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In Silico Interaction Analysis of Intracranial Pressure Reducing Agent Mannitol and its Derivatives with Human Serum Albumin

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Abstract— There is no specific treatment for *Japanese encephalitis* and treatment is supportive; with assistance given for feeding, breathing or seizure control as required. The recent data reported that mannitol (MNT) diluted into the human serum reduce the intracranial pressure, which may be effective in intracranial pressure management. Therefore, the present study was designed to find out the molecular interaction of mannitol with human serum albumin (HSA). Docking results showed that mannitol was efficiently bounded with HSA. HSA Pdb Id: 1E7H docked with Mannitol like Compounds DB00742, DB03955, DB04733, and DB03206 was -6.65 Kcal/Mol. -5.46 Kcal/Mol.and -4.54 Kcal/Mol and -6.02 Kcal/Mol, respectively. The Study reveals that *in silico* approach can easily explore the molecular interaction of mannitol with HSA and it will lead to understand the binding pattern of mannitol with HSA.

Index Terms— Mannitol (MNT), human serum albumin (HSA), *Japanese encephalitis*, molecular interaction.

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1 Introduction

Mannitol is used clinically in osmotherapy to condense strongly raised intracranial pressure until more definitive treatment can be applied, e.g., after head trauma. It is also used to treat patients witholiguric renal failure. It is administered intravenously, and is filtered by the glomeruli of the kidney, but is incapable of being resorted from the renal tubule, resulting in decreased water and Na^+reabsorption via its osmotic effect. Consequently, mannitol increases water and Na^+ excretion, thereby decreasing extracellular fluid volume [1].

Mannitol can also be used as a facilitating agent for the transportation of pharmaceuticals directly into the brain. The arteries of the blood–brain barrier are much more selective than normal arteries. Normally, molecules can diffuse into the tissues through gaps between the endothelial cells of the blood vessels. However, what enters the brain must be much more rigorously controlled. The endothelial cells of the blood–brain barrier are connected by tight junctions, and simple diffusion through them is impossible. Rather, active transport is necessary, requiring energy, and only transporting molecules that the arterial endothelial cells have receptor signals for. Mannitol is capable of opening this barrier by temporarily shrinking the endothelial cells, simultaneously stretching the tight junctions between them [2]. An intracarotid injection of high molarity mannitol (1.4-1.6M), causes the contents of the artery to be hyperosmotic to the cell.

Water leaves the cell and enters the artery in order to recreate an osmotic equilibrium. This loss of water causes the cells to shrivel and shrink, stretching the tight junctions between the cells [3]. The newly formed gap reaches its peak width five minutes after mannitol injection, and stays widely open for thirty minutes. During this time span, drugs injected into the artery can easily diffuse through the gaps between cells directly into the brain [4]. This makes mannitol indispensable for delivering various drugs directly to the brain (e.g., in the treatment of Alzheimer's disease, *Japanese encephalitis* or in chemotherapy for brain tumors [3].

Current study explores the binding site of mannitol and its derivative on human serum albumin through molecular docking studies.

2 Materails and Method

2.1 Preparation of ligand structures

Ligand files of Mannitol (DB00742), 1,5-Dideoxy-1,5-Imino-D-Mannitol (DB03955), 1,6-Di-O-Phosphono-D-Mannitol (DB04733), 1-Deoxynojirimycin (DB03206) were downloaded in *.mol* format (Fig:1) from DrugBak Database (http://www.drugbank.ca) [5]. These files could not directly use by Autodock 4.2 tools [6] thus; we have to convert it into .pdb files and also further the ligands were submitted for CHARMm [7] energy minimization protocol in Discovery Studio 4.1.

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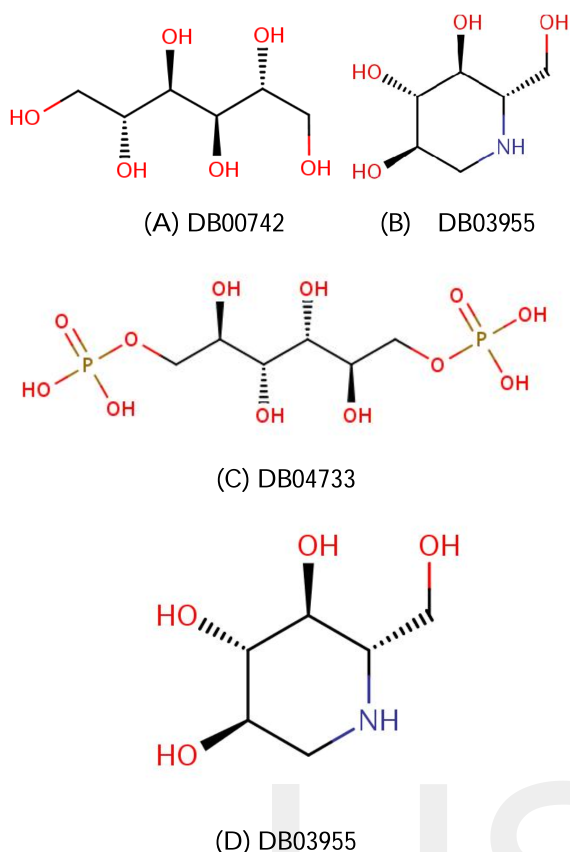

(D) DB03955

Fig 1: A,B,C,D shows ligand 2D structures

2.2 Preparation of protein structure

Human serum albumin (HSA) PDB ID: 1E7H [8] was obtained from Protein Data Bank (Fig: 2). Published structures were edited to remove HETATM,further the protein structure was submitted for CHARMm [7] energy minimization protocol using Discovery Studio 4.1.

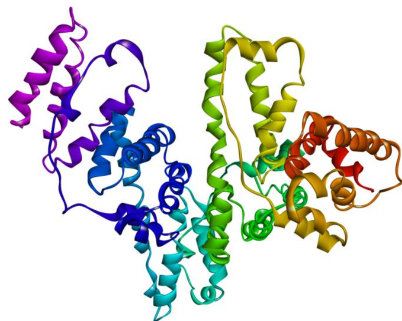

Fig 2: Crystal 3D structure of Human Serum Albumin (PDB ID: 1E7H)

2.3 Molecular interaction analysis

Docking studies were performed by Autodock (Version 4.2) suite [6],[9] and Cygwin interface was used in the *Microsoft Windows 7 professional* Version 2002, Service pack 3 operating System on *Intel (R) Core (i3)* , CPU T6500 @ 2.10 GHz, 1.19 GHz, and 4.00 GB of RAM of *Acer* Machine. Molecular docking methods followed by searching the best conformation of HSA and Mannitol like Compounds DB00742, DB03206, DB03955 and DB04733 on the basis of binding energy. Water molecules were removed from the protein structures before docking and hydrogen atoms were added to all target proteins. Kollman united charges and salvation parameters were added to the proteins. Gasteiger charge was added to the ligands. Grid box was set to cover the maximum part of proteins and ligand. The values were set to 60×60×60 Å in X, Y and Z axis of a grid point. The default grid points, spacing was 0.375 Å. Lamarckian Genetic Algorithm (LGA) [10] was used for proteins ligands flexible docking calculations. The LGA parameters like population size (ga_pop_size) , energy evaluations (ga_num_generation) , mutation rate , crossover rate and step size were set to 150, 2500000 , 27000 , 0.02 , 0.8 and 0.2 Å ,respectively. The LGA runs were set at 40 runs. All obtained 40 conformations of proteins and ligand complex were analysed the interactions and binding energy of the docked structure using Discovery Studio Visualizer (version 4.1).

3 Results and Discussion

We have taken Human serum albumin (HSA) Pdb Id: IE7H as a receptor (Fig: 2) for the docking analysis. Furthermore, we have observed that the binding energy between HSA and Mannitol like Compounds DB00742, DB03955, DB04733, and DB03206 was -6.65 *Kcal/Mol* -5.46 *Kcal/Mol* and -4.54 *Kcal/Mol* and -6.02 *Kcal/Mol*, respectively (Table :1).

The observed inhibition constant (Ki) for DB00742, DB03955, DB04733, and DB03206 was 13.28 *uM*, 100.14 *uM*, 471.56 *uM* and 13.28 *uM*, respectively (Table : 1).

We have also found that the 10 hydrogen bonds between DB00742 and HSA (Fig: 3) , 5 hydrogen bonds between DB03955 and HSA (Fig: 4), 7 hydrogen bonds between DB04733 and HSA (Fig: 5) and 10 hydrogen bonds between DB03206 and HSA (Fig: 6) (Table : 1).

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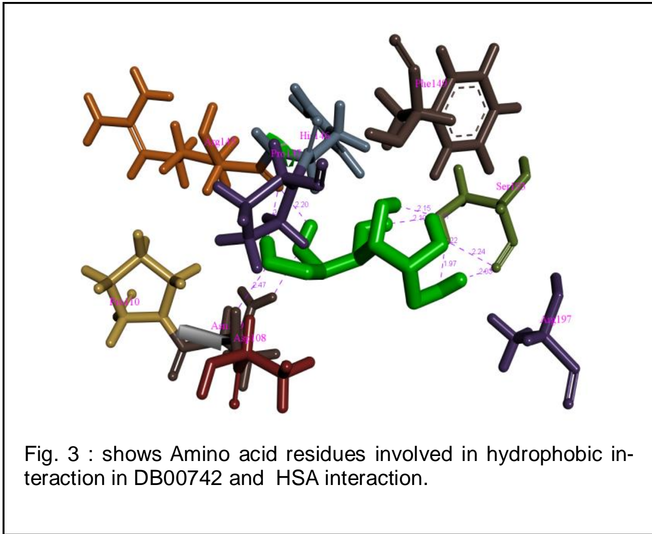

Fig. 3 : shows Amino acid residues involved in hydrophobic interaction in DB00742 and HSA interaction.

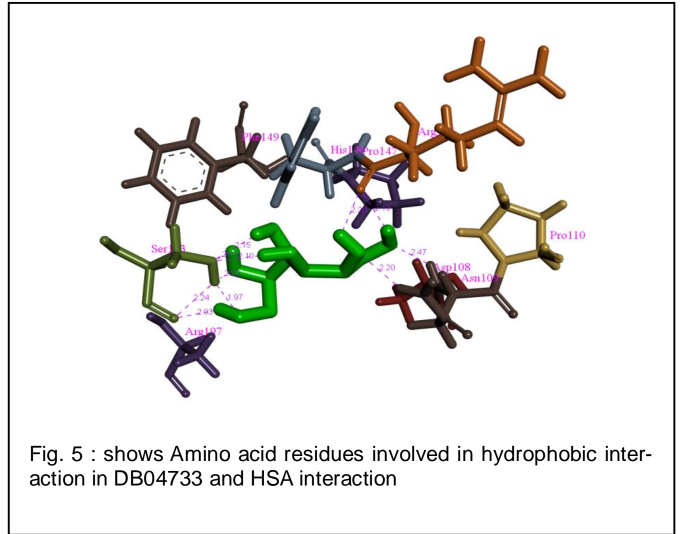

Fig. 5 : shows Amino acid residues involved in hydrophobic interaction in DB04733 and HSA interaction

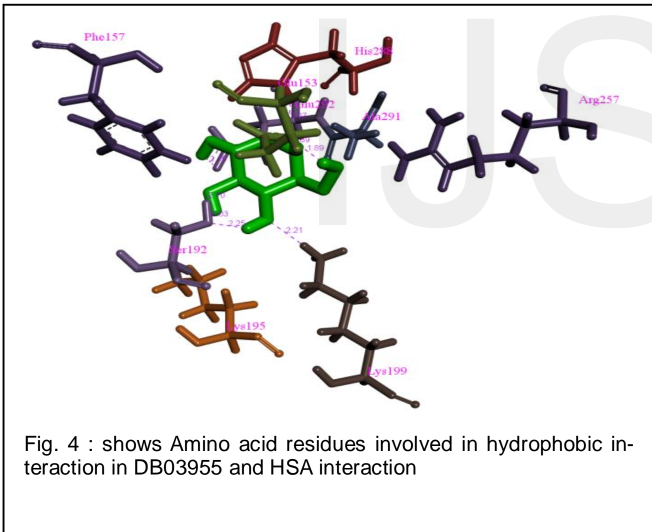

Fig. 4 : shows Amino acid residues involved in hydrophobic interaction in DB03955 and HSA interaction

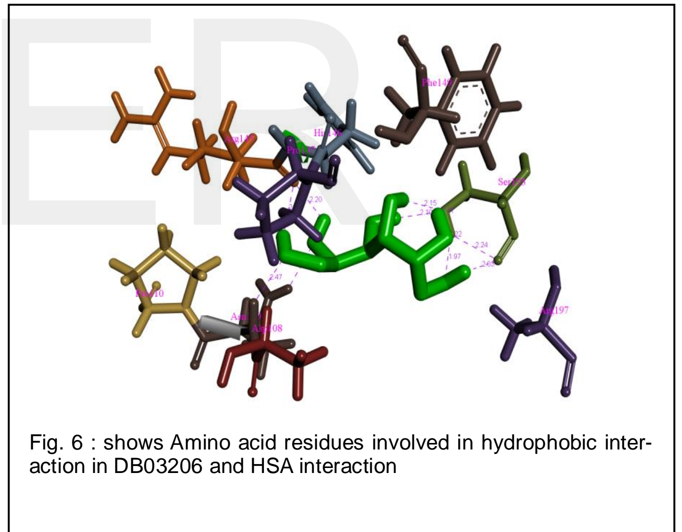

Fig. 6 : shows Amino acid residues involved in hydrophobic interaction in DB03206 and HSA interaction

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TABLE: 1 OBSERVED DOCKING ANALYSIS RESULTS

S.No	Compound id (DrugBank)	Compound Name	Binding energy (Kcal/Mol)	H-Bond	H-Bond Distance (Angstrom)	Inhibition Constant (Ki)	Amino acid residues involved in hydrobphoibc interaction
				A:ASN109:HN - :UNK1:O16	2.46809		
				A:ASN109:HD21 - :UNK1:O15	2.20425		
				A:SER193:HG - :UNK1:O11	1.97491		
1.	DB00742	Mannitol	-6.65	A:SER193:HG - :UNK1:O12	2.22329		Arg197,Asp108,Asn109, Pro110,Pro147,Pro149,His146,Arg145,Ser193
				:UNK1:H26 - A:ARG145:O	2.18835	13.28 uM	
				:UNK1:H25 - A:ARG145:O	2.19841		
				:UNK1:H21 - A:SER193:O	2.03379		
				:UNK1:H22 - A:SER193:OG	2.11041		
				:UNK1:H23 - A:SER193:OG	2.14939		
				:UNK1:H24 - A:SER193:OG	2.10108		
				A:SER454:HG - :UNK1:O12	2.43324		
2.	DB03955	1,5-Dideoxy-1,5-Imino-D-Mannitol	-5.46	:UNK1:H19 - A:GLU450:OE1	1.95423	100.14 uM	Trp214,Arg218,Val343,Leu198,Lys195,Val455,Ser454,Asp451,Glu450
				:UNK1:H16 - A:GLU450:OE1	1.93839		
				:UNK1:H23 - A:ASP451:O	2.06806		
				:UNK1:H22 - A:SER454:OG	2.1525		
				A:SER192:HG - :UNK1:O12	2.09962		
				A:LYS199:HZ2 - :UNK1:O15	2.20661		
3.	DB04733	1,6-Di-O-Phosphono-D-Mannitol	-4.54	:UNK1:H19 - A:GLU153:OE1	1.68525		Lys199,Lys195,Ser192,Arg257,Glu153,Phe157,Ala291,Glu292,His288
				:UNK1:H16 - A:GLU153:OE1	1.89248	471.56 uM	
				:UNK1:H24 - A:SER192:OG	2.24927		
				:UNK1:H23 - A:SER192:OG	2.02963		
				:UNK1:H22 - A:GLU292:OE2	2.1642		
				A:ASN109:HN - :UNK1:O16	2.46809		
				A:ASN109:HD21 - :UNK1:O15	2.20425		
				A:SER193:HG - :UNK1:O11	1.97491		
4.	DB03206	1-Deoxynojirimycin	-6.02	A:SER193:HG - :UNK1:O12	2.22329		Pro110,Arg145,Asn109,Ser193,His146,Arg197,Asp108,Pro147,Phe149
				:UNK1:H26 - A:ARG145:O	2.18835	13.28 uM	
				:UNK1:H25 - A:ARG145:O	2.19841		
				:UNK1:H21 - A:SER193:O	2.03379		
				:UNK1:H22 - A:SER193:OG	2.11041		
				:UNK1:H23 - A:SER193:OG	2.14939		
				:UNK1:H24 - A:SER193:OG	2.10108		

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4 Conclusion

As we know that every drug development study depend on the Clinical Trial Designs of Therapeutic Interventions. All techniques are time taking and need a lot of financial support. With the help of *in silico* approach we can reduce the time and cost of the clinical trials and make our study specific and concise on specific targets. Structure based techniques like docking analysis play important role to understand molecular dynamic properties of the ligands and receptor interactions and we can easily analyze the properties of binding pockets.

Furthermore, our study suggests that mannitol and its derivatives could be used as a primary treatment in the case of *Japanese encephalitis* like diseases related to blood brain barriers. *In vivo* and *In vitro* validation is needed to authenticate *in silico* results reported in the current study.

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