

Phytochemical, Admet and Docking Studies on *Valeriana Officinalis* for Predicting Antiepileptic Drug Molecules



Bioinformatics

KEYWORDS : Laforin, EPM2A, Valeriana officinalis, docking

R. Caroline Nirmala

Department of Bioinformatics, CMS College of Science and Commerce, Coimbatore, India

V. K. Gopalakrishnan

Department of Biochemistry and Bioinformatics, Karpagam University, Coimbatore, India.

ABSTRACT

Epilepsy is a second common neurological disorders characterized by repeated seizures. This is a genetic disorder caused by mutation in Laforin, encoded by the EPM2A gene. Laforin is a protein mutated in patients with Lafora disease. EPM2A codes for the protein laforin, a dual-specificity phosphatase with a carbohydrate binding domain (CBM-20). In order to inhibit the dual specificity action of laforin protein we perform docking analysis by using phytochemicals from the medicinal plant Valeriana officinalis. For this the phytochemicals of the plant valeriana has been retrieved from plant databases and its ADMET properties have been studied. The phytochemical compounds satisfying ADMET properties were selected for docking analysis. To carry out docking analysis the target Laforin has been retrieved from Protein modeling database. The active site has been predicted for this model and analysed. Molecular docking studies have been performed for this model. The phytochemical compounds with good docking score and binding affinity was investigated from this study.

INTRODUCTION

Epilepsy is a chronic disorder characterized by recurrent seizures or convulsions. Lafora disease is a brain disorder in which a person has repeated seizures or convulsions over time. This disease is an autosomal recessive type of Progressive myoclonus epilepsy caused by mutations in the EPM2A gene [1].

The EPM2A gene provides instructions for making a protein called Laforin. This protein is active in cells throughout the body, and it plays an important role in the survival of nerve cells in the brain. To carry out these functions, Laforin interacts with several other proteins, including malin. These proteins are part of complex networks that transmit chemical signals and break down the abnormal proteins. [2]

Laforin play a critical role in regulating the production of a glycogen which is a major source of stored energy in the body. The body stores this sugar in the liver and muscles, breaking it down when it is needed for the metabolism. About 50 mutations in the EPM2A gene have been identified in people with Lafora progressive myoclonus epilepsy. These mutations change amino acids in the Laforin protein. Other mutations delete or insert genetic material in the EPM2A gene. [3] Almost all mutations in this gene prevent cells from producing any Laforin or lead to the production of a nonfunctional version of the protein. Hence Laforin serves as a Potential target for drug design. [4]

Valerian (*Valeriana officinalis*, *Valerianaceae*) is a hardy perennial flowering plant, with heads of sweetly scented pink or white flowers which bloom in the summer months. The mechanism of action of valerian in general, and as a mild sedative in particular, remains unknown. Valerian extracts appear to have some affinity for the GABAA receptor, a class of receptors on which benzodiazepines are known to act. Valerian also contains isovaltrate, which has been shown to be an inverse agonist for adenosine A1 receptor sites. [5]

The main objective of this study is to evaluate the antiepileptic activity which involves the prediction of ADMET (Absorption, Distribution, Metabolism, Excretion, toxicity) properties and docking studies of the compounds present in this plant which helps in the prediction of suitable drugs for epilepsy.

MATERIALS AND METHODS

Database screening for phytochemicals for *Valeriana officinalis*

The phytochemicals from *Valeriana officinalis* showing antiepileptic activity was identified from the plant databases. There were about 31 compounds were screened for antiepileptic activity.

Structure generation of phytochemicals The structures of these compounds were obtained from Pubchem database. The mol files of the phytochemicals were generated using ISIS Draw.

ADME-Toxicity investigation

Lipophilicity plays a critical role in the drug discovery and design. Lipophilicity plays a key role in the determination of physicochemical property which has a crucial role in finding out the ADMET (absorption, distribution, metabolism, excretion, and toxicity) and the over suitability of drug candidates. [6] ADMET studies gives insight into the pharmacokinetic property of the ligand compounds. There is enhanced evidence to show that control of key physicochemical properties such as lipophilicity, within a defined range ameliorate the quality of compound. The studies of aqueous solubility, blood brain barrier level, CYP 2D6, Hepatotoxicity and plasma protein binding levels were carried out. [7]

Target retrieval and Active site prediction

The modeled protein laforin was retrieved from PMD Database for molecular docking studies. The active sites of the protein were predicted using DS 3.5, which is based on the receptor cavity method using Eraser algorithm [8].

Docking studies

Molecular docking studies were performed using Accelrys Discovery studio. The results of interaction between modeled proteins with eleven phytochemical compounds are shown in Table 2 and the best docked complex is displayed in Figure 1. All the amino acid and Ligand atom residues which involved in molecular interactions are displayed. The results show that a good interaction occurs between the protein and the Ligand of cryptofaurinol which showed more binding capacity than the other compounds.

RESULTS AND DISCUSSION

Active site prediction

Modeled protein potential energy was analyzed before and after minimization by using

Calculate energy protocol in DS 3.5 and the results was given in [Table 1]. Based on the receptor cavity method we identified 9 active sites in the modeled structure. Based on the size of the volume, we selected the first active site for further study.

Table: 1 Energy values of modeled protein before and after Minimization

Modelled Protein	Forcefield	Potential Energy (kcal/mol)	Vander Waals Energy (kcal/mol)	Electrostatic Energy (kcal/mol)	RMS Gradient (kcal/(mol x Å))
Before Minimization	CHARMm	19898.05374	25591.23409	-9453.47273	1377.99046
After minimization	CHARMm	18280.05355	-1939.18195	-19427.83275	1377.99046

Ligand retrieval from *Valeriana officinalis*

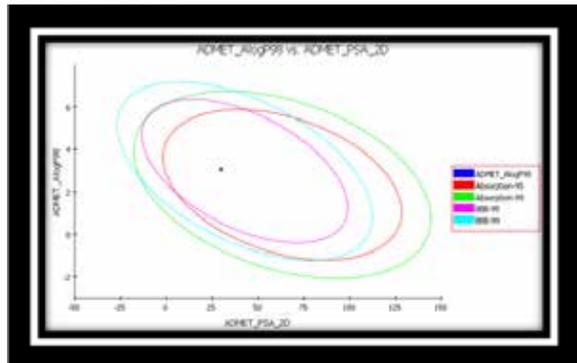
Valeriana officinalis consists of 31 compounds and these compounds were prepared and optimized by ADMET properties which evaluates drug likeness and toxicity for all compounds were predicted using TOPKAT to check the mutagenicity and probability values of the compounds. Among the 31 compounds the following 11 compounds satisfies ADMET properties is given in table 2.

**TABLE 2
COMPOUNDS SATISFIED ADMET PROPERTIES**

SL. NO.	COMPOUND NAME	MOL.WT	MOL. FORMULA
1.	ACTINIDINE	147	C10H13N
2.	CHATININE	149	C9H11NO
3.	CRYPTOFAURINOL	238	C15H26O2
4.	DIDROVALTRATE	424	C22H32O8
5.	ISOVALERIC ACID	102	C5H10O2
6.	ISOVALTRATE	422	C22H30O8
7.	MONOTERPENES	328	C10H13BR2CL
8.	SKYANTHINE	167	C11H21N
9.	VALERANONE	222	C15H26O
10.	VALERENAL	218	C15H22O
11.	VALERENIC ACID	234	C15H22O2

**Table 3
LIGAND PROTEIN INTERACTIONS WITH DOCKING SCORES**

S.No.	MOLECULE NAME	ABSOLUTE ENERGY	LIB DOCK SCORE	AMINO ACIDS AND LIGAND ATOMS	DISTANCE	NO OF H BONDS
1. 1.	CHIATININE	16.4265	62.9221	THR 721 OG1	A 2.338 , A 2.497	1
2. 2	ACTINIDINE	34.476	74.5036	ARG690 HE-N2, HH21-N2	2.165(ARG, HE-N2); 2.412(ARG, HH21-N2)	2
3. 3	CRYPTOFAURINOL	47.5443	87.8825	ALA909 HN-O13	2.357(ALA HN-O13)	6
4. 4	DIDROVALTRATE	42.5519	139.622	ARG690 HE-O15	1.927(ARG,HE-O15)	3
5. 5	ISOVALERIC	4.61686	54.2061	ARG651 HH1-O4	2.035(ARG, HH1-O4)	3
6. 6	ISOVALTRATE	60.3438	117.726	ARG649 HH21-O11	1.845(ARG, HH21-O11)	1
7. 7	MONOTERPENES	34.2666	78.1527	ARG690 HH21-CL11	2.368(ARG, HH21-CL11)	1
8. 8	SKYANTHINE	7.40132	61.2204	ARG627 HE-N1	2.376(ARG, HE-N1)	1
9. 9	VALERANONE	26.0426	82.7471	LEU907 HN-O14	2.359(LEU, HN-O14)	4
10.10	VALERENAL	35.6751	90.4829	ARG690 HH12-O13	2.139(ARG, HH12-O14)	2
11.10	VALERENIC ACID	36.7603	97.5532	ARG690 HH21-O1	1.986(ARG, HH21-O1)	2

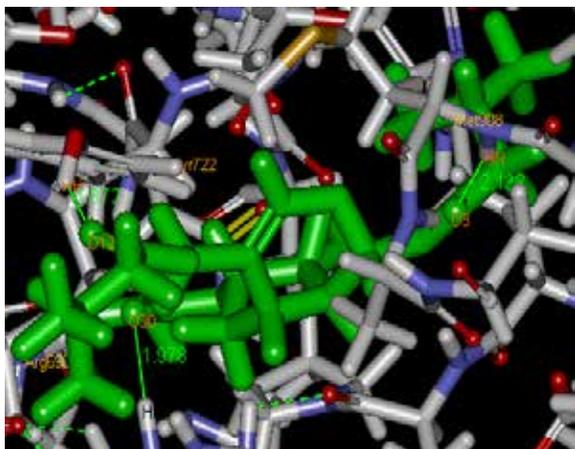
Fig1. GRAPHICAL REPRESENTATION OF ADMET SATISFIED PHYTOCHEMICALS

Based upon the ADMET values from Accelrys Discovery studio, the compounds listed in Table 2 have good ADME nature which is graphically represented in (figure 1). The toxicity profile of AMES mutagenicity in most compounds was found to be zero. The compounds having AMES and hepatotoxicity values is found to be 1. Then, Blood brain barrier, Human Intestinal absorption, Aqueous solubility, hepato- toxicity and CPY2D6 inhibition of the compounds were found to be good. Hence, the above 11 compounds can be further proceeded for docking studies.

DOCKING RESULTS OF *Valeriana officinalis*

Molecular docking studies were performed using Accelrys Discovery studio. The results of interaction between modeled protein with eleven phytochemical compounds and its docking results are shown in Table3. All the amino acid and Ligand atom residues which involved in molecular interactions are displayed. The results show that a good interaction occurs between the protein Laforin and Isovaleric which showed more binding capacity than the other compounds with best Lib dock score as 54.2061. The interaction of the best docked complex has been displayed in fig 2.

FIG 2 BEST DOCKED COMPLEX



CONCLUSION

Medicinal Plants are potential and powerful to deliver new drugs. The selected medicinal plant contains phytochemicals with various activities. Here we focused mainly on antiepileptic activity. The phytochemicals present in these plants are well-targeted to laforin. All the 11 phytochemicals targeted to the protein and bound to the active site with high docking score and had good affinity. Based on the hydrogen bonds, lib dock score and binding affinity to the active site, **Isovaleric** from *Valeriana officinalis* can be further proceeded for wet lab preparations to deliver a new drug for epilepsy.

ACKNOWLEDGEMENT

The authors are thankful to our Chancellor, Chief Executive officer, Vice Chancellor and Registrar of Karpagam University for providing facilities and encouragement.

REFERENCE

- Ahmed, S. N.; Spencer, S. S., An approach to the evaluation of a patient for seizures and epilepsy. WMJ : official publication of the State Medical Society of Wisconsin 2004, | 103 :49-55. | 2. Serratos, J. M.; Gomez-Garre, P.; Gallardo, M. E.; Anta, B.; de Bernabe, D. B.; Lindhout, D.; Augustijn, P. B.; Tassinari, C. A.; Malafosse, R. M.; Topcu, M.; Grid, D.; Dravet, C.; Berkovic, S. F.; de Cordoba, S. R., A novel protein tyrosine phosphatase gene is mutated in progressive myoclonus epilepsy of the Lafora type (EPM2). Human molecular genetics 1999, 8 : 345-52. | 3. Solaz-Fuster, M. C.; Gimeno-Alcaniz, J. V.; Ros, S.; Fernandez-Sanchez, M. E.; Garcia-Fojeda, B.; Criado Garcia, O.; Vilchez, D.; Dominguez, J.; Garcia-Rocha, M.; Sanchez-Piris, M.; Aguado, C.; Knecht, E.; Serratos, J.; Guinovart, J. J.; Sanz, P.; Rodriguez de Cordoba, S., Regulation of glycogen synthesis by the laforin-malin complex is modulated by the AMP-activated protein kinase pathway. Human molecular genetics 2008, 17 : 667-78. | 4. Ganesh, S.; Puri, R.; Singh, S.; Mittal, S.; Dubey, D., Recent advances in the molecular basis of Lafora's progressive myoclonus epilepsy. Journal of human genetics 2006, 51: 1-8. | 5. Benke D, Barberis A, Kopp S, Altmann KH, Schubiger M, Vogt KE, Rudolph U, | Möhler H. GABA A receptors as in vivo substrate for the anxiolytic action of valerianic acid, major constituent of valerian root extracts. Neuropharmacology. | 2009;56:174-81. | 6. B.W.Dominy ,C.A.Lipinski, I.Franco, ,P.J.Feeney, Experimental and computational | approaches to estimate solubility and permeability in drug discovery and development settings. Adv. DrugDeliv.Rev.1997;23:3-25 | 7. Egan WJ and Lauri G. Prediction of intestinal permeability. Advance Drug Delivery Review, 2002, 54: 273. | 8. CM, Jiang X, Oldfield T,Waldman M.Ligand Fit: a novel method for the shape-directed rapid docking of ligands to protein active sites, J. Mol. Graph. Model, 2003, 21, 289- 307.