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In silico antidiabetic activity of bioactive compounds in *Ipomoea mauritiana* Jacq

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Abstract
In the present study molecular interactions of 15 bioactive compounds in *Ipomoea mauritiana* Jacq viz., taraxerol, taraxerol acetate, beta-sitosterol, scopoletin, dodecanoic acid/ lauric acid, chloroacetic acid, tetradecanal/myristaldehyde, tetradecanoic acid/ Myristic acid, hexanoic acid/Palmitic acid, octadec-1-ene, octadecan-1-ol, octadecanoic acid/stearic acid, octacosane, nonacosane, tetracosane against diabetic targets namely Glutamine: Fructose – 6 -Phosphate Amidotransferase (GFAT, PDB ID - 2ZJ3) and Peroxisome proliferator activated receptor- gamma (PPARs PDB ID – 3G9E) were assessed. Molecular docking studies were performed using ArgusLab docking software 4.0.1 respectively. The docking studies of multifarious ligands with the target proteins showed good inhibitory activity, amongst the compounds screened sitosterol beta (Binding energy; 2ZJ3: -12.02 kcal/mol, 3G9E: -12.55 kcal/mol), taraxerol (Binding energy; 2ZJ3: -9.93 kcal/mol, for 3G9E: -13.70 kcal/mol) and taraxerol acetate (Binding energy; 2ZJ3: -11.58 kcal/mol, 3G9E: -13.12 kcal/mol). Sitosterol beta has shown maximum inhibition for 2ZJ3 protein whereas taraxerol shown maximum inhibition for 3G9E protein, both these phytocompounds can be further subjected to fractionation and isolation to confirm their activity towards in vitro and in vivo studies and can be commercialized as a potent antidiabetic agents.

Keywords: Ipomoea mauritiana, glutamine: fructose-6-phosphate amidotransferase, peroxisome

1. Introduction
Diabetic mellitus is a progressive metabolic disorder portrayed by disturbed protein, fat and sugar metabolism and associated complications like retino, nephro and neuropathies and macro vascular complications (Umar *et al*., 2010) [1] due to insufficient insulin secretion or action or both (Bastaki., 2005) [2] affecting peoples of all age groups worldwide (Nair, 2007) [3]. According to International Diabetes Federation (IDF, 5th Edn. of world diabetes atlas), it has been predicted that diabetes mellitus affects nearly 10% of the world population, the prevalence will increase from 135 million in 1995 to 350 million in 2030 respectively (Balamurugan *et al*., 2017, Menaka *et al*., 2010 and Amos *et al*., 2010) [4-6], which accounts from an increase from 4% to 5.4 % by the year 2025 (Ramachandran *et al*., 2002) [7]. The process of generating energy from carbohydrates does not function properly due to malfunction of pancreas, resulting in elevated glucose levels i.e., hyperglycaemia causing polyuria, polydipsia and polyphagia. The WHO reports that >347 million worldwide have diabetes mellitus, which will be seventh leading cause of death by the year 2030 (Kayarohanam and Kavimani, 2015) [8] approximately affecting about 77 million people with prediabetes in India (Kaushik *et al*., 2014) [9].
Presently there are five distinct classes of oral hypoglycemic which includes sulfonylureas, meglitinides, biguanides, thiazolidinediones and alpha glycosidase inhibitors and some under clinical trials like protein tyrosine phosphatase-1 beta inhibitors (Murthy and Kulkarni, 2002) [10]. The limitations of the oral hypoglycaemic agents includes biguanides are related with lactic acidosis, sulfonylureas with lethal hypoglycemic episodes from treatment failures, thiazolidinediones with obesity. Considering the side effects and exorbitant cost of the many current medicines, in the past few years, herbal medicines are gaining momentum in treating various diseases because of their natural origin and less or no side effects (Begum *et al*., 2017) [11, 32]. Native extracts play a decisive role in conventional medicines for the therapy of diabetes mellitus (Guasch *et al*., 2011). Nearly, more than 21,000 plants have been listed by WHO with enormous medicinal properties around the world, among them 2500 species are in India, out of which 150 species are commercially used on large scale (Seth and Sharma, 2004) [13].
The use of medicinal plants has turned out to be an alternative method for the treatment of diabetes mellitus. The recommendation of the World Health Organization Committee on

diabetes encouraging research on hypoglycemic agents of plant origin used in traditional medicine has greatly motivated research in this area (Pandey *et al*., 2013) [14]. Generally more than 90% of the world's population in the rural areas of developing countries rely solely on traditional medicines for their primary healthcare (Hassan *et al*., 2010) [15]. Literature survey reported more than 800 plants has been used for the empirical therapy for diabetes, one tenth of them is characterized as hypoglycaemic plants with active compounds like glycans, flavonoids, Triterpenes and alkaloids (Patino *et al*., 2001) [16]. Treatment of diabetes without any side effects is a challenge and hence there is a growing interest in natural drugs from medicinal plants for its treatment. Plant drugs are considered as alternative remedies due to fewer side effects and low cost (Kavishankar *et al*, 2011 & Noor *et al*., 2013) [17].

Ipomoea mouritiana Jacq. (Convolvulceae) is an outspread glabrous twining perennial ethnobotanical shrub with large tuberous roots also known as giant potato. The species is distributed throughout India in deciduous and evergreen forests and coastal tracts and widely naturalized in tropical parts of the world. The tubers are taken orally to mitigate spinal cord injury, as galactogogue, to treat tuberculosis, as appetite stimulant, aphrodisiac, blood purifier, treatment of biliary disorders (Jahan *et al*., 2013, Anzumi *et al*., 2014, Walid *et al*., 2013) [19-21]. The leaves of the plant used to treat leucorrhea, diabetes and obesity (Azad *et al*., 2014) [22]. It contains phytoconstituents such as taraxerol, taraxerol acetate, β-sitosterol, scopoletin, and 7-O-β- D-glycopyranosyl scopoletin (Khan *et al*., 2009, Dharmaratne, 1997) [23]. The GC-MS analysis of tuber of *I mauritiana* conceded the presence of 27 major phytochemical constituents with different therapeutic properties viz., 6,8 Dioxabicyclo (3,2,1) octan 3a ol - 2,2,4,4- D4, 4- acetyl butyric acid, 2- methyl 4,5 dihyroxy benzaldehyde, thiosulphuric acid, dodecanoic acid, chloroacetic acid, tetradecanal, tetradecanoic acid, E-15-Heptadecenal, Iso propyl myristate, ethyl – 3- 8- aza- bicycle- oct- 2 – ene 8 – carboxylate, hexadecen-1-ol-trans-9, Hexadecanoic acid, 1-octadecene, 9-octadecene-1-ol, 1-octadecanol, 2,2 dideutro octadecanal, 9,12, octadecadienoic acid, octadecanoic acid, 1-docosanol methyl ether, hexatricontane, 4,6 fluro coumarin, n-tetracosanol-1, hahnfett, octacosane, nonacosane, tetratetracontane respectively. The compounds identified in the tuber of *I. mauritiana* possessed various biological activities like, hexadecanoic acid – Palmitic acid (14.22%) has antioxidant and anti-inflammatory activity (Aparna *et al*., 2012) [24] and selective cytotoxicity against human leukemic cells hypocholesterolemic, nematicide, pesticide, lubricant activities (Harada *et al*., 2002) [25].

In silico virtual screening techniques are ideal for basic elementary evaluations of the possible anti-diabetic activity of conventional medicinal plants. As herbs are the complicated mixture of considerable distinctive compounds, with *in silico* screening methods, thousands of the compounds can be screened in contrast to multiple targets expeditiously and efficaciously (Chen *et al*., 2018, Dai *et al*., 2016 and Liu *et al*., 2017) [26- 28].

The present study was carried out to dock the major phytoconstituents of *Ipomoea mauritiana* viz., taraxerol, taraxerol acetate, beta-sitosterol, scopoletin, dodecanoic acid/ lauric acid, chloroacetic acid, tetradecanal/myristaldehyde, tetradecanoic acid/ Myristic acid, hexanoic acid/Palmitic acid, octadec-1-ene, octadecan-1-ol, octadecanoic acid/stearic acid, octacosane, nonacosane, tetracosane against diabetic targets like Glutamine: Fructose – 6 -Phosphate Amidotransferase (GFAT, PDB ID - 2ZJ3), a rate limiting enzyme in hexosamine biosynthetic pathway and performs a crucial role in type 2 diabetes (Paarakh, 2017 and Chou, 2004) [29, 30]. Peroxisome proliferator activated receptor- gamma (PPARs PDB ID – 3G9E) are the nuclear receptor family which controls glucose and lipid metabolism, contributing exemplary approach for diabetes treatment (Stephanie and Josep, 2010) [31]. PPAR-Gamma is considered as justifiable target to design anti-diabetic drugs (Begum *et al*., 2017) [11, 32]

2. Materials and Methods

2.1 Selection of protein and preparation of its structure

Human PPAR gamma in complex with nonanoic acids (PDB ID: 4EM9) with R value 2.1 ^{0}A, R-value free 0.235 and R value work 0.205 and Isomerase domain of human glucose: fructose-6-phosphate Amidotransferase (PDB ID: 2ZJ3) with R value 1.9 ^{0}A, R-value free 0.217 and R-value work 0.185 were selected in the present study (Rekha and Chandrashekhara, 2017) [33]. The protein structures were downloaded from protein data bank (http://www.rcsb.org/pdb/) established by Brookhaven national laboratory (BNL) in 1971 (Sheela Devi *et al*., 2015) [34] necessary hydrogen atoms were added along with Gasteiger- Marsili charges (Begum, 2017, Paarakh, 2017, Anagha, 2016) [11, 32, 29, 35]. All the solvent molecules and co-crystallized ligands were removed from the structures in order to use as a receptor for docking (Suganya and Radha Mahendran, 2016) [36] by removing the water not involved in ligand binding and ligand molecules, inserting missing atoms, and correcting the valancies (Priyanka James *et al*., 2017) [37].

2.2 Active Site

The active site is predicted using PDBsum, which is a pictorial database of 3D structures in the Protein Data Bank database. The default active site were considered of docked complexes, Amino acid within 10 ^{0}A by cogitating ligand of interest in center (Rekha and Chandrashekhara, 2017) [33].

2.3 Selection of ligand and preparation of its structure

A total of 15 ligands of *Ipomoea mauritiana* were selected by literature survey and used for the present study. They include, taraxerol, taraxerol acetate, beta-sitosterol, scopoletin, dodecanoic acid/ lauric acid, chloroacetic acid, tetradecanal/myristaldehyde, tetradecanoic acid/ Myristic acid, hexanoic acid/Palmitic acid, octadec-1-ene, octadecan-1-ol, octadecanoic acid/stearic acid, octacosane, nonacosane, tetracosane respectively. The JSmol 3D file were retrieved from Chemspider database (www.chemspider.com). Energy minimization, geometrical confirmations and hydrogen bond is supplemented by using Argus Lab 4.0.1.

2.4 Molecular Docking

The computational docking of 15 phytoconstituents of *Ipomoea mauritiana* and two enzymes viz Glutamine: Fructose – 6 -Phosphate Amido transferase (GFAT, PDB ID 2ZJ3) and Peroxisome proliferator activated receptors (PPARs PDB ID – 3EM9) were carried out by using Argus Lab 4.0.1 software. The prepared 3D structure of proteins was downloaded into the Argus Lab program and binding sites were made by choosing "Make binding site for this protein" option. The ligand was then introduced and docking calculation was allowed to run using shape-based search algorithm and A Score scoring function. The scoring function

is responsible for evaluating the energy between the ligand and the protein target. Flexible docking was conceded by formulating grids over the binding sites of the protein and energy stationed rotation is set for that ligand's group of atoms that don't have rotatable bonds. For separate rotation, torsions are created and poses (conformations) are generated during the docking mechanism. The best docking model was selected according to the lowest A score calculated by Argus Lab and the most suitable binding conformation was selected on the basis of hydrogen bond interactions between the ligand and protein near the substrate binding site. The lowest energy poses (highest negative value) indicate the highest binding affinity as high energy produces the unstable conformations (Joy *et al*., 2006, Shiny *et al*., 2015). Argus Lab is implemented with shape based search algorithm. Docking has been done using "Argus Dock" exhaustive search docking function of Argus Lab with grid resolution of 0.4^0A. Docking precision was set to ˚ "Regular precision" and "Flexible" ligand docking mode was employed for each docking run. The stability of each docked pose was evaluated using Argus Lab energy calculations and the number of hydrogen bonds formed (Thomson, 2004) [38].

3. Results

Table 1: Characteristics of Phytoconstituents of *Ipomoea mauritiana* Jacq.

Sl No.	Compound name	Chemspider ID	Molecular formula	Average mass (in Dalton)
1	Taraxerol	83146	$C_{30}H_{50}O$	426.717
2	Taraxerol acetate	85034	$C_{32}H_{52}O_2$	468.754
3	Sitosterol beta	192962	$C_{29}H_{50}O$	414.707
4	Scopoletin	4444113	$C_{10}H_8O$	192.168
5	Dodecanoic acid / Lauric acid	3756	$C_{12}H_{24}O_2$	200.318
6	Chloroacetic acid	10772140	$C_2H_3ClO_2$	93.982
7	Tetradecanal	29031	$C_{14}H_{28}O$	212.372
8	Tetradecanoic acid / Myristic acid	10539	$C_{14}H_{28}O_2$	228.371
9	Hexanoic acid	8552	$C_6H_{12}O_2$	116.158
10	Octadec-1-ene	10539	$C_{14}H_{28}O_2$	228.37
11	Octadecan-1-ol	7928	$C_{18}H_{38}O$	270.49
12	Octadecanoic acid	5091	$C_{18}H_{36}O_2$	284.477
13	Octacosoic acid / Montanic acid	10038	$C_{28}H_{56}O_2$	424.743
14	Nonacosane	11903	$C_{29}H_{60}$	408.787
15	Tetracosane	12072	$C_{24}H_{50}$	338.654

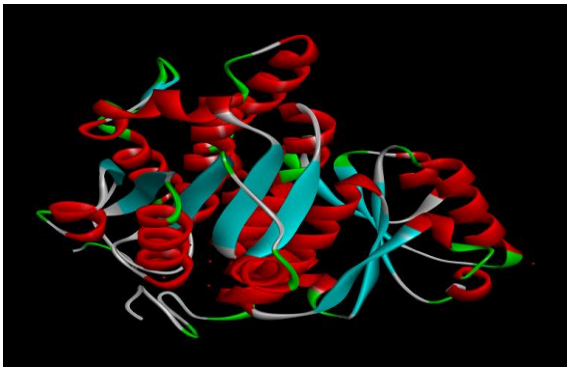

Fig 1: Crystal structure of Glutamine: Fructose – 6 -Phosphate Amidotransferase (GFAT, PDB ID 2ZJ3)

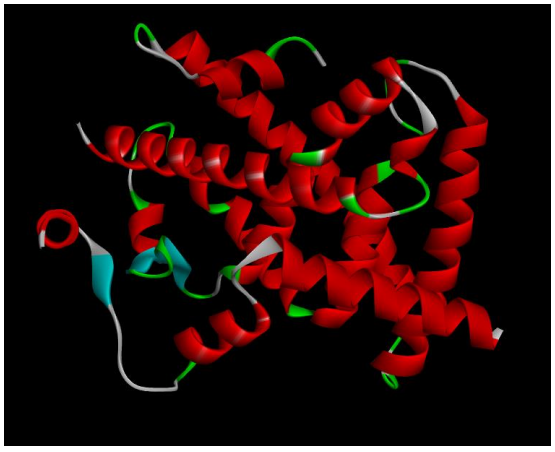

Fig 2: Crystal structure of Peroxisome proliferator activated receptors (PPARs PDB ID – 3EM9)

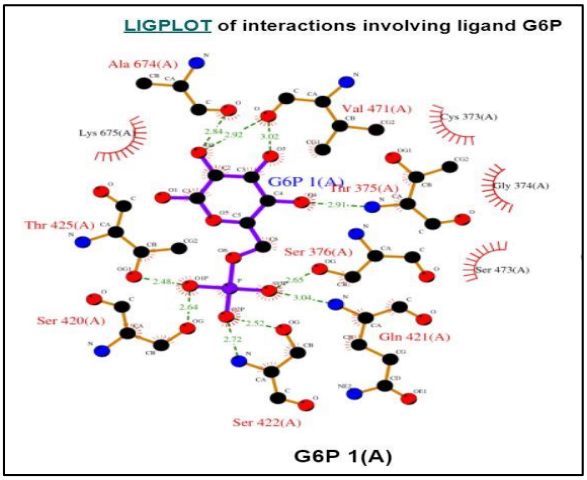

Fig 3: PDBsum calculation on the active site residue of Glutamine: Fructose – 6 -Phosphate Amidotransferase (GFAT, PDB ID 2ZJ3)

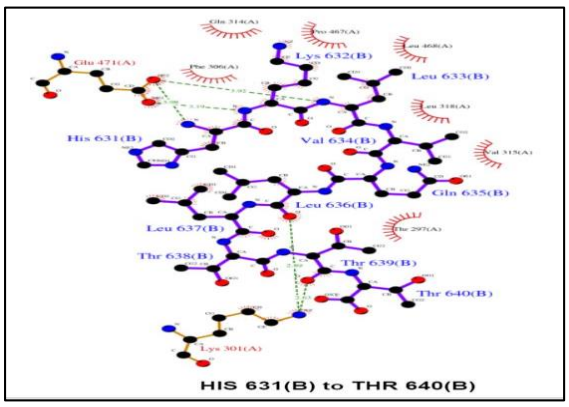

Fig 4: PDBsum calculation on the active site residue of Peroxisome proliferator activated receptors (PPARs PDB ID – 3EM9)

Table 2: PDBsum calculation on the active site residue of Glutamine: Fructose – 6 -Phosphate Amidotransferase (GFAT, PDB ID 2ZJ3) and Peroxisome proliferator activated receptors (PPARs PDB ID – 3EM9)

Sl No.	Protein module	Contacts	Active site residues
1	Glutamine: Fructose – 6 -Phosphate Amidotransferase (GFAT, PDB ID - 2ZJ3)	Non bonded contacts	CYS 373, GLY 374, THR 375, SER 376, SER 420, GLN 421, SER 422, THR 425, VAL 471, SER 473, ALA 674, LYS 675
		Hydrogen bonds	THR 375, SER 376, SER 420, GLN 421, SER 422, THR 425, VAL 471, ALA 674
2	Peroxisome proliferator activated receptor- gamma (PPARs PDB ID – 3G9E)	Non bonded contacts	THR 297, LYS 301, PHE 306, GLN 314, VAL 315, LEU 318, PRO 467, LEU 468, GLU 471,
		Hydrogen bonds	LYS 301, GLU 471,

Table 3: Docking results of Glutamine: Fructose 6 Phosphate Amidotransferase (GFAT, PDB ID: 2ZJ3) with ligands of *Ipomoea mauritiana* Jacq

Sl No.	Drug / Ligands	Maximum number of poses	Number of ligand torsions	Precision	Search points	Total Grid points	Best ligand pose energy (kcal/mol)
1	Chloroacetic acid	150	1	Regular	11793	16007	-6.33
2	Dodecanoic acid	150	10	Regular	11689	16007	-8.52
3	Hexanoic acid	150	4	Regular	11689	16007	-8.13
4	Nonacosane	150		Regular	12199	16007	
5	Octacosoic acid	150	26	Regular	11688	16007	-7.86
6	Octadec-1-ene	150	15	Regular	12198	16007	-7.98
7	Octadecan-1-ol	150	17	Regular	12198	16007	-9.26
8	Octadecanoic acid	150	16	Regular	11589	16007	-8.69
9	Scopoletin	150	3	Regular	10121	16007	-7.56
10	Sitosterol beta	150	7	Regular	6643	16007	-12.02
11	Taraxerol acetate	150	2	Regular	3224	16007	-11.58
12	Taraxerol	150	1	Regular	3242	16007	-9.93
13	Tetracosane	150	11	Regular	12199	16007	-8.26
14	Tetradecanal	150	12	Regular	12198	16007	-8.59
15	Tetradecanoic acid	150	12	Regular	11688	16007	-7.86

Table 4: Docking results of Peroxisome proliferator activated receptor- gamma (PPARs PDB ID – 3G9E) with ligands of *Ipomoea mauritiana* Jacq

Sl No.	Drug / Ligands	Maximum number of poses	Number of ligand torsions	Precision	Search points	Total Grid points	Best ligand pose energy (kcal/mol)
1	Chloroacetic acid	150	1	Regular	8245	11267	-6.43
2	Dodecanoic acid	150	10	Regular	8152	11267	-11.64
3	Hexanoic acid	150	4	Regular	8154	11267	-8.49
4	Nonacosane	150	18	Regular	8146	11267	-9.05
5	Octacosoic acid	150	26	Regular	8152	11267	-9.23
6	Octadec-1-ene	150	13	Regular	8531	11267	-8.36
7	Octadecan-1-ol	150	12	Regular	8530	11267	-9.06
8	Octadecanoic acid	150	16	Regular	8150	11267	-8.64
9	Scopoletin	150	3	Regular	6956	11267	-8.50
10	Sitosterol beta	150	7	Regular	4430	11267	-12.55
11	Taraxerol acetate	150	2	Regular	2069	11267	-13.12
12	Taraxerol	150	1	Regular	2049	11267	-13.70
13	Tetracosane	150	8	Regular	8530	11267	-8.69
14	Tetradecanal	150	12	Regular	8531	11267	-10.97
15	Tetradecanoic acid	150	12	Regular	8152	11267	-11.07

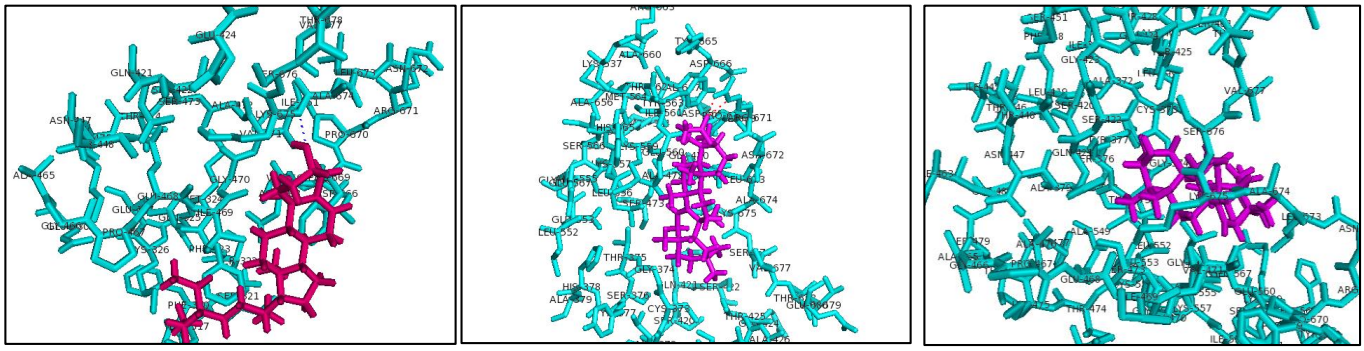

Fig 5: Docking interactions of Sitosterol beta, Taraxerol acetate and Taraxerol with active sites of Glutamine: Fructose 6 Phosphate Amidotransferase

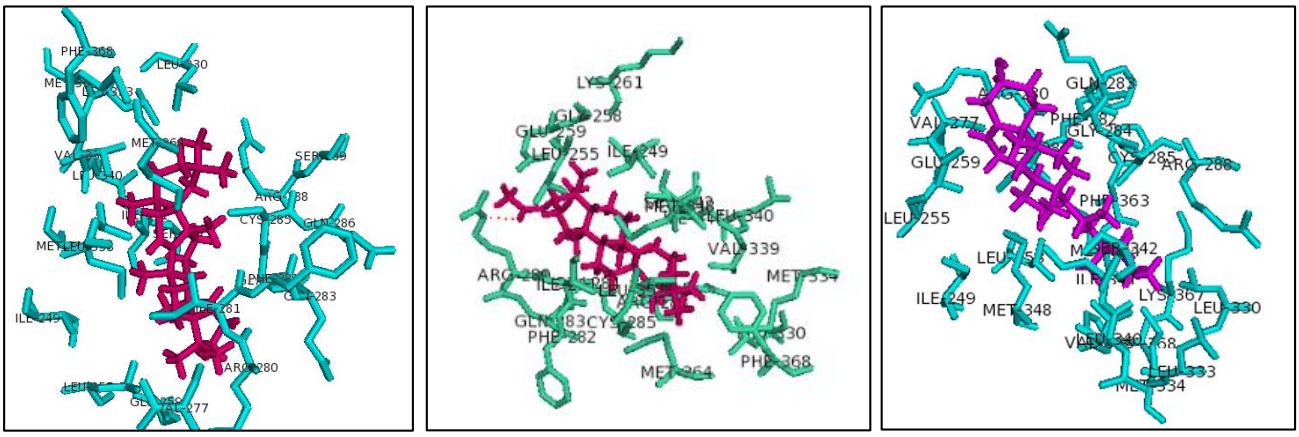

Fig 6: Docking interactions of Taraxerol, Taraxerol acetate and Sitosterol beta with active sites of Peroxisome proliferator activated receptor-gamma (PPARs PDB ID – 3G9E)

4. Discussion

Computer aided drug design (CADD) is one of the prodigious methods bestowing in the field of drug discovery and development in the recent years. The process of designing and developing a drug is a time consuming and expensive process, on an average it takes 10-15 years and $ 500-800 million to introduce a drug in to market (Song *et al*., 2009) [39]. In these regard, CADD approaches has been extensively used in the pharmaceutical industries to expedite the process of drug development, which bolstered the scientist in focusing on most promising compounds to curtail the biological testing efforts (Selvaraj, 2018) [40].

Ipomoea mauritiana Jacq, a ubiquitous plant in many parts of the world, taken orally to alleviate spinal cord pain and as galactogogue (Jahan *et al*., 2013) [19]. The tubers are used to treat tuberculosis and as appetite stimulants (Anzumi *et al*., 2014) [20]. Bangladeshi medicinal folk practitioners used the leaves of the plants to treat leucorrhea and diabetes with obesity (Azad *et al*., 2014) [22]. In the present study the bioactive phytoconstituents of the plants are used to predict the potential ligand molecule having antidiabetic activity.

Glutamine: Fructose-6-Phosphate Amidotransferase (GFAT) is a key enzyme in the hexoamine biosynthetic pathway and plays an imperative role in type 2 diabetes. The intensified activity of GFAT has been involved in insulin resistance in both animal and cellular models. The enzyme controls the influx of glucose in to the hexosamine pathway and mediates the formation of glucosamine – 6- phosphate, it also regulates the products of hexosamine pathway. Thus the enzyme is perceived as an interesting possible target for type 2 diabetes complications (Paarakh, 2017 & Chou, 2004) [29, 30]. Peroxisome proliferator activated receptors (PPARs) belongs to nuclear receptor family are ligand triggered transcription factors bind to specific DNA response elements as heterodimers with retinoid X receptors (RXR) and regulates lipid and glucose metabolism, offering distinguished therapeutic approach for treating diabetes. (Stephanie and Josep, 2010) [31]. Specifically, PPARγ, one of the isoforms, is highly sensitivity and glucose tolerance (Dusica *et al*., 2011). PPARγ is considered as legitimate target to design anti-diabetic drugs and PPARγ agonists are effective to control diabetes, however due to side effects of these existing drugs there is a pressing need for the retrieval of new ligands/agonists with antidiabetic activity with minimum or no side effects. Using bioinformatics approach, the novel ligands are identified from Indian herbal plants (Begum *et al*., 2017) [11, 32].

The present study was carried out to examine whether the bioactive components of *Ipomoea mauritiana* as ligands with diabetic targets like Glutamine: Fructose – 6- phosphate Amidotransferase and Peroxisome proliferator activated receptors (PPARs). An extensive docking was carried out using 15 active phytoconstituents of the plant as ligand with two diabetic targets viz GFAT and PPARγ using Autodock 4.0.1 respectively. The present study revealed that amidst phytoconstituents screened for the antidiabetic activity with two targets, sitosterol beta with binging energy of -12.02 followed by taraxerol acetate with binding energy of -11.58 and taraxerol with binding energy of -9.93 for Glutamine: Fructose 6 Phosphate Amidotransferase (GFAT) and first three most potent avitve component for Peroxisome proliferator activated receptor- gamma (PPARγ) includes taraxerol with binding energy -13.70, taraxerol acetate with binding energy of -13.12 and sitosterol beta with binding energy of -12.55 respectively. In both the studies sitosterol beta, taraxerol and taraxerol acetate have shown highest inhibitory action against the protein mediating diabetes. Beta sitosterol is an active phytosterol useful in the treatment of hypercholesterolemia, prostate cancer, breast cancer, coronary heart disease and diabetes mellitus (Matsuoka *et al*., 2008 and Rajnish *et al*., 2011) [42], the mechanism underlying the therapeutic potential may be attributed to the apoptosis induced by increased FAS levels and caspase activity (Aguirre-Hernandez *et al*., 2007) [43], phosphorylation of extracellular signal regulated kinase (Awad *et al*., 2007) [44] and mitogen activated protein kinase (Moon *et al*., 2007) [45]. Taraxerol and its acetate is a triterpenoids compound isolated from multifarious medicinal plants known to exhibit anti-inflammatory, anticancerous activity, antidiabetic and cytoprotective activity (Tsao *et al*., 2008, Takasaki *et al*., 1999, Setzer *et al*., 2000, Jang *et al*., 2004, Sangeetha *et al*., 2013 and Sangeetha *et al*., 2010). The present investigation also shows critical findings regarding anticancerous activity of sitosterol beta, taraxerol and taraxerol acetate.

5. Conclusion

As Diabetes Mellitus is epidemic throughout the world, effective drugs with less/no toxicity need to be developed. And one such way is the use of herbal medicines which will have no side effects. Docking studies of phytoactive compounds in *Ipomoea mauritiana* Jacq against two crucial anticancer drug targets related to diabetes mellitus showed conducive results with prominent inhibitory activity was observed with sitosterol beta, taraxerol and taraxerol acetate

with Glutamine: Fructose-6-Phosphate Amidotransferase (GFAT) and Peroxisome proliferator activated receptors (PPARs) respectively. Thus the mentioned drugs can be used for developing in to a potent antidiabetic drugs.

6. References

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