MOLECULAR DOCKING ANALYSIS OF SELECTED MEDICINAL PLANTS FOR TREATING GENETIC DISORDER- CJD

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***Abstract*:** Genetic disorders are increasing by recent years due to exposure to harmful radiations and mutations in the gene sequence due to the period of time evolution, and also depends on one person's life. Genetic disorders are increasing by recent years due to exposure to harmful radiations and mutations in the gene sequence due to the period of time evolution, and also depends on one person's life. The genetic disorder Creutzfeldt-Jakob disease (CJD) is a human degenerative disease and has four categories, sporadic, familial, iatrogenic and variant. CJD is a type of transmissible spongiform encephalopathies (TSEs) or prion disease. The abnormal prions PrPSc were observed with similar aminoacid sequences with normal cellular prions PrPC, which implicated that mutated genes responsible for PrPC replicates itself and spontaneously changes its shape into infectious form. The rate of mutation and variation defines the disease type, however, it is defined that the population with mutated prion may not develop the diseased condition. Medicinal plants and their secondary metabolites were analyzed through docking studies and predicted for ADME properties. The chemical compound Catechin/cianidanol had a much significant G.score value of -8Kcal/ol and the interactions with active site residues GLN-160, GLN-186, TYR-157, ASN-159, THR-190.

Keywords: Creutzfeldt-Jakob disease (CJD); Prion Protein; catechin; Molecular docking analysis, Medicinal plants

I. INTRODUCTION

The modern world witnesses periodical changes in the field of health care system due to the emergence of newer diseases and also the expectations on period of medication should be short, curing rate is to be quick.Genetic disorders are increasing by recent years due to exposure to harmful radiations and mutations in the gene sequence due to the period of time evolution, and also depends on one person's life. Genetic disorders are increasing by recent years due to exposure to harmful radiations and mutations in the gene sequence due to the period of time evolution, and also depends on one person's life. In the present study, the docking study was employed to analyze the efficiency of plant compounds in reverting the diseased situations to normal. Here, the genetic disorderCreutzfeldt-Jakob disease (CJD) was focused. CJD is a human degenerative disease and has four categories, sporadic, familial, iatrogenic and variant. CJD is a type of transmissible spongiform encephalopathies (TSEs) or prion disease. It is a fatal disorder which progresses the destruction of nervous system. It was Stanley Prusiner in 1982 proposed that prion proteins are responsible for TSEs, which are produced in many tissues. The cellular form of prions (PrP^{C}) are found in follicular dendritic cells, endothelial cells and platelets, whereas in nerve cells they are abundant (Wastergard et al., 2007). The abnormal forms of prions are represented as (PrP^{Sc}) prototypical prion protein scrapie. Infectious prions are developed due to the mutations in the genes especially located in the chromosome 20, responsible for prion production. In normal condition, the cellular prions PrP^{C} possess short half-life, dissolves in water and could be easily digested by proteolytic enzymes (Altmeppen et al., 2012). Though the exact function of PrP^{C} is not known, a few information on its role is found in the transmission of nerve signals and against oxidative stress. More biological functions of cellular prions were updated by Wulf et al. (2017). In diseased condition, the abnormal PrP^{Sc} gets accumulated in the central nervous system (CNS), as well as PrP^{Sc} are water insoluble and resists proteolytic degradation, which might be due to its differed 3D shape (Prusiner, 1998). In recent decades of research, the different existence of prion in acquiring resistance to proteolytic degradation has been reported (Kuczius et al., 2004; Concha-Marambio et al., 2014).

The abnormal prions PrP^{Sc} were observed with similar aminoacid sequences with normal cellular prions PrP^{C}, which implicated that mutated genes responsible for PrP^{C} replicates itself and spontaneously changes its shape into infectious form. The prion disease are hereditary, once the altered or mutated gene occurred in a person's sperm or egg cell. The rate of mutation and variation defines the disease type, however, it is defined that the population with mutated prion may not develop the diseased condition. In the field of CJD, still more effective medical solutions and mechanisms are required to overcome the worst scenario.

Human population are mostly relying onherbal medicines fortreatments due to their safe consistency over conventional drugs, the cost is also less which added its credit. China, is the first country which promoted a number of licensed traditional medicine provider in US (Patwardhan et al., 2005). In the ancient times, due to lack of scientific technologies, the traditional based medicines does not has any scientific validation. The present era has made the countries like India, China, Korea and Japan to continuously validate the fundamental principle for evidence-based traditional medicines (Chakraborty, 2018). Among 21000 medicinal plants listed by World Health Organization (WHO), India has 2500 species which made India as the largest producer of medicinal herbs (Modak et al., 2007).

Gingko biloba is a maidenhair tree with traditional value in various fold medicines in Japan. Extracts of ginkgo leaves contain phenolic acids,proanthocyanidins, flavonoid, glycosides, suchas, myricetin, kaempferol, isorhamnetin and quercetin, terpene trilactones, ginkgolides and bilobalides, as well as alkyl phenols and polyprenols (van Beek, 2002).In the present study, bioinformatics techniques has been utilized to evaluate the secondary metabolites that are reported to be present in the plants for Absorption, Distribution, Metabolism and Excretion (ADME) and interactions were observed with the target protein prion using molecular docking studies.

II. MATERTIALS AND METHODS

The compounds in 3D structure was retrieved from PubChem database and the 3D structure of prion protein was retrieved from protein databank (PDB) of ID: 2KU4. The docking was carried out in Glide module of Schrodinger software. The protein was prepared by removing the water molecules, energy minimized and optimized, as well as the ligands also prepared and chirality was optimized. The Adsorption, Distribution, Metabolism and Excretion (ADME) properties for the chemical molecules were analyzed through Qikprop module of Schrodinger software.

The compound which obeyed the ADME property was taken for docking studies and the interactions were visualized using PYMOL.

III. RESULT

The retrieved compounds were subjected to analyze the Absorption, Distribution, Metabolism and Excretion properties and the results were tabulated (Table 3.1). The compound caralene violated the Lipinski's rule of five, where the hydrogen bond donor and acceptor were 0.The first- hand knowledge of these information are much necessary before drug discovery as it have a great impact on the cost, labor and the time duration. The lipophilicity was calculated to determine the range of solubility and permeability in octanol/water partition coefficient, in-order to understand the mechanism of transportation brain/blood barrier was also determined. The Lipinski's rule of five is also called as Pfizer's rule of five or the rule of thumb to evaluate drug likeness to indicate the following properties like molecular weight, octanol/water partition coefficient, hydrogen bond donor and acceptor. The rule has some limits in multiple of five, hence the name has been given as rule of five. Apart from these parameters other functions such as surface area in square Armstrong (polar surface area, PSA), brain/blood barrier and percentage of human oral absorption were also predicted. In the table for ADME test it was shown all the compounds came in the predicted range. The results of the docking studies were recorded in the table 3.2 and found that the compound Catechinfrom the plant sample *Gingko biloba* shows a glide score (G. score)-8.1Kcal/mol. The interactions were observed using PYMOL (Fig.3.2).

Table 3.1: ADME property of Plant Compounds

Molecule	**mol_MW (Molecular weight)**	**donorHB (Donor - Hydrogen Bonds)**	**acceptHB (Acceptor - Hydrogen Bonds)**	**QPlogPo/w**	**QPlogBB (Predicted brain/blood partition coefficient)**	**Human Oral Absorption**	**Percent Human Oral Absorption**	**Rule of Five**	**Rule of Three**
Range	**130 - 725**	**0 - 6**	**2.0 - 20.0**	**–2.0 – 6.5**	**–3.0 – 1.2**	**1- Low, 2- Medium, 3- High**	**>80% is high <25% is poor**	**Maximum 4**	**Maximum 3**
2-pentyl-2-nomenal	210.36	0	2	4.18	-0.676	3	100	0	0
Verbenone	150.22	0	2	1.903	0.171	3	100	0	0
Bojkultulysras-fjmazlmlsa-n	350.454	3	8.1	1.399	-1.352	3	78.863	0	0
Apigenin	270.241	2	3.75	1.923	-1.65	3	75.253	0	0
L-ascorbic acid	176.126	4	7.9	-1.852	-1.703	2	44.988	0	0
Calarene	204.355	0	0	5.105	1.04	3	100	1	1
Bilobalide	326.302	2	11.45	-1.278	-1.025	2	55.995	0	0
Borneol	154.252	1	1.7	-2.071	0.241	3	100	0	0
Bornly acetate	196.289	0	2	2.646	0.046	3	100	0	0
Caffeic acid	180.16	3	3.5	0.558	-1.569	2	54.231	0	1
Camphene	136.236	0	0	3.241	0.844	3	100	0	0
Camphor	152.236	0	2	1.938	0.259	3	100	0	0

Table 3.2: Interactions of plant compounds with the prion protein

Name of ligand	**Residues Interacted**	**Bond length (Å)**	**No. of bonds formed**
Cianidanol (or) Catechin	GLN-160(H-O)	2.3	5
	GLN-186 (O-H)	1.7	
	TYR-157 (O-H)	1.8	
	ASN-159 (H-O)	1.9	
	THR-190 (H-O)	2.1	
Epicatechin	GLN-160 (H-O)	2.3	6
	ASN-159 (H-O)	2.3	
	THR-190 (H-O)	2.1	

	GLN-186 (O-H)	1.7	
	THR-183 (O-H)	2.1	
	TYR-157 (O-H)	1.8	
Chlorogenic acid	ARG-156 (O-H) ARG-156 (H-O) ARG-156 (H-O) ARG-156 (H-O)	2.3 1.9 2.5 2.3	8
	LYS-194 (H-O) LYS-194 (H-O)	2.3 2.3	
	ASN-159 (H-O)	1.8	
	GLN-160 (O-H)	2.6	
Hyperoside	HIE-187(H-N)	2.4	6
	ASN-159(O-H)	2.4	
	GLN-160(O-H) GLN-160 (H-O)	2.1 1.7	
	ARG-136(O-H)	1.9	
	ASN-159(H-O)	2.1	
Apigetrin	ASN-159(O-H)	2.0	5
	GLN-160(O-H) GLN-160(H-O)	2.1 2.2	
	ARG-156(O-H) ARG-156 (O-H)	2.3 1.8	
Catechin	GLN-186 (H-O)	1.7	4
	THR-183(H-O) PRO-158(H-O)	2.1 1.8	
	GLN-160(O-H)	2.3	
Epicatechin	THR-190(O-H)	2.1	6
	GLN-186(H-O)	1.7	
	THR-183(H-O)	2.1	
	ASN-159(O-H)	1.9	
	GLN-160(O-H)	2.3	
	TYR-157(H-O)	2.3	
Theophylline rutoside	THR-216(O-H)	1.7	7
	GLN-212(H-O) GLN-212 (H-O) GLN-212 (H-O)	2.3 2.5 2.1	
	SER-135(O-H)	2.0	
	ILE-138(O-H) ILE-138 (O-H)	1.7 2.1	
Chlorogenic acid	ASN-159(O-H)	2.6	7
	GLN-160(H-O)	1.8	
	ARG-156(H-O) ARG-156 (O-H) ARG-156 (O-H) ARG-156 (O-H) ARG-156(O-H)	2.3 1.9 2.5 2.3 2.3	
Rutin	ARG-136 (O-H) ARG-136 (H-O)	1.8 1.8	10
	ARG-156 (O-H) ARG-156 (O-H) ARG-156 (O-H)	1.9 2.0 2.4	
	THR-191 (H-O)	2.0	
	ASN-159 (O-H)	1.9	
	GLN-160 (H-O)	2.5	
Noringin	ASN-159 (O-H)	1.9	6

	GLN-160 (H-O) GLN-160 (H-O) ARG-156 (O-H) ARG-156 (O-H) ARG-156 (O-H)	2.O 2.2 2.1 1.8 2.0	
Sappanchalcone	ARG-156 (O-H)	2.0	7
	ASN-159 (O-H)	2.0	
	GLN-160 (O-H) GLN-160 (H-O) GLN-160 (H-O)	2.1 2.1 2.1	
	LYS-194 (O-H)	2.4	
Laffeic acid	ASN-159 (O-H) ASN-159 (O-H)	2.5 2.2	5
	TYR-157 (H-O)	2.2	
	ARG-156 (O-H)	1.6	
	THR-191 (O-H)	1.7	
Vitexin	THR-191 (H-O) LYS-194 (O-H) LYS-194 (O-H)	1.8 2.3 2.0	5
	ASN-159 (H-O)	2.1	
p-Coummaric acid	ARG-156 (O-H)	1.6	3
	LYS-194 (O-H)	1.6	
	ASN-159 (O-H)	1.8	

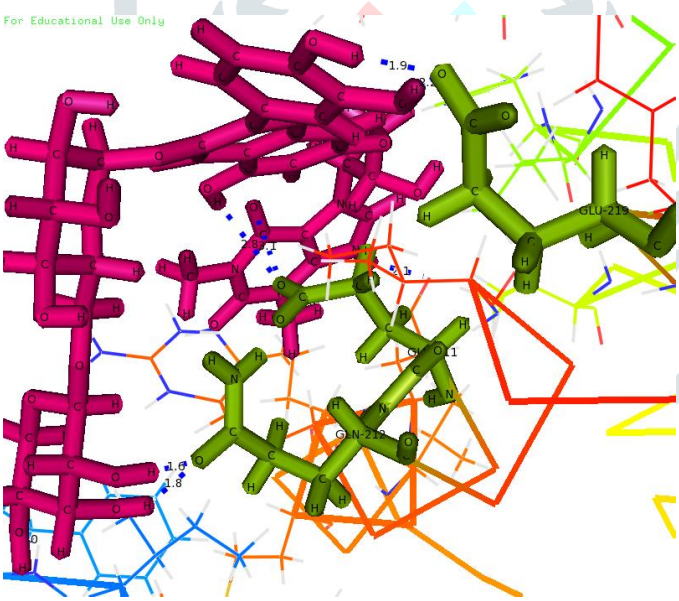

Figure 3.1: Interactionsof catechin with prion protein

IV. CONCLUSION:

The chemical compound Catechin/cianidanol had a much significant G.score value and the interactions with active site residues GLN-160, GLN-186, TYR-157, ASN-159, THR-190. A wide variety of plant were taken into account for studies out of these only the compounds of plants like *Ginkgo biloba, Witthania somnifera, Bacopa monnieri* showed positive results for drug likeness in the ADME studies. The above plant compounds could be explored more for the identification of an efficient and potential drug molecule.

ACKNOWLEDGEMENT:

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