Journal of Chemical and Pharmaceutical SciencesISSN: 0974-2115

Molecular Docking studies of Resveratrol against Neurodegenerative Diseases

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ABSTRACT

Neurodegenerative diseases refer to the impairments in human body which arise due to progressive degeneration of nerve cells. In such cases, neurons undergo the structural as well as the functional damage. Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis and systemic lupus erythematosus are major neurodegenerative diseases. The most common reason of neurodegenerative disease is the excess generation of free radicals inside the body which results into a condition called oxidative stress. Neurons are more susceptible to the damage caused by oxidative stress as compared to the other tissues of the body. In this paper we have done molecular docking of Resveratrol against proteins involved in neurodegenerative diseases six proteins were selected from different neurodegenerative diseases and docking is performed using Schrödinger software. Docking of Resveratrol with protein targets shows good binding affinity of Resveratrol against neuronal diseases. Docking results signifies potential role of Resveratrol against neurodegenerative diseases.

KEY WORDS: Neurodegenerative Disease, Resveratrol, Molecular Docking, Alzheimer's disease, Parkinson's disease

1. INTRODUCTION

Neurodegenerative diseases refer to such ailments where there is either structural or functional loss of neurons sometimes both of these conditions could be met the loss in neurons are progressive. In severe cases, neurons start dying. Such conditions arise when there is some abnormality associated with the components which have got a significant role in uninterrupted and smooth running of the nervous system. Apparently, these diseases are incurable. Major concern is Parkinson's disease, Alzheimer's disease, Amyotrophic lateral sclerosis, Systemic lupus erythematosus, and Multiple sclerosis that are caused by abnormality in protein folding or mutation.

Neurodegenerative diseases represent the severe damage to neurons. Abnormal aggregation of several proteins has been found in such disorders. The most common reason of this damage is the excess generation of free radicals inside the body which results into a condition called oxidative stress. Neurons are more susceptible to the damage caused by oxidative stress as compared to the other tissues of the body. Resveratrol is one such antioxidant which has got a great potential to be used in the therapies against the neurodegenerative diseases. The interaction studies of Resveratrol with the proteins involved neurodegenerative diseases can be predicted through docking studies which would further help us to find the best drug target for Resveratrol.

Proteins targets in neorodegenerative diseases:

Dopamine Receptor D3*:* Dopamine Receptor D3 **(**DRD3) is basically a G- protein coupled receptor which is found in limbic areas of the brain. D3 is the subtype of dopamine receptors family. DRD3 plays a major role in maintaining memory of an individual and it is responsible for emotional behaviors and endocrine functions too. It is a drug target in neurodegenerative diseases like Parkinson's disease, schizophrenia.

Rho-Associated Protein Kinase: Rho-associated protein kinase (ROCK) has a major role in axonal transport and regeneration of axons. It regulates cellular migration by promoting the cell contraction by phosphorylating myosin light chain and preventing the depolymerization of actin filaments. It has been observed that ROCK signaling pathways play a pivotal role in many neurodegenerative diseases. Rho Associated Protein Kinase is associated with amyotrophic lateral sclerosis (Tonges, 2012).

Microtubule associated protein: Microtubule associated protein which has got a significant role in stabilization of microtubules. It is found mainly in axons of central nervous system. If we talk about the amino acid composition of tau, it is hydrophilic and that's why the biophysical structure prediction methods like NMR and small angle X-ray have revealed that tau has got an unfolded native structure or an intrinsically disordered structure. Any mutation in tau causes front temporal dementia which proves that tau has got a major role in degeneration of neurons. In case of Alzheimer's, there is an abnormal aggregation of hyper phosphorylated tau. Tau has got potential cleavage sites which are easily accessible to proteases. Such proteolytic cleavages pose a threat to neurons as they have got toxic effects on neurons.

B-Cell Activating Factor Receptor: B-cell activating factor receptor (BAFF-R) belongs to tumor necrosis factor receptor superfamily. BAFF is basically a cytokine. It promotes the differentiation and survival of B- cells. It also enhances the production of antibodies. It has been found over expressed in the persons with systemic lupus erythematosus and multiple sclerosis.

B-Cell Maturation Antigen: B-cell maturation antigen (BCMA) promotes the maturation of lymphocytes. It belongs to tumor necrosis factor receptor superfamily. It also enhances the production of immunoglobulins. It has got an important role in autoimmune response and involved in Amyotrophic lateral sclerosis.

Transmembrane Activator and Calcium Modulator Cytophilin Ligand Interactor: Transmembrane activator and calcium modulator cytophilin ligand interactor (TACI) stimulates the survival of plasma cells and production of IgM. TACI has been found up regulated in the monocyte and brain of the patients having multiple sclerosis. In such patients, TACI is produced by the astrocytes present in the brain.

Oxidative stress in neurodegenerative diseases: Whenever there is an alteration in mitochondrial functionality, which is termed as mitochondrial dysfunction, it leads to certain specific neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, Amyotrophic lateral sclerosis, and Systemic lupus erythematosus. It is well known that mitochondria have got a significant role in the proper management of oxygen inside our body through the process of oxidative phosphorylation thus helping in preventing the body from the ill effects of oxidative stress. Whenever there is some sort of abnormality in the working of mitochondria, due to mutations in their DNA, the process of oxidative phosphorylation is affected which might lead to a condition where neurons are unable to perform their normal functions. Neurons become very sensitive to oxidative stress in such cases as neurons have got lesser antioxidant activity as compared to other body cells and hence they are more prone to oxidative damage as compared to other tissues of the body.

Reactive oxygen species affect the regulation of intracellular Ca^{2+} signaling pathways. These reactive oxygen species abnormally induce intracellular Ca^{2+} influx which has toxic effects and as a result, glutamate receptors are activated and neurons undergo apoptosis in diseases like Huntington's disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis. There are two reasons associated to death of neurons in such cases:

a) Abnormal regulation of microtubules assembly.
b) Dysregulation of transport of axons.

Both of these abnormalities arise due to reactive oxygen species induced intracellular Ca^{2+} influx.

Resveratrol potential antioxidant against neurodegenerative diseases: Resveratrol is a polyphenolic compound which has been derived from plants. Resveratrol activates sirtuin1 (an enzyme which deacetylates the proteins which contribute to the regulation of cells) which further binds to PGC-1 alpha (a transcriptional coactivator which takes care of biogenesis and functioning of mitochondria) and activates it by the process of deactivation. It has been observed that the cells treated with Resveratrol show an enhanced action of Mn superoxide dismutase (MnSOD). MnSOD reduces superoxide and hence lowers the risk of mitochondrial dysfunction. Resveratrol has been found to be effective against neuronal dysfunction and neuronal death and hence, there are optimal chances that Resveratrol can have a significant role in treatment of neurodegenerative diseases like Parkinson's, Alzheimer's, and Huntington's.

In the case of Alzheimer's, it has been observed that Resveratrol inhibits the formation of amyloid beta fibrils and also destabilizes fibrilized amyloid beta. Resveratrol interacts with the lipid bilayer of the cell membrane of neurons and prevents the process of lipid peroxidation. It also interacts with Hb and prevents it from oxidative damage. Upregulation of p53 tumor suppressor gene leads to accumulation of hyper phosphorylated tau protein which ultimately leads to neuronal damage and death of neurons in case of Alzheimer's. Sirtuin1 which is being activated by Resveratrol activates heat shock factors which further activate heat shock protein 70 which regulates the homeostasis of cellular proteins as a result of which there is a decrease in aggregation of alpha- synuclein protein in case of Parkinson's.

After having an overview of mode of functioning of Resveratrol, it can be concluded that it might prove itself as a potential antioxidant drug for the treatment of the neurodegenerative diseases by targeting the proteins associated with the neurodegenerative diseases.

Ligand-protein docking: Docking enables us to study the best possible interaction between two molecules (a ligand and a protein). It makes the use of scoring functions to predict the binding affinity between the two molecules. The scores basically include glide score, docking score, binding energy, potential energy, ionization energy. These scores help us to predict the strength of the non-covalent interactions which exist between the two molecules. With the help of docking, we can easily detect the type and the strength of signals which are produced as a result of interaction existing between the two molecules. Docking also helps us to study the orientation in which the two molecules are bound to each other which means the binding conformation can easily be analyzed through docking.

2. MATERIALS AND METHODS

Proteins involved in different neurodegenerative diseases were retrieved from Uni Prot database and protein structure from PDB database. Six neurodegenerative disease were selected (Parkinson's Disease DRD3 protein, Alzheimer's Disease TAU protein, Amyotrophic Lateral Sclerosis ROCK protein, Systemic Lupus

Erythematosus BAFF-R , Multiple Sclerosis BCMA and TACI protein) Table.1, describes the list of proteins and PDB id that are involved in neurodegenerative diseases.

Resveratrol structure and chemical file is retrieved from Pub Chem database (Pub Chem CID: 445154, Chemical names: 3, 5, 4'-Trihydroxystilbene). Docking is done through Schrödinger software, Glide program.

Table.1. List of proteins associated with different neurodegenerative diseases

Neurodegenerative disease	Protein	PDB ID
Parkinson's Disease	DRD3	3PBL
Alzheimer's Disease	TAU	2MZ7
Amyotrophic Lateral Sclerosis	ROCK	4YVC
Systemic Lupus Erythematosus	BAFF-R	1OSG
Multiple Sclerosis	BCMA	1XU2
Multiple Sclerosis	TACI	1XU1

Schrodinger software suite (Schrodinger Software Release 2015-4, www.schrodinger.com): Schrodinger software basically focuses on the use of computational chemistry. It provides services to the researches being carried out in the field of life sciences. Some of these services are drug designing including ligand and structure based methods, modeling of biomolecules (such as homology modeling of proteins). It is widely used for docking purposes which helps us to study the interaction between two molecules (a protein and a drug or a ligand). The docking has been performed through Maestro which is a molecular modeling interface of Schrodinger.

3. RESULTS

Resveratrol (RV): Resveratrol is a polyphenolic compound which has been derived from plants. Resveratrol activates sirtuin1 (an enzyme which deacetylates the proteins which contribute to the regulation of cells) which further binds to PGC-1 alpha (a transcriptional coactivator which takes care of biogenesis and functioning of mitochondria) and activates it by the process of deacetylation.

In the case of Alzheimer's, it has been observed that Resveratrol inhibits the formation of amyloid beta fibrils and also destabilizes fibrilized amyloid beta. Resveratrol interacts with the lipid bilayer of the cell membrane of neurons and prevents the process of lipid peroxidation. It also interacts with Hb and prevents it from oxidative damage. Fig.1, describes Structure of Resveratrol.

PubChem CID : 445154
Chemical names : 3,5,4'- Trihydroxystilbene
Molecular formula : $C_{14}H_{12}O_3$
Molecular weight : 228.24328 g/mol

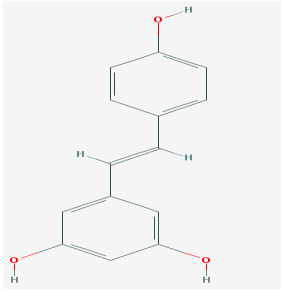

Figure.1. Structure of Resveratrol

Docking of DRD3 with Resveratrol: Docking of DRD3 with Resveratrol Fig.2 shows hydrogen bonds formed between Resveratrol and amino acid residues of the protein DRD3. The yellow dashed line represents a hydrogen bond of Resveratrol with the amino acid residues aspartic acid110 and valine189.

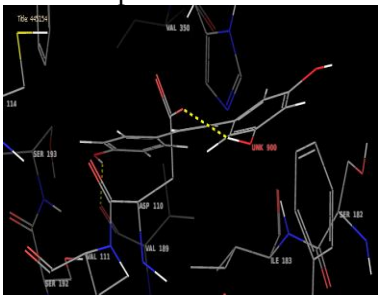

Fig. 1 Hydrogen Bond between RV and DRD3

Fig.2 describe the overall interaction of Resveratrol with DRD3. Resveratrol forms a hydrogen bond with Asp110 and this hydrogen bond is formed with one of the residues of side chain and pi-pi stacking with Phe 345 and Phe 346.

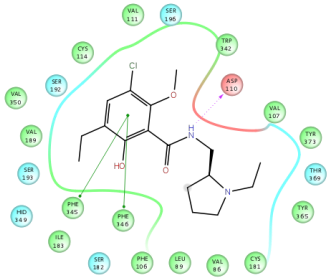

Fig.3. Interaction Map of RV with DRD3

Docking of tau with resveratrol: Fig. 4 show the interaction of Resveratrol with ASN286 and ASP295 residues of Tau by forming hydrogen bonds with them. Resveratrol forms both, side chain and backbone hydrogen bonds with ASP295.

This figure represents the hydrogen bond interaction between Resveratrol and tau. With ASN, RV forms a single hydrogen bond which is present in the backbone but it forms two hydrogen bonds with ASP295, one is backbone hydrogen bond and another is side chain hydrogen bond. The figure also depicts the pi-pi interaction between Resveratrol and LYS290 residue.

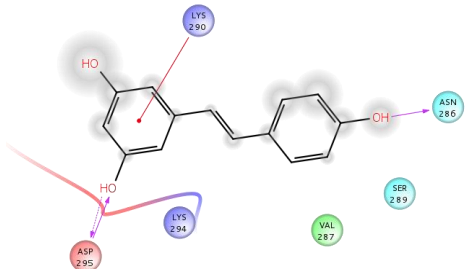

Fig.4. Interaction Map of RV with Tau

Docking of rock with resveratrol: Resveratrol forms side chain hydrogen bonds with ASP216 and ASP160 residues. With MET153 and MET156, it forms backbone hydrogen bonds.

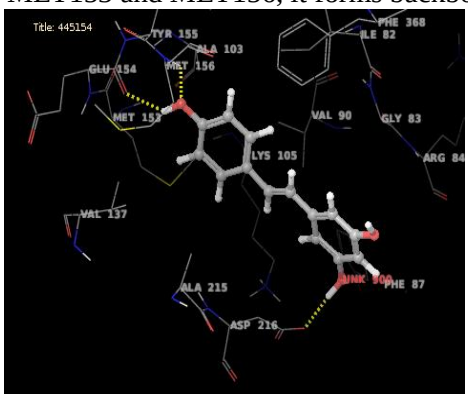

Fig.5. Docking of RV with ROCK

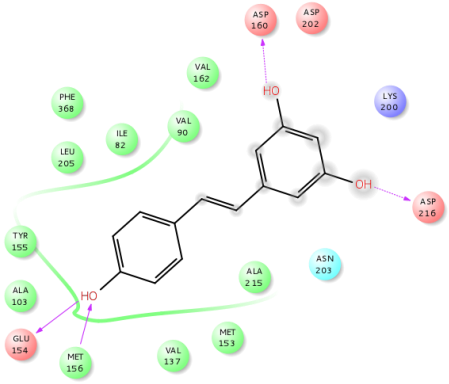

Fig.6. Interaction Map of RV with ROCK

Docking of BAFF-R with resveratrol: Fig.7 describes the docking of RV with BAFF-R protein. RV forms a side chain hydrogen bond with GLU254 residue of ROCK. It also interacts with two ARG residues by pi-pi stacking.

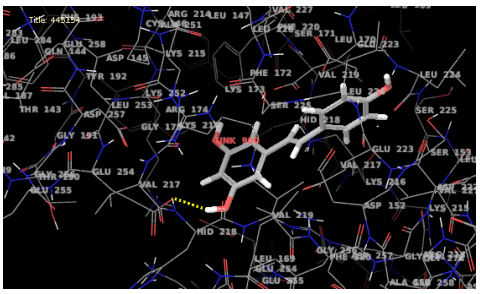

Fig.7. Docking of RV with BAFF-R

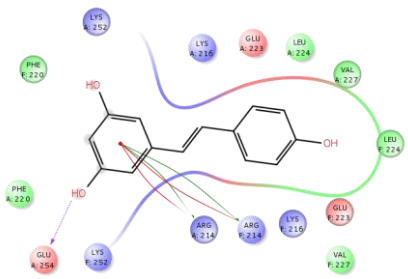

Fig.8. Interaction Map of RV with BAFF-R

Docking of BCMA with resveratrol: Fig 8 describes interaction plot of RV with BCMA .Resveratrol forms hydrogen bonds with two amino acid residues of BCMA and these two are the parts of the backbone structure of BCMA. These two residues are: serine190 and methionine191.

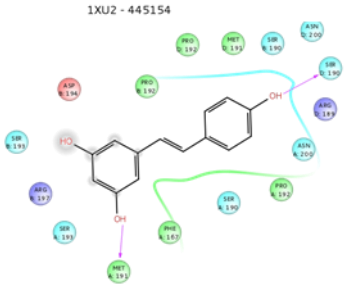

Fig.9. Interaction Map of RV with BCMA

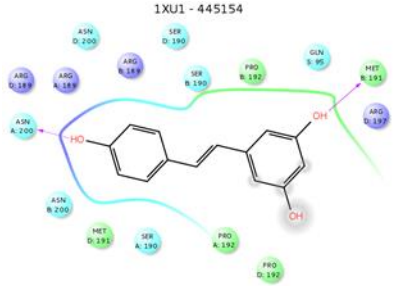

Fig.10. Interaction Map of RV with TACI

Resveratrol interacts with the protein TACI by forming two hydrogen bonds with the amino acid residues of TACI. One hydrogen bond is formed between Resveratrol and MET191 residue, which is present in the backbone of TACI. Another hydrogen bond is formed between Resveratrol and ASN200 residue, which is a part of the side chain of TACI.

Docking scores analysis: Glide score, glide Emodel and Hydrogen bond interactions are the three parameters which play a pivotal role in the prediction of the best interaction between the protein and the ligand. A lower value of glide score indicates that the ligand has got an enhanced binding affinity for the protein. The lowest value of the glide Emodel implies that the ligand has got the best binding affinity for the protein and also signifies that the ligand is buried in the cavity of the protein. The binding affinity of the ligand is higher if the number of Hydrogen bond interactions is more.

4. CONCLUSION AND DISCUSSION

TABLE II describes the docking energies of different proteins. Resveratrol has got the highest binding affinity for the protein ROCK involved in progression of Amyotrophic Lateral Sclerosis as ROCK has the lowest values of glide score -7.404 and glide Emodel -56.064 amongst all the six proteins. Resveratrol has comparatively got more number of Hydrogen bond interactions (three in number, which is the highest among all proteins) with ROCK protein.

Table.2. Docking Analysis of Resveratrol with target proteins

Protein	Docked ligand	Glide score	Docking score	Glide Emodel
DRD3	Resveratrol	-6.765	-6.765	-53.172
Tau	Resveratrol	-3.531	-3.531	-22.222
ROCK	Resveratrol	-7.404	-7.404	-56.064
BAFF-R	Resveratrol	-4.000	-4.000	-29.227
BCMA	Resveratrol	-5.580	-5.580	-41.368
TACI	Resveratrol	-5.987	-5.987	-42.810

This study signifies that Resveratrol can be considered as a potential drug against amyotrophic lateral sclerosis. Resveratrol also shows good binding affinity with DRD3,BCMA and TACI protein having docking energies of -6.765,-5.580,-5.987 respectively. With this study we conclude that Resveratrol can be potent drug against other neurodegenerative diseases like Multiple Sclerosis, Parkinson's disease and Alzheimer's disease

5. ACKNOWLEDGMENT

I acknowledge to all those who are directly or indirectly helped me in this work. Further I wish to acknowledge Bioinformatics analysis tools and data bases for conducting this study.

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