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Molecular docking analysis of tetracyclic triterpenoids from *Cassia fistula L.* with targets for diabetes mellitus

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Abstract:
It is of interest to develop effective drugs for diabetes mellitus. We document the molecular docking analysis data of tetra-cyclic-tri-terpenoids from *Cassia fistula* L. with targets for diabetes mellitus.

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Background:

Molecular docking is a crucial approach in computer-aided drug design that has been increasingly popular in recent years for quickly predicting the binding mechanisms and affinities of small molecules to their target molecules **[1]**. Tetracyclic triterpenoids are active components present in a variety of higher plants that have been studied extensively for their potential to treat diabetes and associated complications **[2]**. The hypoglycemic action of these tetracyclic triterpenoid compounds was previously reported in our study **[3]**. Therefore, it is of interest to document the molecular docking analysis data of tetracyclic triterpenoids from Cassia fistula L. with targets for diabetes mellitus involved in glycolysis, gluconeogenesis, glycogenolysis, de novo lipogenesis, insulin secretion and sensitivity, activation of incretin hormones, reabsorption of intestinal glucose from carbohydrate metabolism and peripheral glucose uptake (**Table 1**).

Table 1: Molecular receptors focused as targets for diabetes treatment

Targets	Mechanism of action of drugs in maintaining glucose homeostasis	Experimental and in-silico evidences	References
Glucokinase	Glucokinase activators improves the glycemic control through hepatic glucose metabolism and pancreatic insulin secretion	The phytoconstituents of Enicostemma littorale showed promising glucokinase enzyme activation efficacy	**[4]**
		γ-sitosterol isolated from Lippia nodiflor showed good anti diabetic effect by increasing glucokinase activity	**[5]**
Glycogen phosphorylase	Glycogen phosphorylase inhibitors restrains the enzymatic synthesis of glucose from glycogen thus lowering the rise in blood glucose	Active chemical constituents of Tinospora cordifolia showed good binding affinity with catalytic site of the enzyme	**[6]**
Peroxisome proliferator-activated receptor gamma	Peroxisome proliferator-activated receptor gamma agonists restores glucose and lipid metabolism	Bio-active molecules from traditional plants virtually screened for Peroxisome proliferator-activated receptor gamma activation	**[7]**
Insulin receptor kinase	Insulin receptor kinase activators regulates the signal transduction via PI3K–AKT pathway	Compounds from Lycopersicon esculentum explored for binding affinities with insulin receptor	**[8]**
		Flavanoids from banana flower explored as potential insulin receptor tyrosine kinase activatiors	**[9]**
Protein Tyrosine Phosphatase 1B	Protein Tyrosine Phosphatase 1B inhibitors prevents the dephosphorylation of insulin receptor which in turn promotes insulin signaling	The synthetic compounds 5-acetyl-2-aryl-6-hydroxybenzo[b]furans showed significant inhibitory effect against PTP1B activities binding to the allosteric site of the enzyme	**[10]**
		The naturally isolated compounds Morus alba root bark exhibited PTP1B inhibitory activity	**[11]**
Dipeptidyl peptidase (IV)	Dipeptidyl peptidase (IV) inhibitors prevent the degradation of the incretin hormones (GIP and GLP-1), thereby stimulating insulin secretion from pancreatic β-cells and decreasing blood glucose levels	Compounds from Curculigo latifolia inhibited the DPP (IV) enzyme in the gut, increasing insulin production and lowering glucose levels in the bloodstream.	**[12]**
		Piperazine-derived compounds evaluated as inhibitors for DPP (IV) enzyme	**[13]**
Glycogen synthase kinase 3	Reduces glycogen synthesis by phosphorylating glycogen synthase	Naproxen and cromolyn identified as novel GSK-3β inhibitors in diabetes and obesity management.	**[14]**
		(4Z, 12Z)-cyclopentadeca-4, 12-dienone isolated from Grewia hirsute reported as promising candidate in type-2 diabetes treatment	**[15]**
α-glucosidase	α-glucosidase inhibitors inhihbits the absorption of complex carbohydrates into the intestine and reduces the postprandial blood glucose levels	Several herbal compounds control postprandial hyperglycemia by blocking the enzyme α-glucosidase.	**[16]**
		The synthesized compound indeno[1,2-c]pyrazol-4(1H)-ones identified as potential enzyme inhibitor in the pathogenesis of type 2 diabetes	**[17]**

Table 2: Receptor-ligand interactions of triterpenoid compounds with diabetic targets

Ligand	Target	Binding affinity score (kcal/mol)	H-bond interactions
Cpd-1	Glucokinase	-6.8	Asp 205, Ile 225, Gly 229
	Glycogen phosphorylase	-9.1	Glu 382
	Peroxisome proliferator-activated receptor gamma	-7	Lys 474
	Insulin receptor kinase	-8.3	Gly1152, Met 1153
	Dipeptidyl peptidase (IV)	-8.5	Thr 351, Gly 355
	Protein Tyrosine Phosphatase 1B	-7.3	Glu 276
	α-glucosidase	-9.1	Asp 379, Val 380, Lys 398, Gly 399
	Glycogen synthase kinase 3β	-7.6	Glu 97
Cpd-2	Glucokinase	-7.3	Arg 186
	Glycogen phosphorylase	-8.8	Gln 71, Tyr 155
	Peroxisome proliferator-activated receptor gamma	-8.1	Leu453, Leu 465
	Insulin receptor kinase	-7.9	His 1130, Asp 1132, Tyr 1162
	Dipeptidyl peptidase (IV)	-9.1	Arg 669
	Protein Tyrosine Phosphatase 1B	-7.6	Arg 254
	α-glucosidase	-8.1	Val 380
	Glycogen synthase kinase 3β	-7.9	Lys 85
Cpd-3	Glucokinase	-6.9	Asn 283, Glu 290
	Glycogen phosphorylase	-9.3	Tyr 155, Arg 310
	Peroxisome proliferator-activated receptor gamma	-6.7	Leu 465
	Insulin receptor kinase	-7.8	Trp 1200
	Dipeptidyl peptidase (IV)	-9.1	Arg 669
	Protein Tyrosine Phosphatase 1B	-7.3	His 60, Gln 61
	α-glucosidase	-7.9	Val 380
	Glycogen synthase kinase 3β	-7.4	Leu 88, Glu 97
Glibenclamide	Glucokinase	-8	Gly 295, Thr 332, Arg 333
	Glycogen phosphorylase	-8.9	Tyr 155, Arg 242, Arg 310
	Peroxisome proliferator-activated receptor gamma	-8.7	Lys 275
	Insulin receptor kinase	-8.6	Arg 1000, Ala 1080, Asp1083
	Dipeptidyl peptidase (IV)	-9.1	Thr 350, Thr 351, Ser 376, Asp 588
	Protein Tyrosine Phosphatase 1B	-7.3	Glu 26, Lys 248, Lys 255
	α-glucosidase	-10	Gly 228, Ala 229
	Glycogen synthase kinase 3β	-8.1	Asn 64

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Metformin	Glucokinase	-4.6	Gly 295, Phe 330, Thr 332
	Glycogen phosphorylase	-5.4	Tyr 280, Phe 285
	Peroxisome proliferator-activated receptor gamma	-5.6	His 323, Tyr 327, Tyr 473
	Insulin receptor kinase	-4.7	Asn 1137
	Dipeptidyl peptidase (IV)	-5	Glu 205, Glu 206
	Protein Tyrosine Phosphatase 1B	-5.3	Ser 80, Ser 205, His 208
	α-glucosidase	-5.3	His 332
	Glycogen synthase kinase 3β	-4.8	Leu 343, Asp 345, Pro 346, Thr 356, His 381

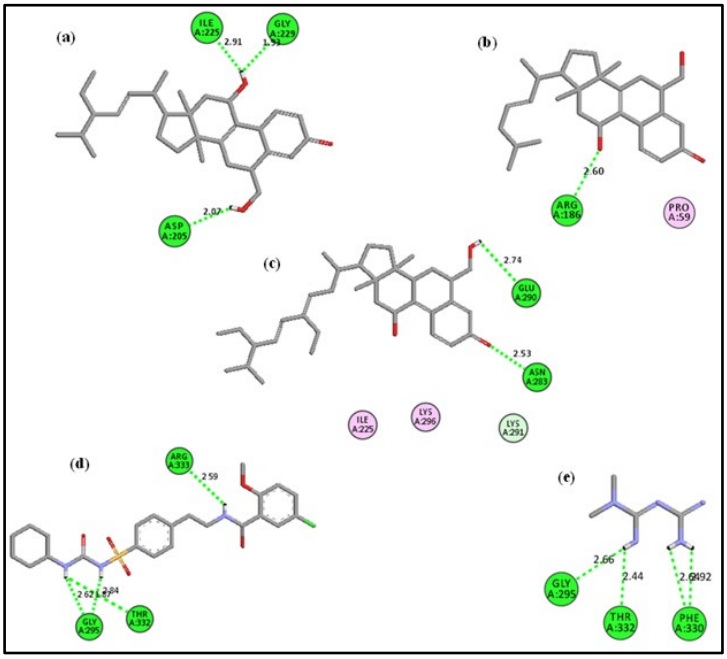

Figure 1: Molecular interactions with Glucokinase a- Cpd-1, b- Cpd-2, c- Cpd-3, d- Glibenclamide, e- Metformin. The green color represents the amino acids in the receptor proteins involved in covalent interactions forming hydrogen bonds with the ligands.

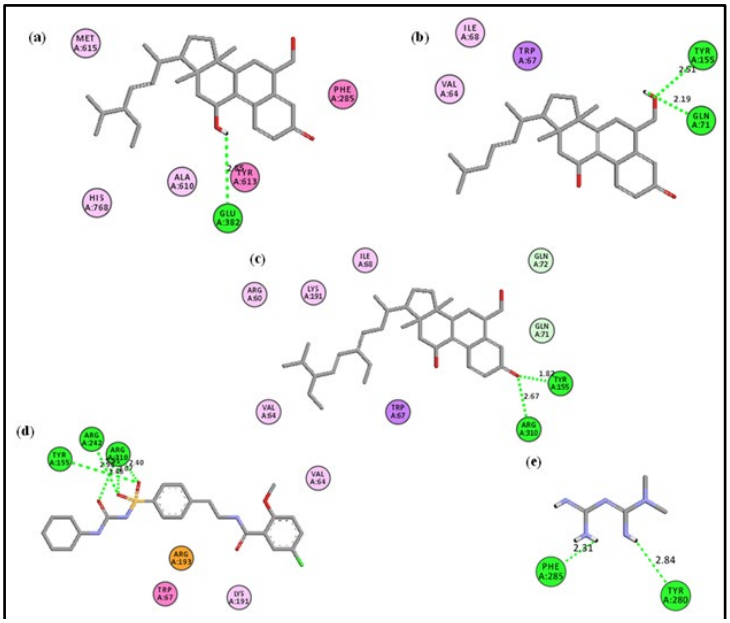

Figure 2: Molecular interactions with Glycogen phosphorylase a- Cpd-1, b- Cpd-2, c- Cpd-3, d- Glibenclamide, e- Metformin. The green color represents the amino acids in the receptor proteins involved in covalent interactions forming hydrogen bonds with the ligands.

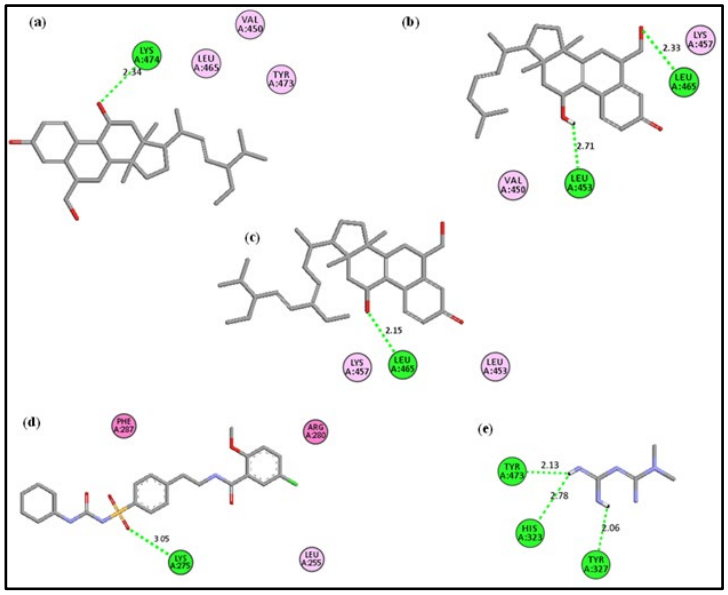

Figure 3: Molecular interactions with Peroxisome proliferator-activated receptor gamma a- Cpd-1, b- Cpd-2, c- Cpd-3, d- Glibenclamide, e- Metformin. The green color represents the amino acids in the receptor proteins involved in covalent interactions forming hydrogen bonds with the ligands.

Material and Methods:

Preparation of receptors:

The 3D X-ray crystallographic structures of the target proteins, Glucokinase (PDB ID: 1W98), Glycogen phosphorylase (PDB ID: 1W98), Dipeptidyl peptidase (IV) (PDB ID: 1W98), Protein Tyrosine Phosphatase 1B (PDB ID: 1W98), Insulin receptor kinase (PDB ID: 1IRK), Peroxisome proliferator-activated receptor gamma (PDB ID: IZGY), α-glucosidase (PDB ID: 3WY1), Glycogen synthase kinase 3β (PDB ID: 1Q4L) were obtained from Protein Data Bank (PDB) as shown in **Figure 9**. The receptors were prepared by removing the hetero-atoms and water molecules and adding polar hydrogen atoms using the Discovery Studio Visualizer 2017 R2 Client software.

Preparation of ligands:

The structures of triterpenoid compounds were drawn using ACD/Chemsketch tool and imported in mol2 format. The 3D structures of glibenclamide and metformin were downloaded from the PubChem database in SDF format. All the ligands were

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transformed to PDBQT file format and saved for PyRx-Virtual screening tool.

Molecular Docking:

The receptor proteins and ligands were docked using the PyRx Version 0.8 which enables preparing of binding site of the target protein and of screening of compound library. The results were visualized using Discovery Studio 2017 R2 Client software.

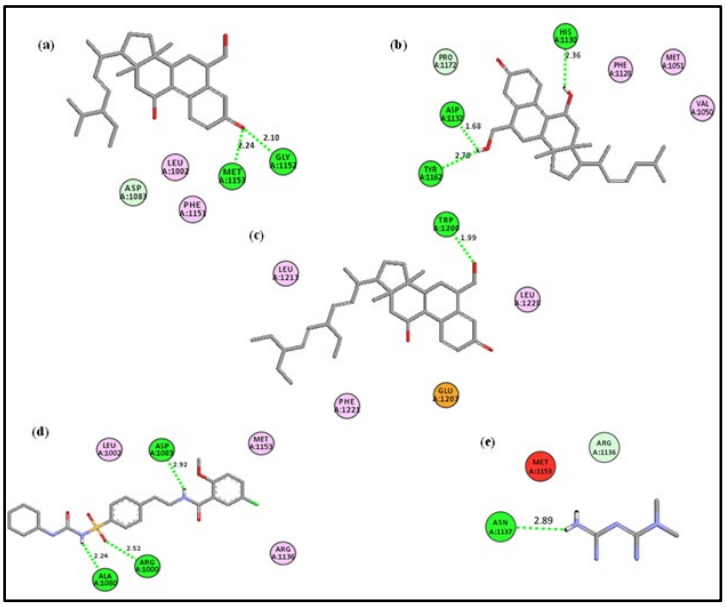

Figure 4: Molecular interactions with Insulin receptor kinase a- Cpd-1, b- Cpd-2, c- Cpd-3, d- Glibenclamide, e- Metformin. The green color represents the amino acids in the receptor proteins involved in covalent interactions forming hydrogen bonds with the ligands.

Results and discussion:

The binding affinity scores and H bond interactions of the tetracyclic triterpenoid drugs with some known diabetes targets (**Figure 9**) were calculated and the results are shown in Table 2. The hot spots produced by 50 percent consensus residues in all of the compounds docked in the same active site areas of the targets. The compounds' docking patterns were similar to those of the authorized diabetic medications glibenclamide and metformin. The findings revealed that the compounds had the lowest binding energy and the highest affinity for binding to receptors. The covalent contacts generated by the ligand with the active site residues of the targets are used to calculate the docking's stability (**Figures 1 to 8**).

Conclusion:

We document the molecular docking analysis data of tetracyclic triterpenoids from Cassia fistula L. with targets for diabetes mellitus for further consideration.

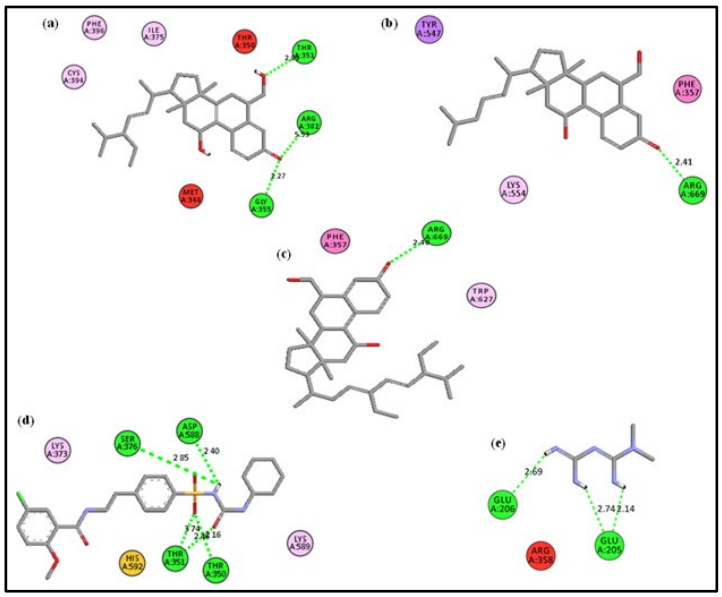

Figure 5: Molecular interactions with Dipeptidyl peptidase (IV) a- Cpd-1, b- Cpd-2, c- Cpd-3, d- Glibenclamide, e- Metformin. The green color represents the amino acids in the receptor proteins involved in covalent interactions forming hydrogen bonds with the ligands.

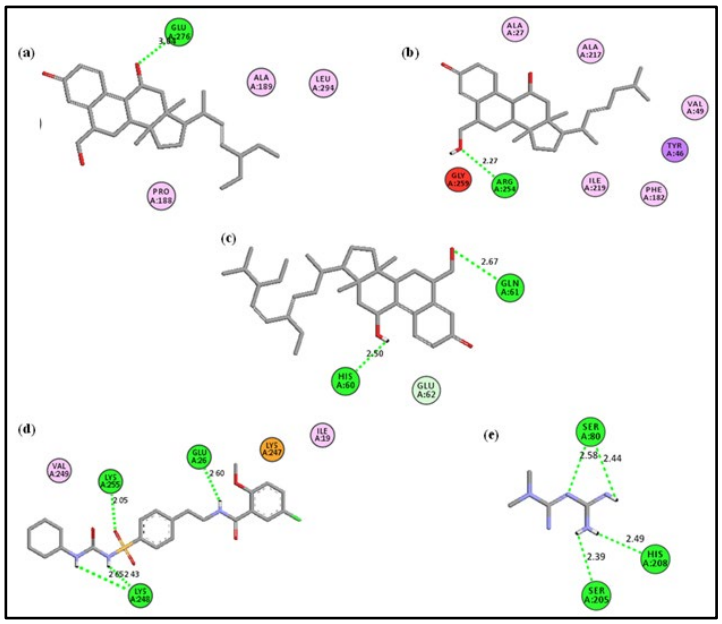

Figure 6: Molecular interactions with Protein Tyrosine Phosphatase 1B a- Cpd-1, b- Cpd-2, c- Cpd-3, d- Glibenclamide, e- Metformin. The green color represents the amino acids in the receptor proteins involved in covalent interactions forming hydrogen bonds with the ligands.

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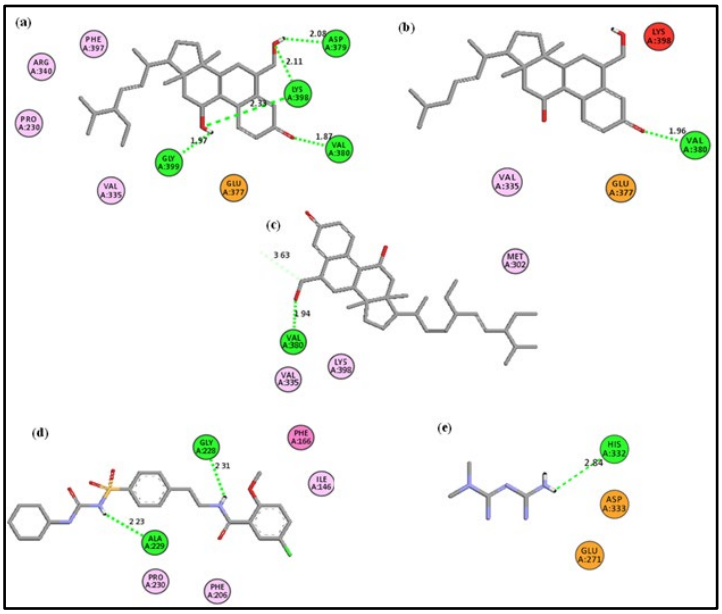

Figure 7: Molecular interactions with α-glucosidase a- Cpd-1, b- Cpd-2, c- Cpd-3, d- Glibenclamide, e- Metformin. The green color represents the amino acids in the receptor proteins involved in covalent interactions forming hydrogen bonds with the ligands.

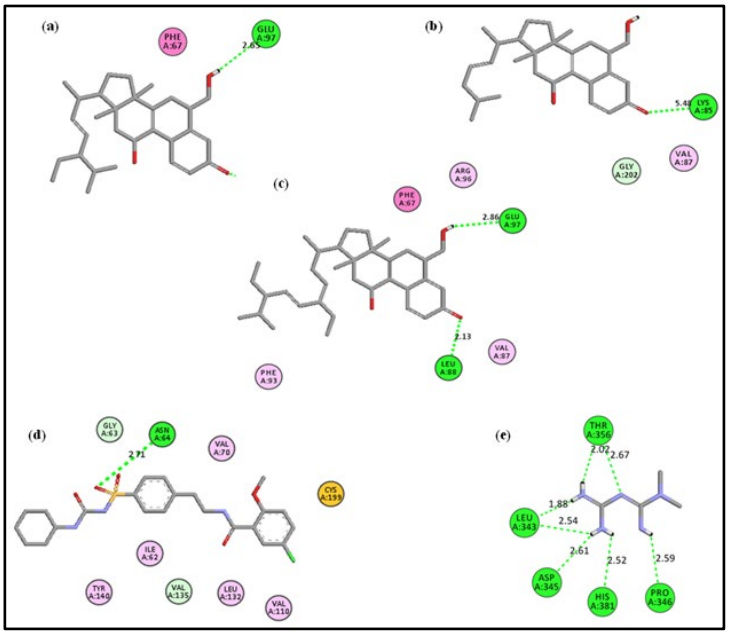

Figure 8: Molecular interactions with Glycogen synthase kinase 3β a- Cpd-1, b- Cpd-2, c- Cpd-3, d- Glibenclamide, e- Metformin. The green color represents the amino acids in the receptor proteins involved in covalent interactions forming hydrogen bonds with the ligands

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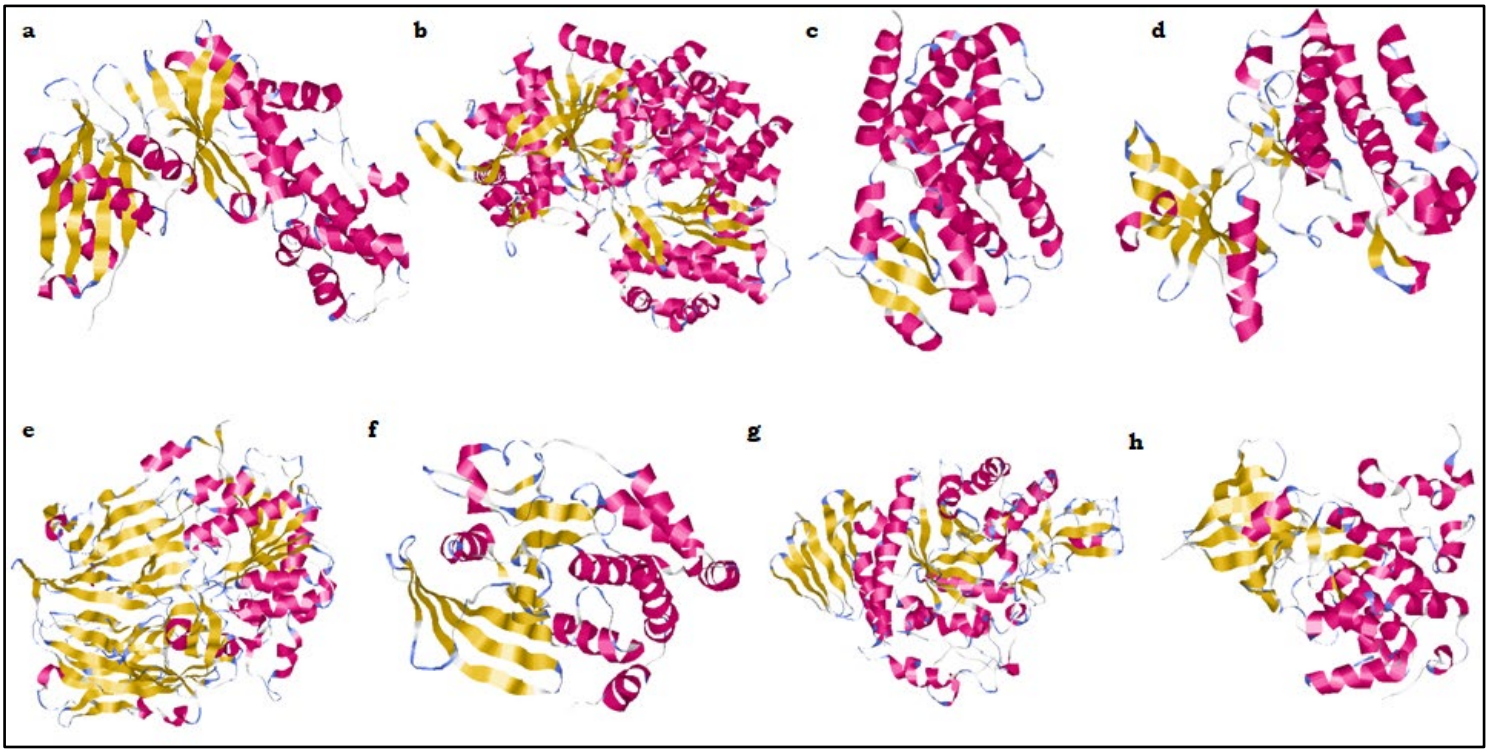

Figure 9: 3D structures of diabetic target proteins a- Glucokinase, b- Glycogen phosphorylase, c- Peroxisome proliferator-activated receptor gamma, d- Insulin receptor kinase, e- Dipeptidyl peptidase (IV), f- Protein Tyrosine Phosphatase 1B, g- α-glucosidase, h- Glycogen synthase kinase 3β.

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