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MOLECULAR DYNAMICS STUDY OF HAEMOGLOBIN COMPLEXED WITH HYPEROSIDE

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ABSTRACT

Diabetes mellitus type 2 (formerly noninsulin-dependent diabetes mellitus (NIDDM) or adult onset diabetes) is a metabolic disorder that is characterized by high blood glucose either due to insulin resistance or insulin deficiency. Using bio-informatics, human hemoglobin was targeted for docking a ligand at pre-specified regions of its three dimensional structure for Type 2 Diabetes mellitus. Wide ligand search from databases identified hyperoside as desirable ligands that docked well with protein haemoglobin. Molecular dynamics simulations were made to study the drugs-protein interactions. It was shown that RMSD (Root Mean Square Deviation) curve for haemoglobin-hyperoside complex are remarkably more stable. The results demonstrate that hyperoside might be potentially used for blood glucose regulation.

KEYWORDS: **Heamoglobin, Hyperoside, RMSD curve and Molecular Dynamics**

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INTRODUCTION

One of the important tools in the study of biological molecules is the method of molecular dynamics simulations (MD). A molecular dynamics simulation describes the time dependent behavior of a molecular system. The first molecular dynamics simulation of a realistic system was done liquid water in 1974[1]. With molecular dynamics simulations, one can study both thermodynamic properties and/or time dependent (kinetic) phenomenon. Since computers are getting faster and cheaper, simulations of solvated proteins are calculated up to the nanosecond time scale. The molecular dynamics simulation method is based on Newton's second law of motion, F=ma, where F is the force exerted on the particle, m is its mass and a is its acceleration.

Average potential energy is defined as follows

$$V = \langle V \rangle = \frac{1}{M} \sum_{i=1}^{M} V_i$$

Where *M* is the number of configurations in the molecular dynamics trajectory and *Vi* is the potential energy of each configuration. Two theoretical methods have been used to study the motions in proteins with characteristic times less than about 10 ps. The first method is molecular dynamics simulation, in which the classical equations of motion for the atoms in the system are solved by numerical techniques for time intervals of 10-loops[2,3]. The second method is the normal-mode approach. This approach describes the motion, as a superposition of harmonic vibrations whose frequencies are determined by the multidimensional parabolic shape of the potential surface near an energy minimum[4]. Globular proteins are essential components of all living organisms. The biological activity of protein molecules depends on their structural fluctuations. For a given globular protein, the polypeptide chain of each molecule is folded compactly into a characteristic three-dimensional structure. Another important characteristic of proteins is their specificity of function. A particular enzyme will bind specific substrate molecules and catalyze a specific chemical transformation of the substrate. During the past few decades, increasing attention has been focused on the dynamic aspects of protein structure and function. Haemoglobin as a target for Type 2 Diabetes mellitus Diabetes mellitus is generally categorized as type 1 (insulin dependant diabetes or Juvenile-onset diabetes), type 2 (non- insulin dependent or adult onset diabetes) and gestational diabetes. Type 1 result due to autoimmunity and type 2 because of insulin resistance. Insulin is produced in the pancreas that enables body cells (muscle and fat cells) to absorb glucose which is in turn transformed into energy needed for daily life[5]. Diabetes type 2 is mainly caused by lifestyle factors (such as smoking, elevated cholesterol levels, obesity, and high blood pressure). Hemoglobin (Hb) is an essential component of the circulatory system of vertebrates. It is the iron-containing oxygen-transport metalloprotein in the red blood cells of all vertebrates[6]. Structure of dimeric haemoglobin is shown in Fig 1(a&b).

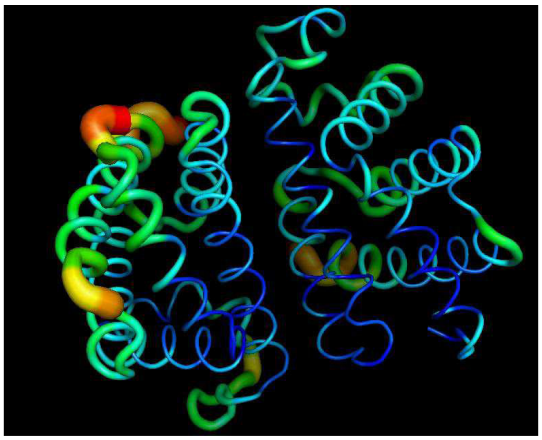

Figure 1(a)
Structure of dimeric haemoglobin (PDB id: 3PI1)

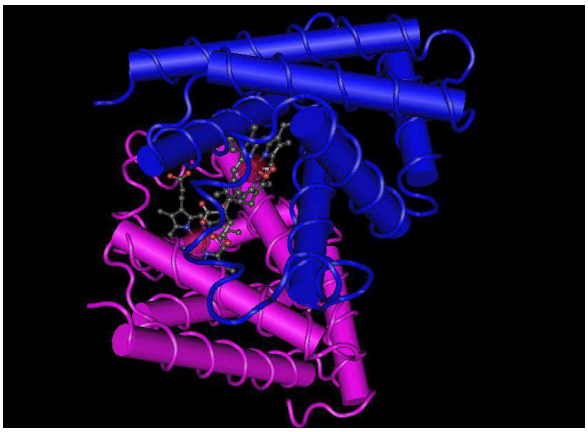

Figure 1(b)
Structure of haemoglobin (3PI1) complexed with a ligand[7].

Using bio-informatics, human haemoglobin was targeted for docking a ligand at pre-specified regions of its three dimensional structure.Structre of the ligand (hyperoside) is shopwn in Fig 2. This paper presents the dynamic behavior of haemoglobin–hyperoside complex.

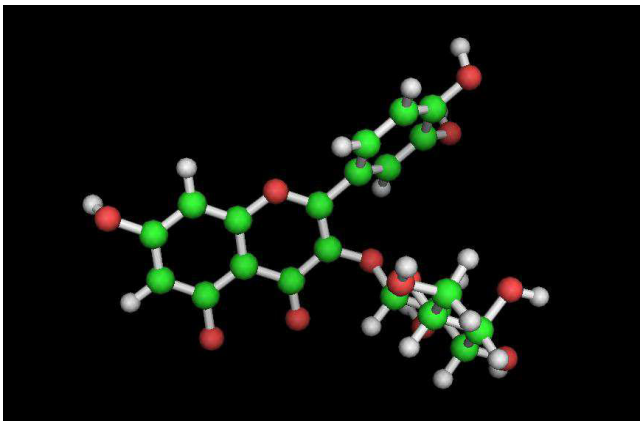

Figure 2
Structure of hyperoside.

MATERIALS AND METHODS

Protein Data Bank (PDB) Haemoglobin structure was downloaded from Protein data bank with the specific resolution and the PDB id is 3PI1 Docking by Glide The molecular docking tool, Glide (Schrodinger - Maestro v9.3.518)[8] software was used for ligand docking studies in to the Haemoglobin binding pocket. Glide is one of the most accurate docking tools available for ligand-protein, protein-protein binding studies. Ligand preparation The LigPrep process consists of a series of steps that perform conversions, apply corrections to the structures, eliminate unwanted structures, and optimize the structures. The process like convert the structure format, select the structures, add hydrogen atoms, remove unwanted molecules, neutralize charged groups, generate ionization states, generate low-energy ring conformations to get the output file.

Dynamics of haemoglobin-hyperoside complex

The complex of protein and hyperoside was observed under water environment for structure stability of protein-ligand complex. Total vanderwaals radii and Electrostatic reward were set up to 80Å and 20 respectively. Floating minimization was chosen to minimize every sample with PRCG (Polak – Ribiere conjugate gradient). The total temperature of the complex maintained to 300K for all samples. The hydrogen bond interaction between ligand and protein atom were set up to 4A distance.

RESULTS AND DISCUSSION

A 100 picosecond (ps) molecular dynamics simulation was performed, for the crystal structures of heamoglobin-hyperoside complex. Meanwhile, the corresponding root mean square deviation (RMSD) value curves of the protein backbone for haemoglobin was also computed. RMSD curves for haemoglobin-hyperoside complex are remarkably more stable. First (0^{th} sample) to last (100^{th} sample) was overlapped to observe the distance moved with 4Å distance. Molecular dynamics simulation of sample for 100 ps was observed against RMS deviation of the sample. After 25 ps the structure has reached its stability after the protein has interacted with ligand atom. Active sites for haemoglobin (3PI1) were PHE 29, TYR 30, LEU 33, GLN 39, THR 40, PRO 43, PHE 44, GLN 65, VAL 68, PHE 69, CYS 70, GLY 72, MET 73, PHE 76, MET 93, HIS 97, GLY 101, ILE 102, ARG 103, ASP 106, LEU 107, ALA 110, TYR 111 and LEU 114. Interaction occurs between PRO 43 (O), THR 40 (O), and ASP 10 (O) and GLN 65 (N) of protein with H, H, H and O atom of ligand respectively having the G score of 10.5. Hydrogen bond length was 1.809, 2.405, 1.852 and 2.04 correspondingly. Superimpose of 100 Trajectories in Ribbon Representation for 100 picosecond are shown in Fig 3.

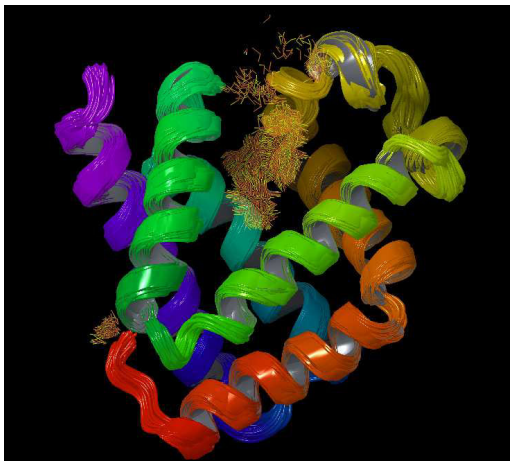

Figure 3
Superimpose of 100 Trajectories for 100 ps.

The binding study of hyperoside with haemoglobin is of great importance in pharmacy, pharmacology and biochemistry. This experiment can supply important information to clinical research and provide the theoretical basis for drug designing. We have simplified the dynamics of haemoglobin by using dimeric haemoglobin as a model for the tetrameric haemoglobin. Previous work shows that haemogobin as a monomer itself gives the same rate constants as it does within the tetramer[9,10]. Molecular dynamic simulation of sample (in ps) against Root mean square deviation of the complex is represented as graph in Fig 4.

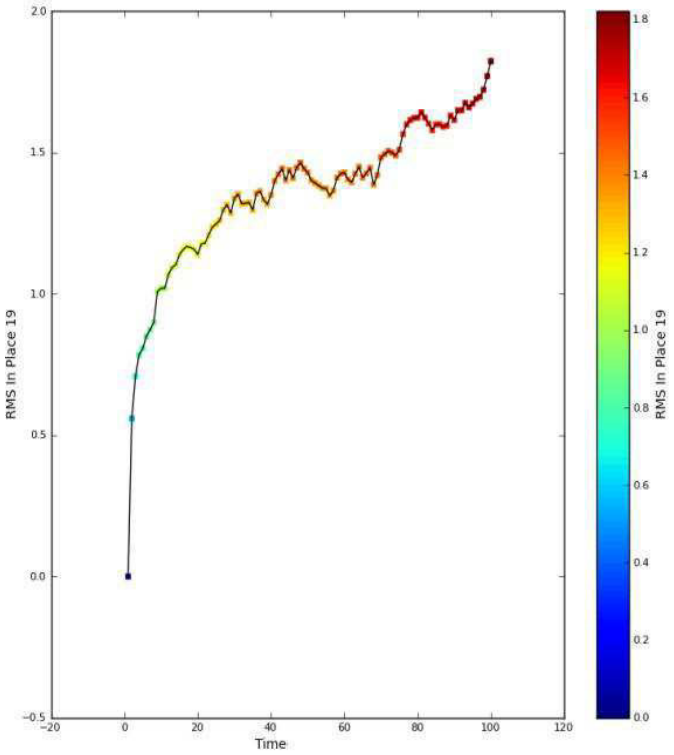

Figure 4
Graph showing molecular stimulation of sample observed (in ps) against RMSD.

CONCLUSION

Molecular dynamics simulations permit the study of complex, dynamic processes that occur in biological systems. Here the haemoglobin-hyperoside complex has attained stability to be in the simulated energy after 25ps (Fig 4). Haemoglobin is a target for Type 2 Diabetes mellitus. Hence hyperoside can be used for blood glucose regulation in the treatment of Type 2 Diabetes mellitus. Such studies also crucially determine the bioavailability and toxicology of injected drug. Curcumin, the major polyphenol of turmeric spice, were subjected to docking analysis for studying obesity related protein[11]. The results achieved during the past few years using the bioinformatics tools suggest that the theoretical work on proteins will become increasingly sophisticated and useful in the coming years.

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REFERENCES

1. Stillinger FH and Rahman A, Improved simulation of liquid water by molecular dynamics, J. Chem. Phys., 60: 1545-1548, (1974).
2. McCammon JA and Wolynes PG, Nonsteady hydrodynamics of biopolymer motions, J. Chem. Phys., 66: 1452-1456, (1977).
3. McCammon JA, Wolynes PG and Karplus M, Picosecond dynamics of tyrosine side chains in proteins, Biochem., 18: 927-942, (1979).
4. Gd N, Noguti T and Nishikawa T, Proc. Nat. Acad. Sci., USA 80: 3696, (1983).
5. Duckworth WC, Kitabchi AE, Insulin metabolism and degradation., Endocr Rev. 2: 210–233, (1981).
6. http://www.ncbi.nlm.nih.gov/Structure/mmdb/mmdbsrv.cgi
7. Maggiora GM, Wiley & Sons: New York, 99–117, (1990).
8. Halgren TA, Murphy RB, Friesner RA, Beard HS, Frye LL, Pollard WT and Banks JL, Glide: A New Approach for Rapid, Accurate Docking and Scoring. 2. Enrichment Factors in Database Screening, *J. Med. Chem.*, *47*: 1750–1759, (2004).
9. Naito N, Huang H, Sturgess W, Nocek JM, Hoffman BM, Binding and electron transfer between ... and ß-subunits through the use of [Zn, Fe] hybrids, J. Am. Chem. Soc., 120: 11256-11262 (1998).
10. Naito A, Hui HL, Noble, RW, Hoffman BM, Determination of the hemoglobin surface domains that react with cytochromeb(5), Biochemistry, 40: 2060-2065, (2001).
11. Archana P, Sathishkumar N, Bharathi Ns, umin- an inhibitor silico docking analysis of Curcumin an inhibitor for obesity, IJBPS, 1:224-235, (2010).