Insilco molecular docking study of Dihydroisoquinolinium derivatives as DPP IV inhibitors in type II Diabetes Mellitus

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ABSTRACT

With the spread of western lifestyles, the occurrence of diabetes in the world's population is rising. Diabetes is a complex metabolic endocrine disorder that occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. It is classified into two basic forms Type I and Type II diabetes.

A major goal for the treatment of type II diabetes is the enhancement of insulin secretion by pancreatic islet b-cells. The current therapeutic agents, although effective in increasing insulin secretion, are associated with undesirable side effects. Dipeptidyl peptidase IV (DPP IV) is responsible for conversion of glucose tolerance (GLP-1), into inactive form. The inhibition of DPP-IV would be beneficial in the treatment of diabetes mellitus. Improved glucose tolerance in diabetic patients was achieved with several small molecules as DPP IV inhibitors, including sitagliptin.

The current study was designed to identify a suitable inhibitor agent for DPP IV. Computer-assisted molecular modeling approach has contributed to the successful discovery of several novel antidiabetic DPP IV agents. Some isoquinoline was designed computationally and screened through insilico docking studies against crystal structure of Dipeptidylpeptidase-IV (DPP-IV) (PDB entry 2P8S)as a projected target for Type 2 Diabetes Mellitus. Insilico docking methodology using Auto Dock vina comprising a search method Genetic Lamarckian algorithm was used. Genetic Lamarckian algorithm performs an Automated Docking and has an advantage of empirical binding free energy force field that allows the prediction of binding free energies for docked ligands. In-silico evaluation shows satisfactory docking results, when compared with standard using docking. It is concluded that investigational ligands has the potential of inhibiting DPP-IV and there by further screening (invitro and invivo) studies can be carried out in order to find out optimized bioflavonoids for treating type2diabetes mellitus.

Keywords: Docking, DPP IV, Autodock vina, Insilco, Dihydroisoquinolinium, Type II Diabetes

INTRODUCTION

Diabetes Mellitus, better known as type II diabetes, is one of the most onerous chronic diseases and undoubtedly one of the most challenging health problems in the 21 century [1]. It is the fourth or fifth leading cause of death in most high-income countries and there is substantial evidence that it is epidemic in many economically developing and newly industrialized countries [2]. Diabetes mellitus is a syndrome of multiple aetiologies [3] characterized by chronic hyperglycaemia with impaired metabolism of glucose [4], lipids and proteins [5]. Juvenile or type I diabetes, occurs at a relatively young age where the beta cells of the pancreas do not produce enough insulin to maintain euglycemia in the plasma [6]. The hallmark of another type of adult onset or type II diabetes is the resistance of peripheral tissues to insulin action [7].

According to the international diabetic federation (IDF) 4.6 million people 20-79 years of age died from diabetes in 2011, accounting for 8.2% of global all-cause mortality of people in this age group. This estimated number of deaths is similar in magnitude to the combined deaths from several infectious diseases that are major public health priorities [8]. Looking at diabetes deaths against spending for diabetes care shows us the impact of a lack of

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treatment very starkly. The complications of type II diabetes and increasing pervasiveness emphasize the urgent need for new treatment strategies [9].

Novel approaches to glycaemic control includes use of inhibitors of the sodium–glucose co-transporter 2 [10, 11],inhibitors of 11 -hydroxysteroid dehydrogenase 1,agonists of the glucagon-like peptide-1 receptor and inhibition of dipeptidyl peptidase IV (DPP-IV) (increatin based treatments), Protein Tyrosine Phosphatase 1-Beta (PTP-1B) [12], Glycogen phosphorylase [13], Dipeptidyl peptidase IV (DPP IV) [14], Glucokinase [15], Peroxisome Proliferator-activated Receptor (PPAR)- [16], 3-hydroxy 3-methylglutaryl(HMG) Co-A Reductase [17].

Diphenyl peptidase IV (DPP IV) is a serine peptidases plays vital role in regulation of incretins hormone (Figure 1). This pleiotropic enzyme inactivates two intestinal hormones glucagonlike peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) both are well known as incretins[18].The GLP-1 stimulates insulin secretion and beta cell function leads to decreases glucagon secretion by lowering the blood glucose level [19]. However, incretins have very short half-lives due to renal degradation and proteolytic cleavage by dipeptidyl peptidase. To extend the incretin effect on enhanced insulin secretion, two approaches can be taken, the intravenous administration of GLP-1 or the oral administration of DPP IV inhibitors to slow down the otherwise rapid inactivation of endogenous GIP and GLP-1 [20]. Compare to GLP-1 analogues, DPP IV inhibitors are orally bioavailable and cause temporary side effects. Over the past few decades, synthetic peptide-derived DPP IV inhibitors including Vildagliptin, Saxagliptin and Sitagliptin had been approved for management of type 2 diabetes mellitus in Western countries. DPP IV inhibitors seem to represent a resourceful new class of oral normoglycaemic agents, with a potential effect on pancreatic function, but the real efficacy and safety have to be firmly assessed in the future [21]. Rather the DPP IV inhibitors would fit into the typical algorithms for treatment of type 2 diabetes mellitus remains a matter for debate.

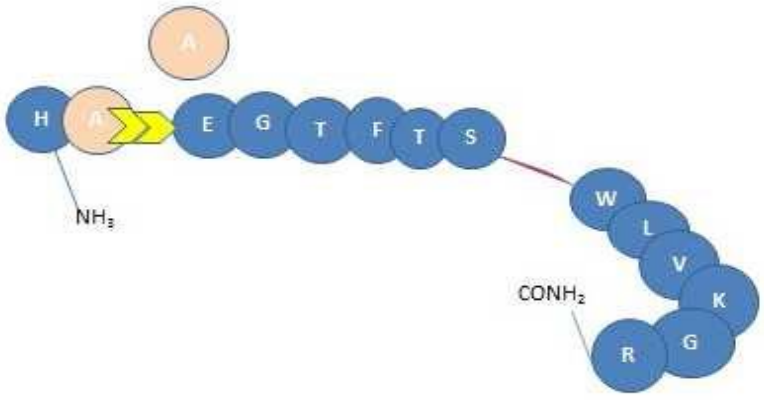


Figure 1: Cleavage site of GLP-1 protein by DPP4 (The yellow colour marking indicates DPP4 interrupting point of GLP-1)

Time and cost required for designing a new drug are immeasurable and at an unacceptable level. Intervention of computers at some plausible steps is vital to bring down the cost and time required in the drug discovery process. The use of paired experimental and informatics techniques increases the chance of success in many stages of the discovery process, from the identification of novel targets and elucidation of their functions to the discovery and development of lead compounds with desired properties.

In Silico techniques save great amounts of time and money in R and D projects. It can help in identifying drug targets via bioinformatics tools. They can also be used to explore the target structures for possible active sites, generate candidate molecules, check for their drug likeness, dock these molecules with the target, rank them according to their binding affinities, further optimize the molecules to improve binding characteristics.

MATERIAL AND METHODS

The crystal structure of DPP-IV with RCSB PDB code: 2P8S was downloaded from www.rcsbpdb.com. Latest version of MGL (Molecular Graphics Laboratory) tools–AutoDock 4.2.5.1 downloaded from www.scripps.edu, Chem sketch downloaded from www.acdlabs.com. Accelry's Discovery studio visualizer 3.1 was downloaded from www.accelerys.com, AUTODOCK VINA downloaded fromvina.scripps.edu/download.html. Chem Office

package- Chem 3D ultrafrom www.cambridgesoft.com.

Protein Data Bank (PDB): The PDB is the single, global archive for information about the 3D structure of bio macromolecules and their complexes, as determined by X-ray crystallography, NMR spectroscopy and cryoelectron microscopy. The crystal structure of DPP IV in complex with the sitagliptin inhibitor was retrieved from the Protein Data Bank (PDB entry 2P8S) [22]

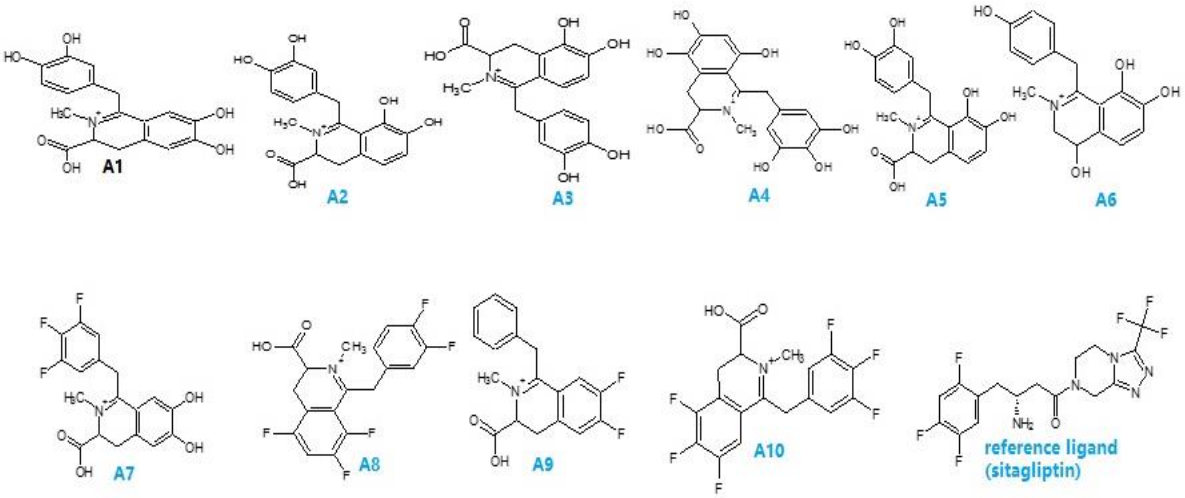
Protein Preparation: A typical PDB structure file consists of heavy atoms, water molecules, cofactors, metal ions and can be multimeric. The structure generally has no information on bond orders, topologies, or formal atomic charges. These structures do not have the information about bond orders, topologies or formal atomic charges. So, the raw PDB structure should be prepared in a suitable manner for docking.

Preparation of ligands

The ligands were designed using chemsketch and their 2d structure was converted to 3D structures using Chem3D ultra 6.1 and they were energy minimized using MM2.These energy optimized ligands were used for docking evaluation. Fig 2 shows the energy minimized ligands and Table 1 shows the ligands with molecular formula, molar mass, and number of torsions in the ligands.

LIGAND	SMILE	M.W.	LOGP	HBA	HBD
A1	Oc1ccc(cc1O)CC2=[N+](C)C(Cc3cc(O)c(O)cc23)C(=O)O	344.3	0.799	6	5
A2	Oc1ccc(cc1O)CC2=[N+](C)C(Cc3ccc(O)c(O)c23)C(=O)O	344.3	0.799	6	5
A3	Oc1ccc(cc1O)CC=2c3ccc(O)c(O)c3CC(C(=O)O)[N+]=2C	344.3	0.799	6	5
A4	Oc1cc(cc(O)c1O)CC=2c3c(O)cc(O)c(O)c3CC(C(=O)O)[N+]=2C	376.1	1.066	8	7
A5	Oc1ccc(cc1O)CC2=[N+](C)C(Cc3ccc(O)c(O)c23)C(=O)O	344.3	0.799	6	5
A6	Oc1ccc(cc1)CC2=[N+](C)CC(O)c3ccc(O)c(O)c23	300.1	0.44	4	4
A7	Fc1cc(cc(F)c1F)CC2=[N+](C)C(Cc3cc(O)c(O)cc23)C(=O)O	366.1	0.88	4	3
A8	Fc1ccc(cc1F)CC=2c3c(F)c(F)cc(F)c3CC(C(=O)O)[N+]=2C	370	0.84	2	1
A9	O=C(O)C2Cc3cc(F)c(F)cc3C(Cc1ccccc1)=[N+]2C	316.1	1.552	2	1
A10	Fc1cc(cc(F)c1F)CC=2c3cc(F)c(F)c(F)c3CC(C(=O)O)[N+]=2C	388	0.961	2	1
**	Fc3cc(C[C@@H](N)CC(=O)N1Cc2nnc(n2CC1)C(F)(F)F)c(F)cc3F	407.1	1.684	6	1

**REFERENCE LIGAND (SITAGLIPTIN)



Active Site Analysis

After getting the PDB (2P8S) structure from RCSB(http://www.rcsb.org/pdb/home/home.do). Active site analysis of the Protein DPP IV with sitagliptinwas performed using Swiss PDB Viewer. The residues found in the binding site of wereDPP IV identified as ARG 125,ARG 669,ARG 358,SER 630,SER 209,ASN 710,HIS 740,TYR 547,TRP 629.

Docking Studies

The Software used for the docking studies are AUTODOCK VINA [23]. Auto Dock Vina is a new open source program for drug discovery, molecular docking and virtual screening, offering multi-core capability, high performance and enhanced accuracy and ease of use. Auto Dock Vina significantly improves the average accuracy of the binding mode predictions compared to Auto Dock 4.2.

Analysing the Docking Results

The search for the best ways is to fit ligand molecules, into DPPIV structure, using AUTODOCK VINA resulted in docking files that contained detailed records of docking. The obtained log files were read in ADT (Auto Dock Tool) to analyse the results of docking. The similarity of docked structures was measured by computing the root mean square deviation (RMSD) between the coordinates of the atoms and creating clustering of the conformations based on the RMSD values. The lowest binding energy conformation in all cluster were considered as the most favourable docking pose. Binding energies that are reported represent the sum of the total intermolecular energy, total internal energy and torsional free energy minus the energy of the unbound system. The top seven ligands were selected based on the energy score after virtual screening.

RESULTS

Docking results (Table 2, Fig 2, Fig 3,Fig 4,Fig 5) indicate that all the compounds interact with DPP IV with best binding energies.

Table 2. molecular docking score.

ligand	SMILE	Auto dock vina score (kcal\mol)
A1	Oc1ccc(cc1O)CC2=[N+](C)C(Cc3cc(O)c(O)cc23)C(=O)O	-8.1
A2	Oc1ccc(cc1O)CC2=[N+](C)C(Cc3ccc(O)c(O)c23)C(=O)O	-7.6
A3	Oc1ccc(cc1O)CC=2c3ccc(O)c(O)c3CC(C(=O)O)[N+]=2C	-7.7
A4	Oc1cc(cc(O)c1O)CC=2c3c(O)cc(O)c(O)c3CC(C(=O)O)[N+]=2C	-7.9
A5	Oc1ccc(cc1O)CC2=[N+](C)C(Cc3ccc(O)c(O)c23)C(=O)O	-7.7
A6	Oc1ccc(cc1)CC2=[N+](C)CC(O)c3ccc(O)c(O)c23	-7.3
A7	Fc1cc(cc(F)c1F)CC2=[N+](C)C(Cc3cc(O)c(O)cc23)C(=O)O	-7.8
A8	Fc1ccc(cc1F)CC=2c3c(F)c(F)cc(F)c3CC(C(=O)O)[N+]=2C	-7.8
A9	O=C(O)C2Cc3cc(F)c(F)cc3C(Cc1ccccc1)=[N+]2C	-7.9
A10	Fc1cc(cc(F)c1F)CC=2c3cc(F)c(F)c(F)c3CC(C(=O)O)[N+]=2C	-8.3
**	Fc3cc(C[C@@H](N)CC(=O)N1Cc2nnc(n2CC1)C(F)(F)F)c(F)cc3F	-8.6

**REFERENCE LIGAND (SITAGLIPTIN)

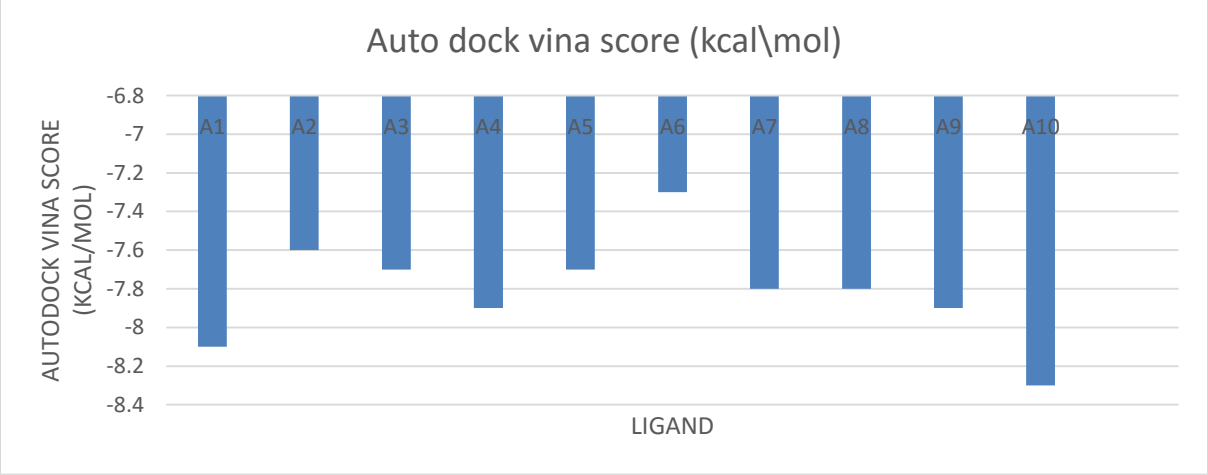


Fig 2. Graphical representation of docking score.

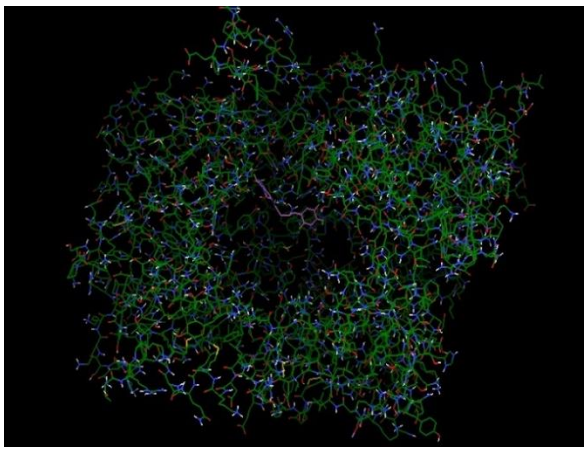


Fig 3. sitagliptin and protein complex

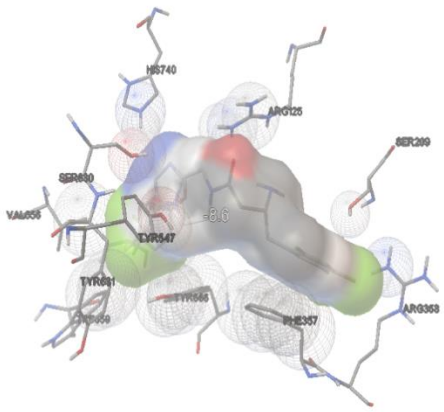


Fig 4.sitagliptin and amino acid interaction

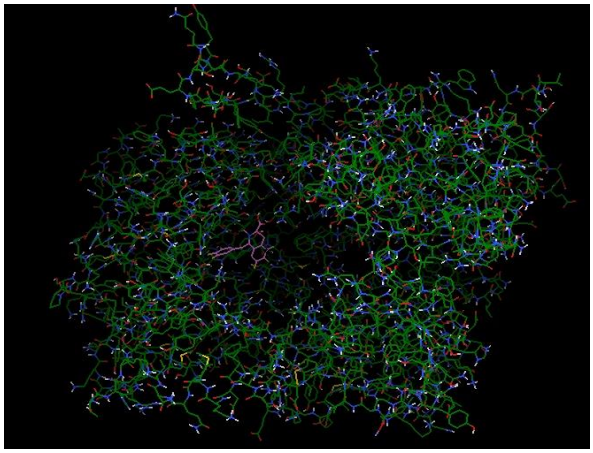


Fig 5. Ligand A10 and protein complex

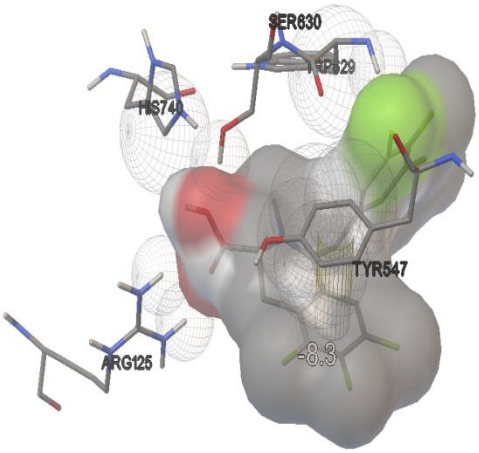


Fig 6.ligand A10 and amino acid interaction

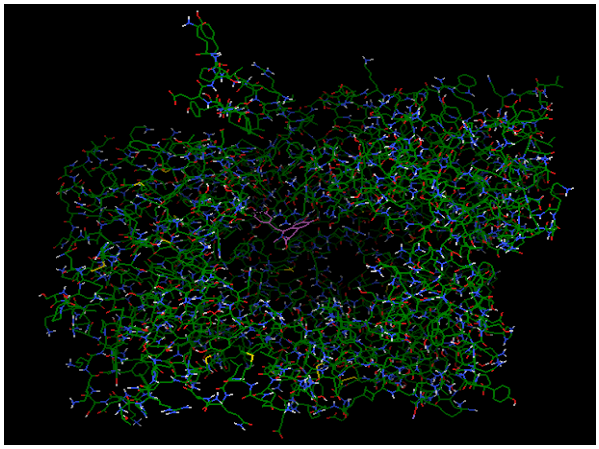


Fig 5. Ligand A1 and protein complex

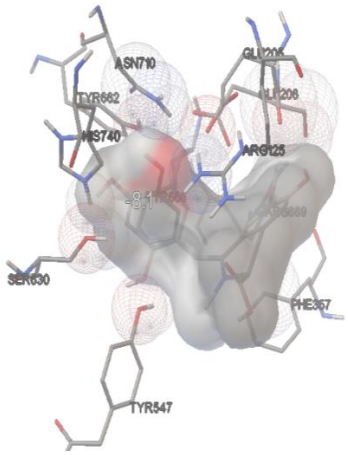


Fig 6.ligand A1 and amino acid interaction

DISCUSSION:

DPP IV is a member of serine peptidase plays a role of inhibitory action to increase blood concentration of the incretin GLP-1. Development of small molecule as selective inhibitors of DPP IV is a major challenge. Natural DPP

IV inhibitors like berberine, group of isoquinoline alkaloids, reported an effective inhibition against the DPP IV enzyme. Current DPP IV drugs in market vildagliptin, sitagliptin and saxagliptin had numerous side effects like tremor, headache, dizziness, low blood sugar levels specially when taken in excess of amount, nausea, feeling weak, weight gain and swelling of the legs and ankles due to excess fluid retention . These drugs have to be taken as combination therapy with natural therapeutic molecule to achieve desired results. Earlier, the extracts from Armenian Highland plants was highly effective in inhibiting DPP IV was reported by St. John's wort and sea-buckthorn leaves could be used, in combination with other antidiabetic drugs, for the treatment of diabetes mellitus. The present study results have been integrated with numerous Dihydroisoquinolinium Derivatives are potent antidiabetic agents through a DPP IV inhibition mechanism. Our present result is a new approach to assess antidiabetic molecule in the form of DPP IV inhibitors.

CONCLUSION

The 3-dimensional structure of the Protein DPP IV incomplex with Sitagliptin was used in the present study.
In conclusion we have identified a group of molecule of Dihydroisoquinolinium derivative as DPP IV inhibitor. From the docking studies (using AUTODOCK VINA software) of Dihydroisoquinolinium derivatives. The interactions were also visualized using autodock tools. we found the molecule A10 (Fc1cc(cc(F)c1F)CC=2c3cc(F)c(F)c(F)c3CC(C(=O)O)[N+]=2C) bound to the active site of DPP IV residues like ARG 125,SER 630,HIS 740,TYR 547,TRP 629.Of all these compounds A1,A10 can be considered as potent inhibitors since they have a better binding energy and also interact with active site residues. This has to be further investigated by wet lab studies.

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↓ REFERENCES

1. Sokeng, S.D., D. Lontsi, P.F. Moundipa, H.B. Jatsa, P. Watcho and P. Kamtchouing, 2007. Hypoglycemic Effect of AnacardiumoccidentaleL.Methanol Extract and Fractions on Streptozotocin-induced Diabetic Rats. Global Journal of Pharmacology, 1(1): 01-05.
2. Baquer, N.Z., D. Gupta and J. Raju, 1998. Regulation of metabolic pathways in liver and kidney during experimental diabetes. Effects of antidiabetic compounds. Indian J Clinical Biochem, 13: 63-80.
3. Visweswara Rao, P. and M. Dhananjaya Naidu, 2010. Anti Diabetic Effect of Rhinacanthusnasutus Leaf Extract in Streptozotocin Induced Diabetic Rats. Libyan Agriculture Research Center Journal International, 1(5): 310-312.
4. Grijesh Kumar Mall, PankajKishor Mishra and Veeru Prakash, 2009. Antidiabetic and Hypolipidemic Activity of Gymnemasylvestre in Alloxan Induced Diabetic Rats. Global Journal of Biotechnology and Biochemistry, 4(1): 37-42.
5. Baquer, N.Z., D. Gupta and J. Raju, 1998. Regulation of metabolic pathways in liver and kidney during experimental diabetes. Effects of antidiabetic compounds. Indian J. Clinical Biochem, 13: 63-80.
6. EilyadIssabeagloo, Reza forughi, Mohammed Taghizadieh and ParvizKermanizadeh, 2012. Effect of Alcohol on Blood Glucose Levels in Streptozotocin Induced Diabetic Rats. Middle-East Journal of Scientific Research, 12(3): 290-293.
7. Mohammad Yaheya Mohammad Ismail, 2009. Clinical Evaluation of Antidiabetic Activity of Trigonella Seeds and Aeglemarmelos Leaves, World Applied Sciences Journal, 7(10): 1231-1234.
8. NisarZamin Shah, Naveed Muhammad, SadiaAzeem and AbdurRauf, 2013. Hypoglycemic Effect of Crude Methanolic Extract as Well as Sub Fractions of Morusalba on Rabbits. Global Journal of Pharmacology, 7(1): 91-94.
9. International Diabetes Federation. The IDF Diabetes Atlas. Fifth Edition. Brussels: International Diabetes Federation, 2011.
10. Chao, E.C. and R.R. Henry, 2010. SGLT2 inhibition-a novel strategy for diabetes treatment. Nat. Rev. Drug.

Discov, 9: 551-559.
11. ManmohanSinghal, ShaileeRasania, Amit Gaur, Manchireddy Vishnu, V.R. Vijaya Rama Raju and S. YozanaUpadhyay, 2012. Overview on Sodium Glucose Transport Inhibitors as a Therapeutic Tool against Diabetes Mellitus. Global Journal of Pharmacology, 6(2): 86-93.
12. Lambeir, A.M., C. Durinx, Scharpe and S. De Meester, 2003. Dipeptidyl-peptidase IV from bench to bedside: an update on structural properties, functions and clinical aspects of the enzyme DPP IV. Crit Rev Clin Lab Sci., 40: 209-294.
13. Wu, X.D., H.J. Deeb, R. Singh and N. Sedkova, 2001. Depot-Specific Variation in Protein-Tyrosine phosphatase activities in human mentaland Subcutaneous adipose tissue: A Potential Contribution to Differential Insulin Sensitivity. J. ClinEndocrinolMetab, 86: 5973-5980.
14. Susie Chang, Marjorie J. Rosenberg, Holmes Morton, Clair A. Francomano and Leslie G. Biesecker, 1998. Identification of a mutation in liver glycogen phosphorylase in glycogen storage disease type VI. Hum Mol Genet, 7: 142-145.
15. Basu, R., A. Basu, C.M. Johnson, W.F. Schwenk and R.A. Rizza, 2004. Insulin dose response curves for stimulation of splanchnic glucose uptake and suppression of endogenous glucose production differ in non-diabetic humans and are abnormal in people with type 2 diabetes mellitus. Diabetes, 53: 2042-2050.
16. Pearson, S.L., M.A. Cawthorne, J.C. Clapham, S.J. Dunmore, S.D. Holmes, G.B. Moore, S.A. Smith and M. Tadayyon, 1996. The thiazolidinedione insulin sensitiser, BRL 49653, increases the expression of PPAR-gamma and aP2 in adipose tissue of high-fat-fed rats. BiochemBiophys Res Commun, 229(3): 752-757.
17. Istvan, E.S., M. Palnitkar, S.K. Buchanan and J. Deisenhofer, 2000. Crystal structure of the catalytic portion of human HMG-CoA reductase: insights into regulation of activity and catalysis. EMBO J, 19: 819- 830.
18. Abbott CA, Yu DMT, Woollatt E, Sutherland GR, McCaughan GW, Gorrell MD. Cloning, expression and chromosomal localization of a novel human dipeptidyl peptidase (DPP) IV homolog, DPP8. Eur J Biochem. 2000; 67: 6140-50.
19. Weber AE. Dipeptidyl peptidase IV inhibitors for the treatment of diabetes. J Med Chem. 2004; 47: 4135-41.
20. Mest HJ, Mentlein R. Dipeptidyl peptidase inhibitors as new drugs for the treatment of type 2 diabetes. Diabetologia 2005; 48: 616-20.
21. Fredenrich A, Palle S, Canivet B. Dipeptidyl peptidase inhibitors: A new step towards normoglycemia. Open Endocrinol J. 2009; 3: 16-21.
22. Biftu, T., G. Scapin, S. Singh, D. Feng, J.B. Becker, G. Eiermann, H. He, K. Lyons, S. Patel, A. Petrov, R. Sinha-Roy, B. Zhang, J. Wu, X. Zhang, G.A. Doss, N.A. Thornberry and A.E. Weber, 2007. (3R)-4-[(3R)- 3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(2,2,2- trifluoroethyl)-1,4-diazepan-2-one,a selective dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. Bioorg. Med ChemLett, 17: 49-52.
23. Trott O & Olson AJ, J Comput Chem. 2010; 31(2): 455-61