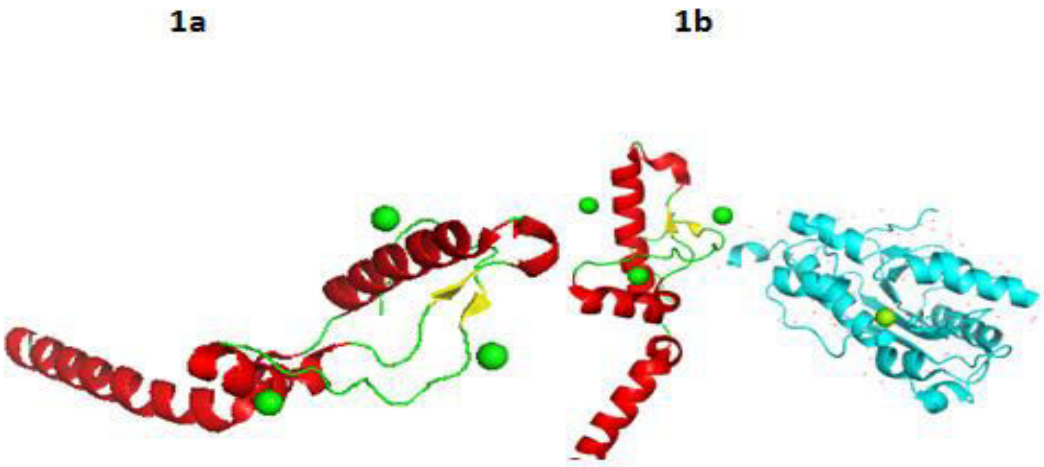
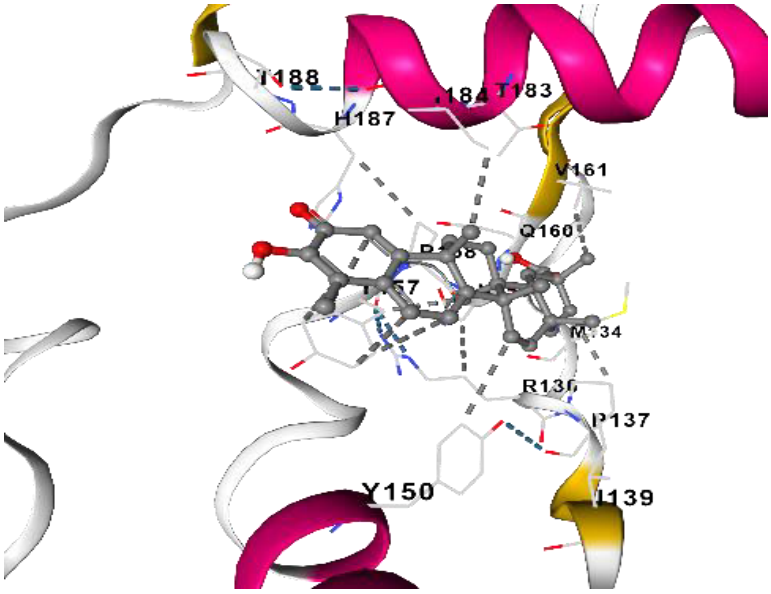


Figure.2 (a) and 2(b) shows the docking of Prion Protein 2 and ERI1 Exoribonuclease 3 with Ligand Celastrol ligand with the vina scores of -8.2 and -9.7 respectively.

2A



2B

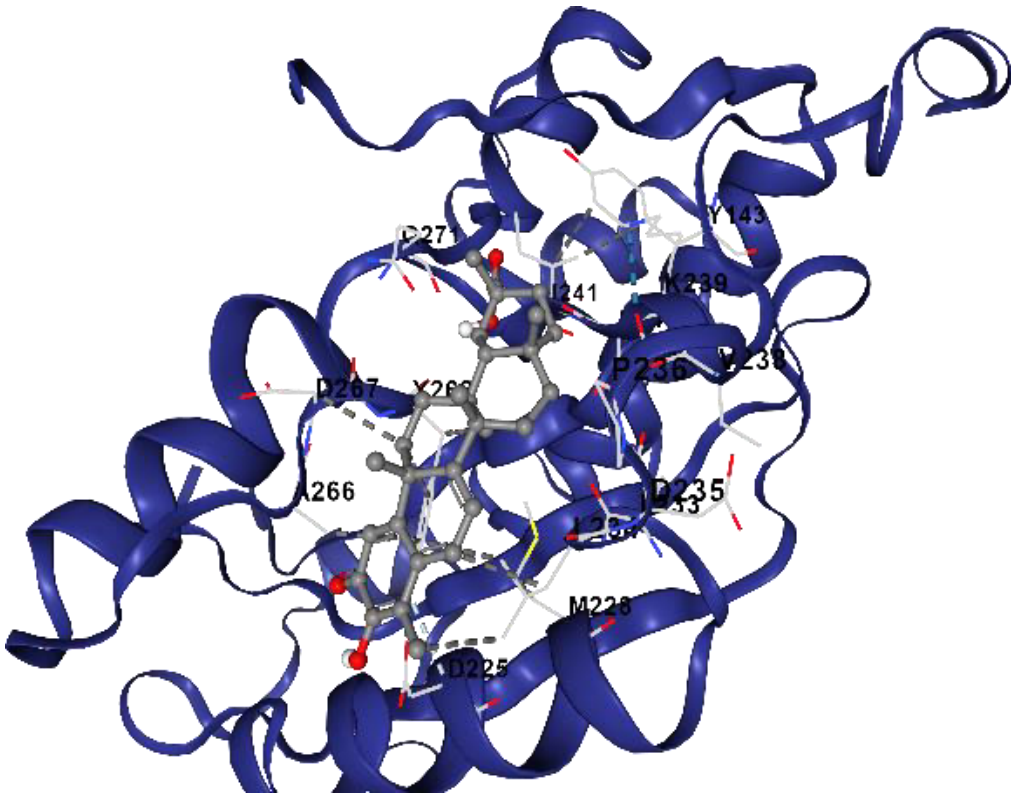
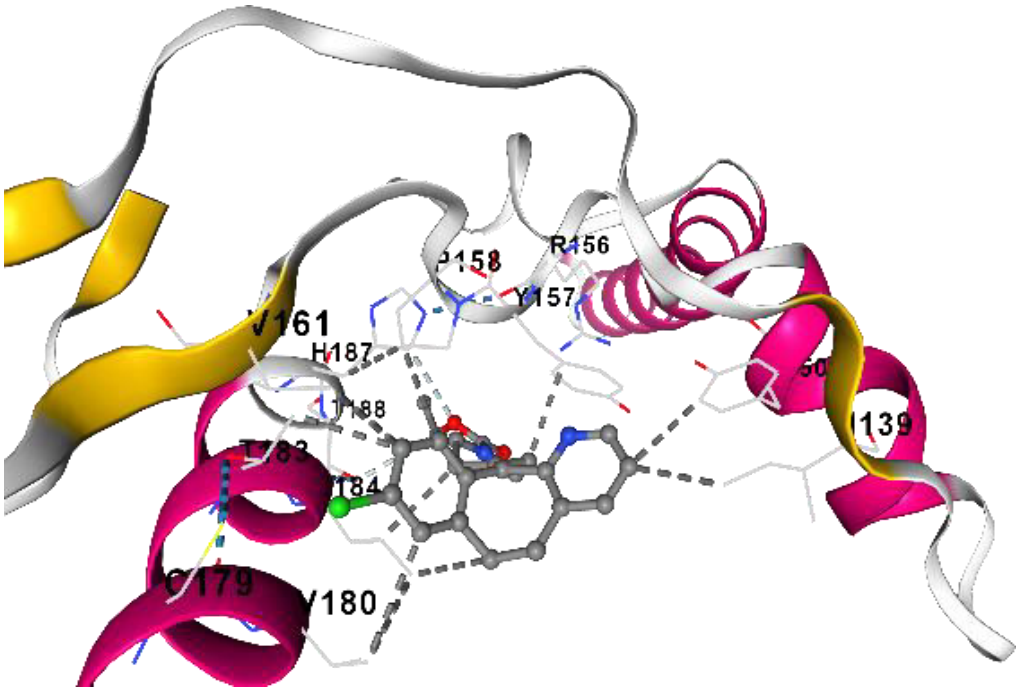


Figure.3 (a) The docked Prion Protein 2 and (b) ER1 Exoribonuclease 3 with the ligand orotidine

3A



3B

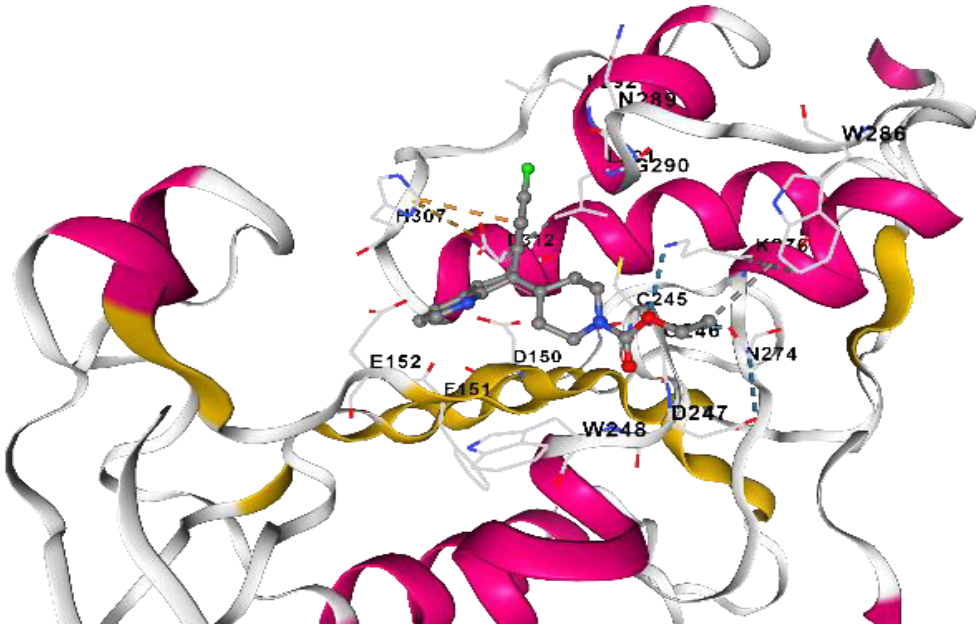
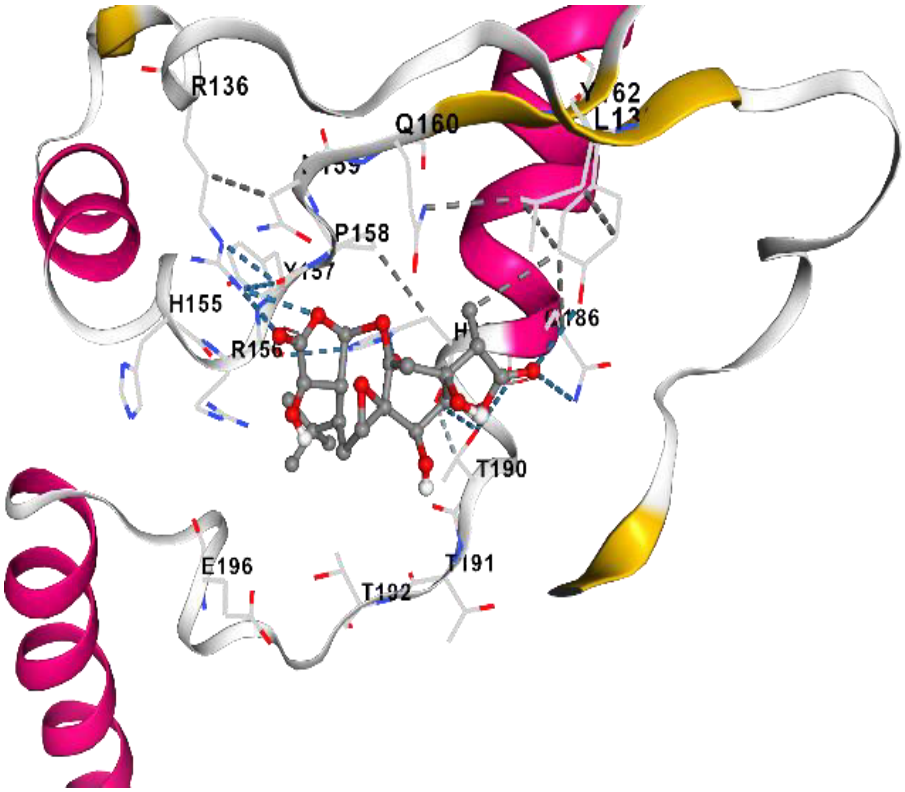


Figure.4 (a) The docked Prion Protein 2 and (b) ER1 Exoribonuclease 3 with the ligand Amisulpride

4A



4B

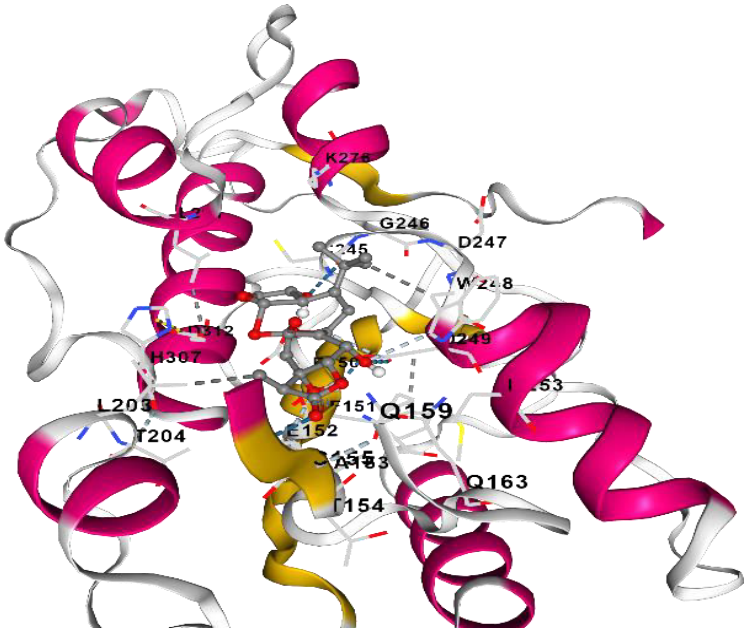
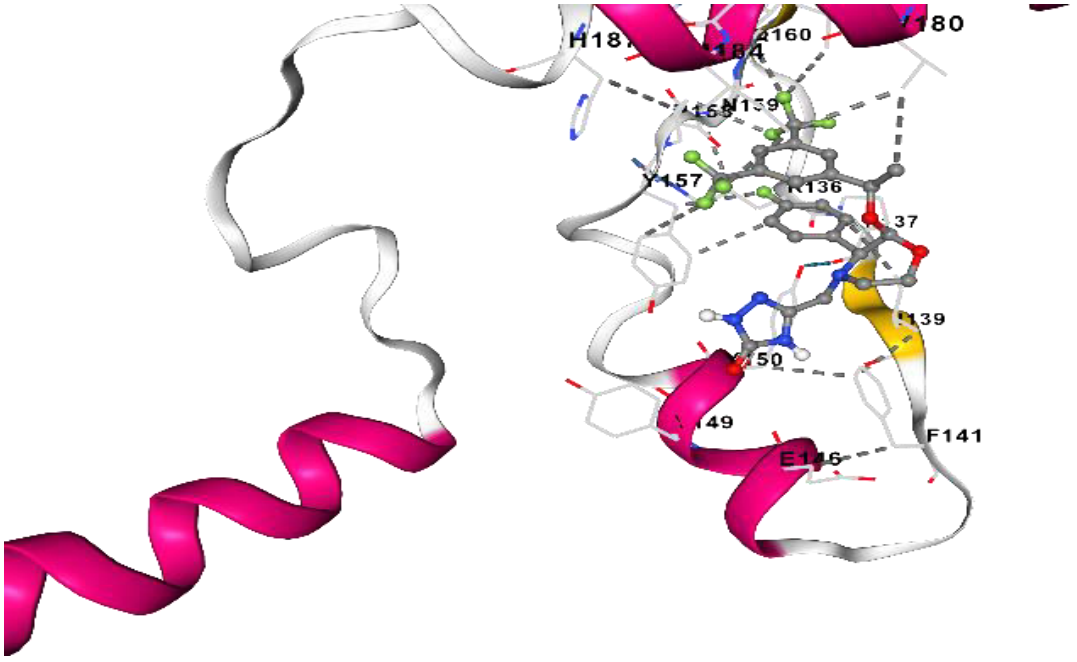


Figure.5 (a) The docked Prion Protein 2 and (b) ER1 Exoribonuclease 3 by the ligand Apreputant

5A



5B

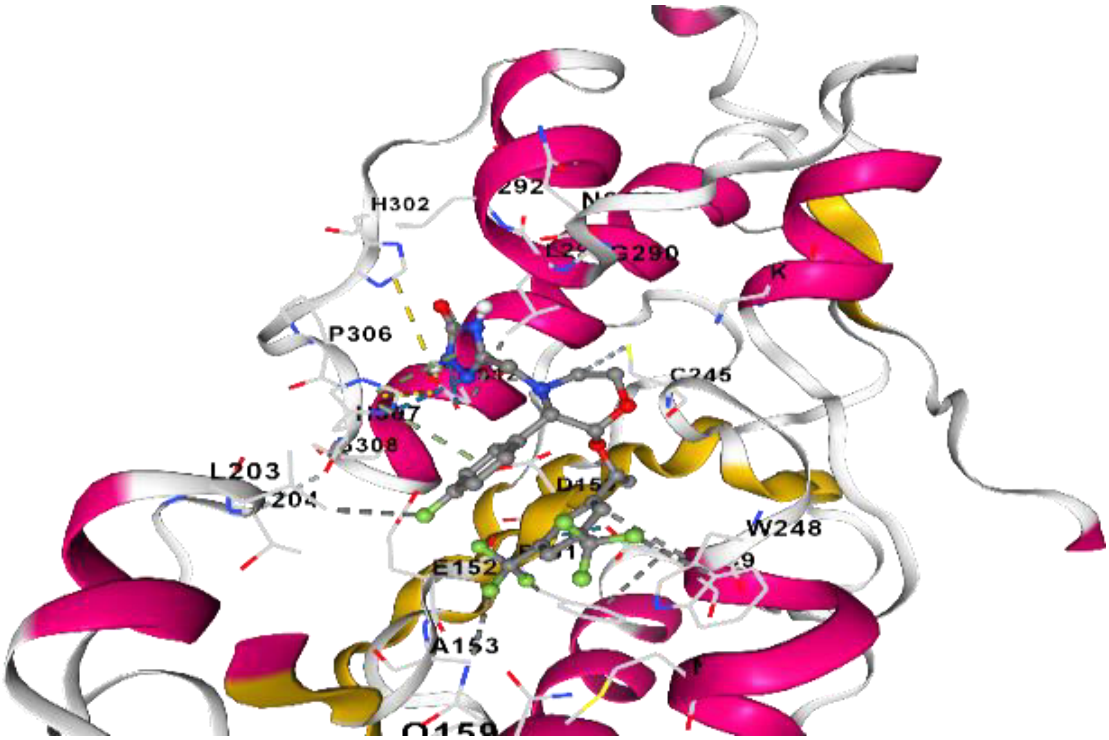
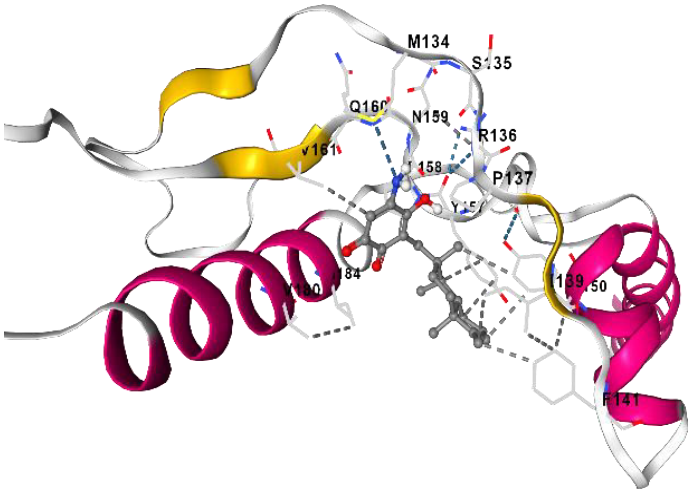
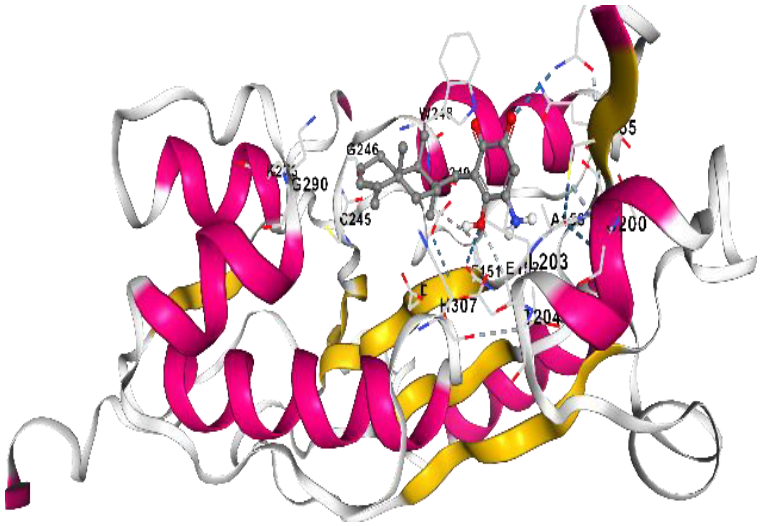


Figure.6 (a) The docked Prion Protein 2 and (b) ER1 Exoribonuclease 3 by the ligand Dysideamine

6A



6B



Docking of Prion Protein 2 and ERI1 Exoribonuclease 3 with the Aprepitant ligand shows that Prions Protein 2 have the Vina score of -7.3 and for ERI1 Exoribonuclease3 Vina score is -7.9. Aprepitant is used with other medications helping to prevent nausea and vomiting caused by cancer drug treatment (chemotherapy). Aprepitant works by blocking one of the body's natural substances (substance neurokinin) that causes vomiting. This medication will not treat nausea or vomiting that has already started (Un *et al.,* 2020).

Aprepitant is a morpholine-based antiemetic, which is or to prevent delayed and acute vomiting and nausea associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

Finally, Dysideamine ligand was analyzed that shows Prions Protein 2 have Vina score of -7.3 (figure 6 (a)) and for ERI1 Exoribonuclease 3 is having Vina score of -7.5 (figure 6 (b)). “Dysideamine (1) inhibited production of reactive oxygen species (ROS) by IAA treatment, whereas it exhibits no effect on depletion of intracellular ATP of the IAA-treated HT22 cells (Nazar *et al.,* 2022).

After docking of all the twenty ligands with the two Proteins: Prion Protein 2 and ERI1Exoribonuclease 3 the

docking scores have been compiled in Table 3. From this table we can interpret that Prion protein 2 shows best interaction with Celastrol with a Vina Score of -8.2 and in ERI1 Exoribonuclease 3 shows best interaction with Celastrol and Amisulpride with a Vina score of -9.7 and -8.8 respectively.

The protein that prions are made of (PrP) is found throughout the body, even in healthy individual and animals. However, PrP found in infectious material has a different structure and is resistant to proteases, the enzymes in the body that can normally break down proteins.

The normal form of the protein is called PrPC, while the infectious form is called PrPSc – the C refers to 'cellular' PrP, while the Sc refers 'scrapie', the prototypic prion disease, occurring in sheep.

The infectious isoform of PrP, known as PrPSc, or simply the prion, can convert normal PrPC proteins into the infectious isoform by changing their conformation, or shape; this, in turn, alters the way the proteins interconnect. The Prion protein is seen participating in biological processes such as neurogenesis, neuronal homeostasis, cell adhesion, cell signaling and protective role against stress.

After the docking of twenty ligands for both the proteins the top five ligands were showing good interaction with the proteins whereas Prion Protein 2 shows the best Interaction with Celastrol with Vina score of -8.2 and ERI1 Exoribonuclease shows best interaction with Celastrol and Amisulpride with a Vina score of -9.7 and -8.8 respectively. The data by this study can be used further in the Drug designing process.

Acknowledgement

We would like to acknowledge Amity Institute of biotechnology, Amity University Uttar Pradesh, Lucknow campus for providing us facilities to conducting this study. This research project is not funded by any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Author Contribution

Adhya Sharma: Investigation, formal analysis, writing—original draft. Ruchi Yadav: Validation, methodology, writing—reviewing.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent to Publish Not applicable.

Conflict of Interest The authors declare no competing interests.

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How to cite this article:

Adhya Sharma and Ruchi Yadav. 2024. Therapeutic Implications of Neurological Drugs For Prions Disease. *Int.J.Curr.Microbiol.App.Sci.* 13(5): 51-63. **doi:** https://doi.org/10.20546/ijcmas.2024.1305.008