



Research Article

ISSN: 2454-5023
J. Ayu. Herb. Med.
2023; 9(2): 89-97
Received: 22-03-2023
Accepted: 31-05-2023
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www.ayurvedjournal.com
DOI: 10.31254/jahm.2023.9207

Virtual screening, Docking and ADMET analysis of bioactive compounds from the Indian medicinal plants for the treatment of Diabetes Mellitus

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ABSTRACT

Background: Diabetes mellitus (DM) is a metabolic condition defined by persistent hyperglycemia caused by either insufficient insulin production by the pancreas or inability of peripheral target tissues to respond to normal insulin concentrations. The present study was designed to find the bioactive compounds from the Indian medicinal plants for the treatment of Diabetes mellitus using Virtual screening, Docking and ADMET studies. The 3D structure of phytochemicals was obtained using IMPPAT and PubChem database. The Lipinski rule of five for all the phytochemicals was tested using SwissADME. The sequence of the target protein was retrieved from the UniProt database and modelled using Swiss-Model. The docking studies were performed using PyRx and the results were analyzed using Discovery Studio 2021. **Results:** The phytochemicals Taraxerol, Obtusifoliol and Kulactone showed very good binding affinity like -9.7, -9.7 and -9.4 Kcal/mol, respectively. Toxicity studies were done for the best-interacted phytochemicals and the results showed that the compounds had very less toxicity. **Conclusion:** The present study concludes that Taraxerol from *Coccinia grandis*, Obtusifoliol and Kulactone from *Azadirachta indica* and may have a potential ability in the treatment of Diabetes Mellitus.

Keywords: Diabetes Mellitus, Phytochemicals, Molecular Docking, PyRx, Discovery Studio, ADMET properties.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a serious global disease marked by chronic hyperglycemia, decreased insulin production, and/or insulin function [1]. Adult diabetes prevalence was estimated at 8.4 percent in 2017 and is expected to climb to 9.9 percent by 2045 [2]. The International Diabetes Federation (IDF) reported in 2013 that 10.9 percent of people in North Africa and the Middle East had diabetes [3]. Obesity and physical inactivity are the primary causes of T2DM [4]. It's linked to both macro and microvascular problems, as well as abnormalities in bone and mineral metabolism [5,6].

Diabetes mellitus (DM) is a metabolic condition defined by persistent hyperglycemia caused by either insufficient insulin production by the pancreas or inability of peripheral target tissues to respond to normal insulin concentrations [7,8]. It is the world's fastest growing disease and a major source of morbidity and mortality, with an increasing prevalence [9,10]. According to the WHO, diabetes affects 347 million people worldwide, resulting in 4.6 million deaths each year. In 2030, the prevalence is predicted to quadruple, with the majority of the rise occurring in Asia, Africa, and South America's low- to middle-income countries [10].

Diabetes is a chronic condition that arises when the pancreas does not create enough insulin (Type 1 Diabetes) or when the body's insulin is not used efficiently (Type 2 Diabetes) (Type 2 Diabetes). Uncontrolled diabetes causes hyperglycemia, or high blood sugar, which can lead to blindness, kidney failure, heart attacks, strokes, and lower limb amputation, among other complications [11].

Type 2 diabetes has become a global chronic epidemic, accounting for 90% of all diabetes cases [12-14]. Diabetes has high personal, societal, and economic consequences, putting great strain on healthcare systems [14]. According to the International Diabetes Federation, half a billion people worldwide have diabetes [15]. In 2015, the global economic burden of diabetes was estimated to be \$1.3 trillion, or about 1.8 percent of global gross domestic product [16]. People with type 2 diabetes use a lot of healthcare resources, including inpatient and outpatient hospital care, visits to general practitioners, endocrinologists, and other specialists, allied health services like podiatry, dietetics, and optometry, and a lot of prescription drugs and medical supplies [17]. Because of recent changes in the food supply and

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dietary patterns, as well as decreased physical activity, most populations are witnessing an increase in obesity and diabetes [18].

Polyuria (generating 8–16 L of dilute urine per day) and polydipsia are the main signs of DI (intake of up to 20 L fluid per day). Dizziness, weakness, nocturia, weariness, and indicators of dehydration are some of the other symptoms (fever, dry skin and mucus membranes, weight loss, poor skin turgor). Hypotension and tachycardia, as well as altered levels of consciousness and decreased right atrial and pulmonary artery occlusion pressures, may occur. Severe dehydration, vomiting, constipation, fever, irritability, sleep disruptions, development retardation, and failure to thrive can all occur in young children. Dehydration that goes unnoticed might lead to mental impairment [19,20].

Periphery, which includes skeletal muscle However, it should not be taken in those who have liver or kidney disease. Metformin's major usage is in the treatment of diabetes mellitus type 2, particularly in overweight patients. Biguanides reduce hepatic glucose production and enhance glucose absorption. Metformin increases insulin sensitivity, promotes peripheral glucose uptake (by phosphorylating GLUT-4 enhancer factor), increases fatty acid oxidation, and lowers glucose absorption from the gastrointestinal tract in addition to reducing hepatic glucose synthesis. Improved insulin binding to insulin receptors could explain the increased peripheral glucose consumption [21-23].

Thiazolidinediones improve insulin resistance in the gastrointestinal tract by activating PPAR-. Increased liver enzymes, weight gain, edema, and moderate anaemia are all side effects of these drugs [21]. Inhibitors of alpha-glucosidase (Miglitol, Acarbose) Because they have no direct effect on insulin secretion or sensitivity, these are not officially hypoglycemic agents. These drugs reduce starch digestion in the small intestine, allowing glucose from a starchy meal to enter the bloodstream more slowly and be better matched by a compromised insulin response or sensitivity. The fats and muscles are the sites of action. It is particularly efficient in treating type 2 diabetes. - Glucosidase inhibitors lower postprandial plasma triglyceride levels in diabetics, but they come with serious side effects such as diarrhoea, stomach pain, and flatulence, as well as an increase in serum transaminase levels at higher doses [24].

Biguanides, such as metformin (which act directly to influence insulin resistance), PPAR activators, such as thiazolidinediones (which improve insulin resistance), vidagliptin and other related "gliptins" (which block DPP-4, an enzyme that degrades the incretin GLP-1) and -glucosidase inhibitors, such as acarbose and miglitol (which block DPP-4, an enzyme (via delaying the digestion of complex carbohydrates). Other diabetic drugs bind to the sulfonylurea receptor subunit of pancreatic beta-cell receptors, inhibiting the K⁺-ATP channel and promoting insulin release [25,26]. Furthermore, combination therapy (e.g., sulfonylureas with biguanides, thiazolidinedione with glucosidase inhibitors) are frequently employed to broaden therapeutic targets and reduce adverse effects.

Alternative medicine's application in disease treatment has recently expanded, attracting the interest of numerous researchers throughout the world [27]. Several researches have looked into the possible benefits of various medicinal plants in diabetic patients [28,29]. One of these

plant-based medicines is *Camellia sinensis* (L.) Kuntze, also known as green tea. It includes catechins like epigallocatechin-3-gallate (EGCG), as well as quercetin, arubigins, theaflavins, theanine, caffeine, chlorogenic acid, and gallic acid [30,31]. Green tea drinking significantly lowered circulating levels of fasting glucose, HbA1c, and fasting insulin, according to a meta-analysis of 17 randomised controlled trials (RCTs) that included both healthy people and patients with chronic disease such as obesity, T2DM, or hypertension [32].

In the present study, the medicinal plants like *Coccinia grandis* [33], *Azadirachta indica* [34], *Trigonella foenum-graecum* [35], *Momordica charantia* [36], *Syzygium cumini* [37], *Zingiber officinale* [34], were taken to find the bioactive compounds for treating Diabetes mellitus.

MATERIALS AND METHODS

Ligand selection

Using literature and IMPPAT database [38] around 430 phytochemical compounds were selected from the different Indian medicinal plants like *Coccinia grandis* [33], *Azadirachta indica* [34], *Trigonella foenum-graecum* [35], *Momordica charantia* [36], *Syzygium cumini* [37], *Zingiber officinale* [34], for treating Diabetes. The 3D structure of phytocompounds was retrieved from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>) and using Swiss ADME [39] they were subjected to test Lipinski Rule of Five. From the results, 363 compounds obeyed Lipinski Rule of Five and these compounds were taken for further study.

Target protein selection

The target protein Peroxisome Proliferator - Activated Receptor gamma (PPAR γ) was found in the literature for Diabetes.[40] The 3D structure of this target protein was retrieved from the PDB database.[41] The UniProt ID of this target protein was taken from the Uniprot database [42].

Docking studies

Docking studies for the target protein PPAR γ and the phytocompounds (ligands) were done using PyRx 0.8 software.[43] The target protein was further prepared for docking studies using this software. All the ligands were uploaded using Open Babel option in the PyRx 0.8. The grid was generated and the docking studies were performed using Vina wizard option in the PyRx 0.8. The values of binding affinity were saved in XL file. The results were analyzed using Discovery Studio 2021 and the 2D and 3D docked images were taken. In the results, the lowest binding affinity indicates good result.

ADMET and CYP properties

ADMET and CYP properties were tested for all the best-interacted phytocompounds using Swiss ADME [39]. Lipinski, BBB (Blood - Brain Barrier), HIA (Human Intestinal Absorption), PGP (P-glycoprotein), XLogP3, TPSA (Topological Polar Surface Area), LogS, Fraction Csp3, Rotatable bonds, CYP enzyme inhibitor properties, Skin permeation and Bioavailability score were evaluated for all the best-interacted compounds.

RESULTS AND DISCUSSION

Ligand and Target Protein selection

The 3D structure of ligands (phytocompounds) was retrieved from the PubChem database. The 3D structure of the target protein PPAR γ was obtained from PDB database and its PDB ID is 2PRG. The 3D structure of the target protein is shown in figure 1.



Figure 1: The 3D Structure of Target Protein PPAR γ

Docking studies

Docking studies were done for the phytocompounds, from the different Indian medicinal plants and the target protein PPAR γ using PyRx 0.8 software to find the potential drug candidate for Diabetes mellitus. For this, 363 phytocompounds which has passed Lipinski Rule of Five were interacted with the target protein using this software. The

results were analyzed using the Discovery Studio 2021 software and binding affinity values were noted. In which, 10 compounds showed very good results with the target protein. Further, the Synthetic drug Rosiglitazone was also taken to find the interaction with the target protein. All the docking results are shown in Table 1. The 2D and 3D interactions of the phytocompounds and Synthetic drug Doxorubicin with the target protein are shown in Figures 2-9.

Table 1: Interaction of Phytocompounds with the Target Protein

S. No.	PubChem (CID)	Compound Name	Plant Name	Binding Affinity (Kcal/mol)	No. of Bonds	Interacting Residues	Bond Length (Å)
1.	92097	Taraxerol	<i>Coccinia grandis</i>	-9.7	1	GLU 259	2.71
2.	65252	Obtusifoliol	<i>Azadirachta indica</i>	-9.7	2	ARG 288 LEU 330	4.20 5.05
3.	15560423	Kulactone	<i>Azadirachta indica</i>	-9.4	4	ARG 288 LEU 330 LEU 377 LEU 377	4.63 5.42 4.95 5.06
4.	441900	Yamogenin	<i>Trigonella foenum-graecum</i>	-9.3	6	LEU 340 LEU 5.38 ARG 288 CYS 285 LEU 270 THR 268	3.37 5.38 4.52 4.58 5.47 2.29
5.	489919	Hennadiol	<i>Coccinia grandis</i>	-9.3	5	GLN 271 ARG 280 ARG 280 ICE 281 GLU 291	2.98 2.93 5.30 4.83 2.07
6.	101699624	Stigmasta-7,22,25-trien-3beta-ol	<i>Momordica charantia</i>	-9.3	8	MET 364 VAL 339	5.18 3.69

						LEU 330 ARG 280 ARG 280 GLU 259 ILE 341 ARG 288	4.69 2.53 5.39 2.46 5.17 3.85
7.	521229	AC1LAVB6	<i>Momordica charantia</i>	-9.3	4	ILE 341 ARG 288 ARG 280 GLN 271	5.33 4.05 4.91 1.91
8.	101341	epi-Friedelinol	<i>Syzygium cumini</i>	-9.2	1	PHE 347	3.86
9.	5742590	Daucosterol	<i>Syzygium cumini</i>	-9.2	5	CYS 285 LEU 330 ARG 288 LYS 265 LYS 265	4.07 4.29 4.07 2.49 2.69
10.	20055192	Apo-6'-lycopenal	<i>Coccinia grandis</i>	-9.1	8	LEU 270 ILE 249 PHE 247 LYS 244 LYS 261 LYS 261 ILE 262 ILE 262	4.09 5.37 4.68 4.17 5.23 4.72 4.83 5.28
SYNTHETIC DRUG							
11.	77999	Rosiglitazone	Synthetic drug	-6.4	7	GLY 284 ARG 280 ARG 280 GLU 259 ILE 262 LEU 270 GLU 272	3.41 3.34 3.57 3.17 5.32 3.46 4.02

From the results (Table 1), among other compounds, 10 compounds showed very good results with the target protein PPAR γ . Of which, the phytocompound Taraxerol showed very good binding affinity (-9.7 Kcal/mol) with the amino acid residues GLU 259 of the target protein. The phytocompound Obtusifoliol also gave very good binding affinity of (-9.7 Kcal/mol) with the amino acid residues. The binding affinity -9.4 Kcal/mol was observed between the phytocompound Kulactone and the amino acid residues ARG 288, LEU 330, LEU 377 of target protein. Among the other 10 compounds, the lowest binding affinity (-9.1 Kcal/mol) was observed between the phytocompound Apo-6'-lycopenal and the amino acid residues LEU 270, ILE 249, PHE 247, LYS 244, LYS 261, ILE 262 of target protein. Besides, the binding affinity of the Synthetic drug Rosiglitazone with the target protein was (-6.4 Kcal/mol) and the interacted the amino acid residues were GLY 284, ARG 280, GLU 259, ILE 262, LEU 270, GLU 272. Besides, in the present study, all the ten phytocompounds showed very good binding affinity, when compared to the Synthetic drug Rosiglitazone.

Further, a recent study reported that in diabetes mellitus, *Zingiber officinale* (ginger) exhibits effective glycaemic control capabilities.^[34] Another study stated that *Momordica charantia* has been utilised as a dietary supplement and ethnomedicine to treat symptoms and illnesses associated with diabetes.^[44] Traditional medicine has employed the Jamun, *Syzygium cumini*, a member of the Myrtaceae family, to cure diabetes.^[37] Earlier study found that *Azadirachta indica* leaf extract may play a key role in the management of type 2 diabetes mellitus.^[45]

A previous study found that EGCG from *Camellia sinensis*, and Glucobrassicin from *Capparis spinosa* and *Brassica oleracea* interacted with the target protein PPAR γ and showed good Glide score.^[46] Similarly, in the present study, among the other phytocompounds, the phytocompounds Taraxerol, Obtusifoliol and Kulactone interacted with the target protein PPAR γ and showed highest binding affinity of -9.7, -9.7 and -9.4 Kcal/mol, respectively.

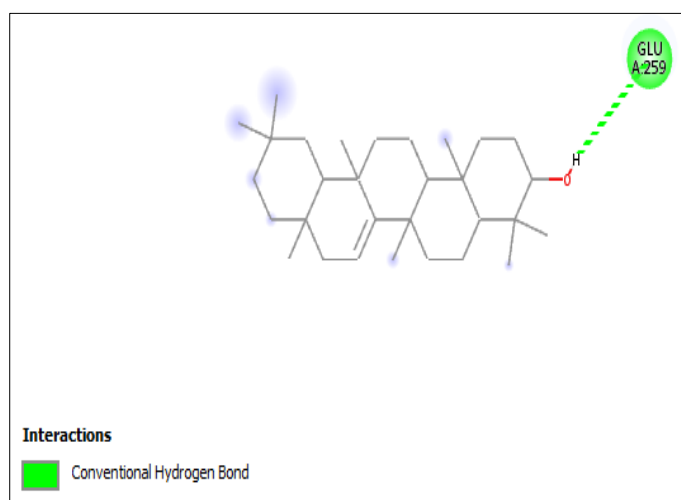


Figure 2: The 2D Interaction of Phytocompound Taraxerol with the Target Protein.

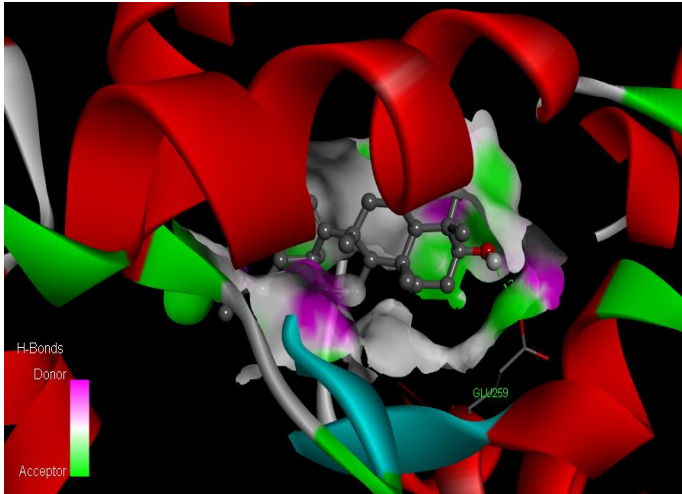


Figure 3: The 3D Interaction of Phytocompound Taraxerol with the Target Protein.

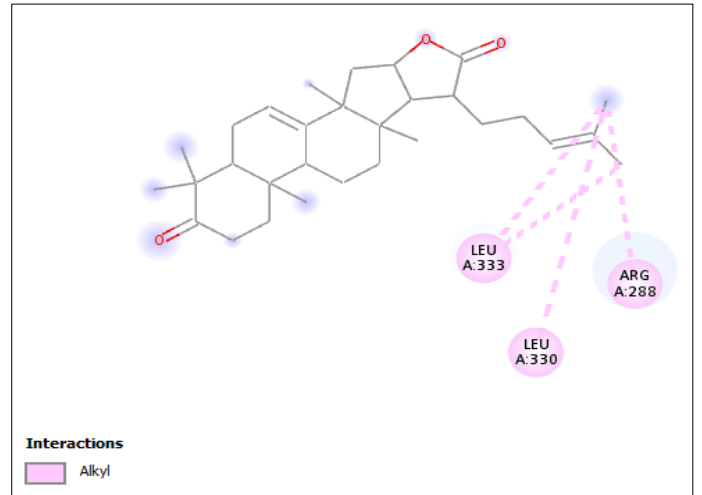


Figure 6: The 2D Interaction of Phytocompound Kulactone with the Target Protein.

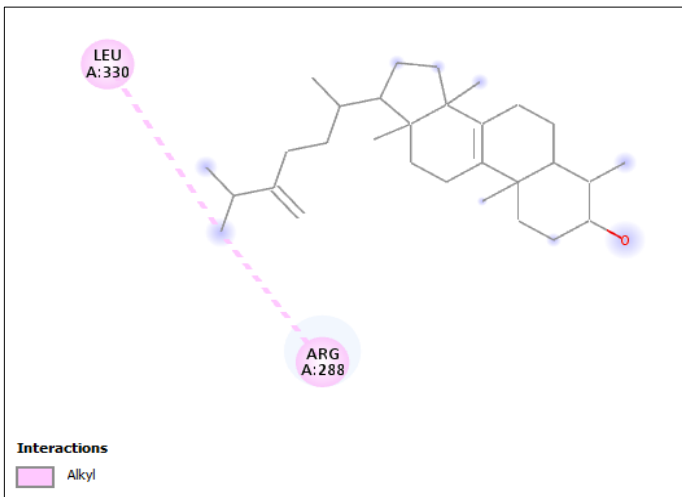


Figure 4: The 2D Interaction of Phytocompound Obtusifoliol with the Target Protein.

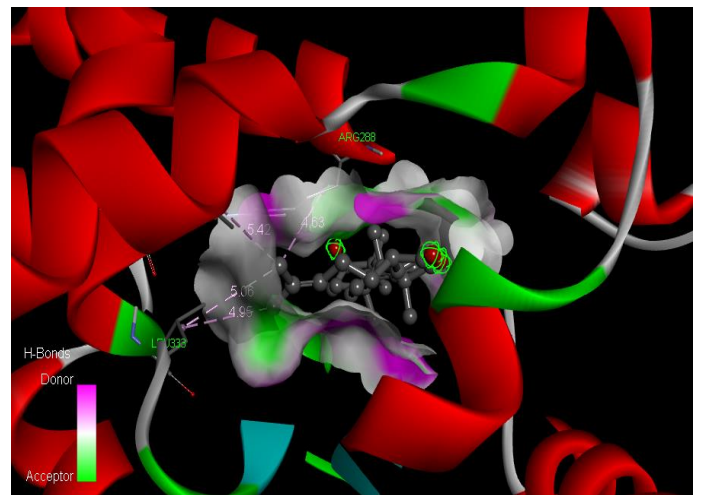


Figure 7: The 3D Interaction of Phytocompound Kulactone with the Target Protein.

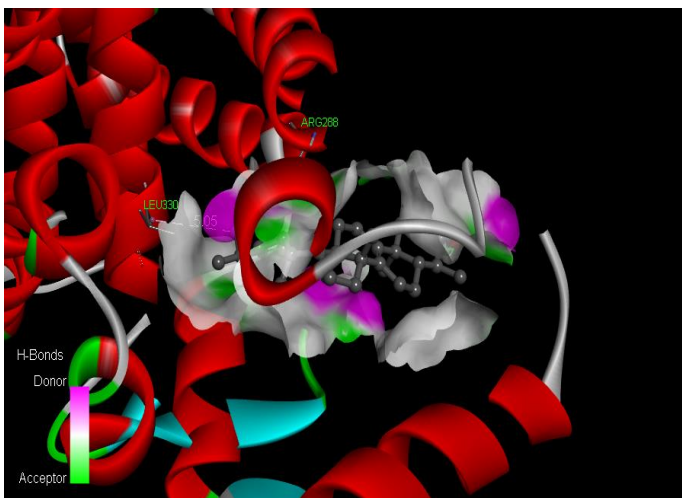


Figure 5: The 3D Interaction of Phytocompound Obtusifoliol with the Target Protein.

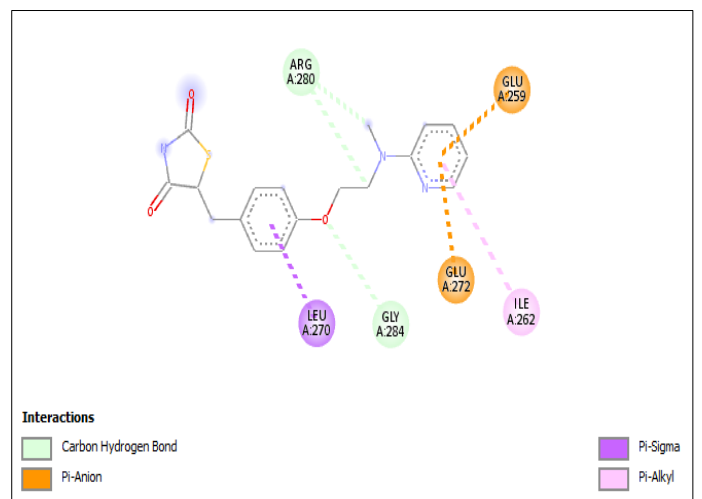


Figure 8: The 2D Interaction of Synthetic drug Rosiglitazone with the Target Protein.

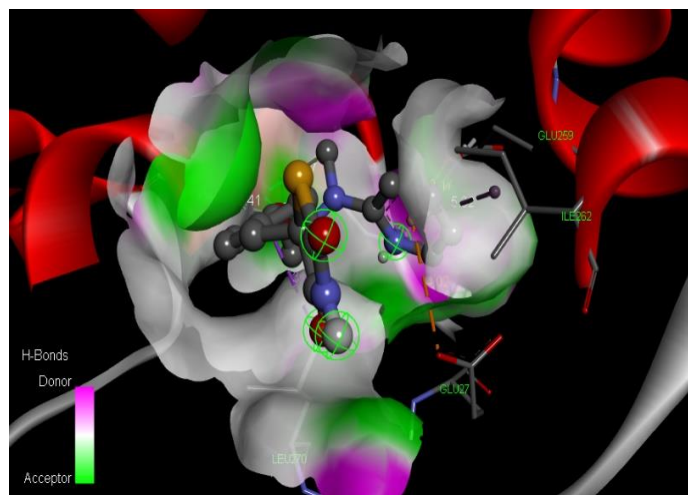


Figure 9: The 3D Interaction of Synthetic drug Rosiglitazone with the Target Protein.

ADMET and CYP Properties

In the present study, ADMET properties were tested for the best interacted phytocompounds and Synthetic drugs Rosiglitazone using SwissADME and the results were tabulated (table 2). From the results, all the best interacted phytocompounds obey Lipinski rule of five and the above Synthetic drugs also obey Lipinski rule. Most of the compounds did not cross Blood – Brain Barrier (BBB) and had low

Table 2: ADMET Properties of Phytocompounds

S. No.	PubChem (CID)	Compound Name	Lipinski	BBB	HIA	PGP-	XLogp3	TPSA (Å ²)	Log S (Esol)	Fraction Csp3	Rotatable Bonds
1	92097	Taraxerol	Yes	No	Low	NA	9.30	20.23	-8.34	3.93	0
2	65252	Obtusifoliol	Yes	No	Low	NA	9.05	9.05	-7.86	0.87	5
3	15560423	Kulactone	Yes	No	Low	No	6.89	43.37	-6.79	0.80	3
4	441900	Yamogenin	Yes	Yes	High	No	5.67	38.69	-5.98	0.93	0
5	489919	Hennadiol	Yes	No	Low	No	8.62	40.46	-7.88	0.93	2
6	101699624	Stigmasta-7,22,25-Trien-3beta-Ol	Yes	No	Low	No	8.40	20.23	-7.35	0.79	5
7	521229	Ac1lavb6	Yes	No	Low	No	8.30	20.23	-7.30	0.86	5
8	101341	Epi-Friedelinol	Yes	No	Low	NA	10.08	20.23	-8.85	1.00	0
9	5742590	Daucosterol	Yes	No	Low	No	7.74	99.38	-7.70	0.94	9
10	20055192	Apo-6'-Lycopenal	Yes	No	Low	NA	11.31	17.07	-8.85	0.28	13
Synthetic Drug											
11	77999	Rosiglitazone	Yes	No	High	No	3.11	96.83	-3.91	0.28	7

Note: Obey Lipinski: Yes means 0 violation and good, BBB (Blood - Brain Barrier): Yes means good, HIA (Human Intestinal Absorption): High means good, PGP- (Molecules predicted not to be effluated from the CNS by P-glycoprotein): Yes means good, Lipophilicity: XLOGP3 value between -0.7 and +5.0 means good, Polarity: TPSA between 20 and 130 Å² means good, Water Solubility (Log S scale: Insoluble < -10 < Poorly < -6 < Moderately < -4 < Soluble < -2 < Very < 0 < Highly): Log S value not higher than 6 means good, Saturation (Fraction Csp3): Fraction of carbons in the sp³ hybridization not less than 0.25 means good, and Flexibility (Rotatable bonds): No more than 9 rotatable bonds means good.

Table 3: Cytochrome P450 properties of phytocompounds

Intestinal Absorption (HIA). Many phytocompounds predicted to be effluated from the CNS by P-glycoprotein. Among the 10 compounds, XLogP3 value of the phytocompounds was not in the range. TPSA (Topological Polar Surface Area) and Log S value of the most of the compounds were within the limit. In all the compounds, Fraction Csp3 value of all the phytocompounds were within the limit and Rotatable bonds of the most of the phytocompounds were within the limit.

From the results of the Boiled Egg image of the phytocompounds (Figure 10), the compound Yamogenin (Pubchem CID:441900) is located in the Egg-yolk region, which means the compound is passively absorbed by the gastrointestinal tract and can also permeate through the blood-brain barrier. Moreover, the compounds Yamogenin (Pubchem CID: 441900), Daucosterol (Pubchem CID: 5742590), Hennadiol (Pubchem CID: 489919), Kulactone (Pubchem CID: 15560423), Ac1lavb6 (Pubchem CID: 521229) and Stigmasta-7,22,25-Trien-3beta-Ol (Pubchem CID: 101699624) are predicted not to be effluated from the central nervous system by the P-glycoprotein.

In the results of CYP properties (from Table 3), most of the compounds does not inhibit the CYP450 enzymes and does not give any adverse reactions. Kulactone, Stigmasta-7,22,25-trien-3beta-ol and Apo-6'-lycopenal inhibits CYP2C9. Synthetic drug Rosiglitazone inhibits the four CYP enzymes except CYP1A2. The value of log Kp (Skin Permeant) is good for all the compounds and A Bioavailability Score (ABS) is good for all the compounds.

S. No.	PubChem (CID)	Compound Name	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log K _p (Skin permeation) (cm/s)	A Bioavailability Score (ABS)
1	92097	Taraxerol	NO	NO	NO	NO	NO	-2.30	0.55
2	65252	Obtusifoliol	NO	NO	NO	NO	NO	-2.48	0.55
3	15560423	Kulactone	NO	NO	YES	NO	NO	-4.17	0.55
4	441900	Yamogenin	NO	NO	NO	NO	NO	-4.80	0.55
5	489919	Hennadiol	NO	NO	NO	NO	NO	-2.88	0.55
6	101699624	Stigmasta-7,22,25-trien-3beta-ol	NO	NO	YES	NO	NO	-2.84	0.55
7	521229	AC1LAVB6	NO	NO	NO	NO	NO	-2.92	0.55
8	101341	epi-Friedelinol	NO	NO	NO	NO	NO	-1.76	0.55
9	5742590	Daucosterol	NO	NO	NO	NO	NO	-4.32	0.55
10	20055192	Apo-6'-lycopenal	NO	NO	YES	NO	NO	-0.97	0.55
Synthetic drug									
11	77999	Rosiglitazone	NO	YES	YES	YES	YES	-6.27	0.55

Note: **No** means good, the compound does not inhibit the CYP450 enzymes and does not give any adverse reactions; **Yes** means the compound inhibits the CYP450 enzymes and gives unanticipated adverse reactions; The **more negative the log K_p**, the less skin permeant is the molecule; **ABS 0.55** means it passes the rule of five and **0.17** means it fails the rule of five.

Boiled Egg Analysis:

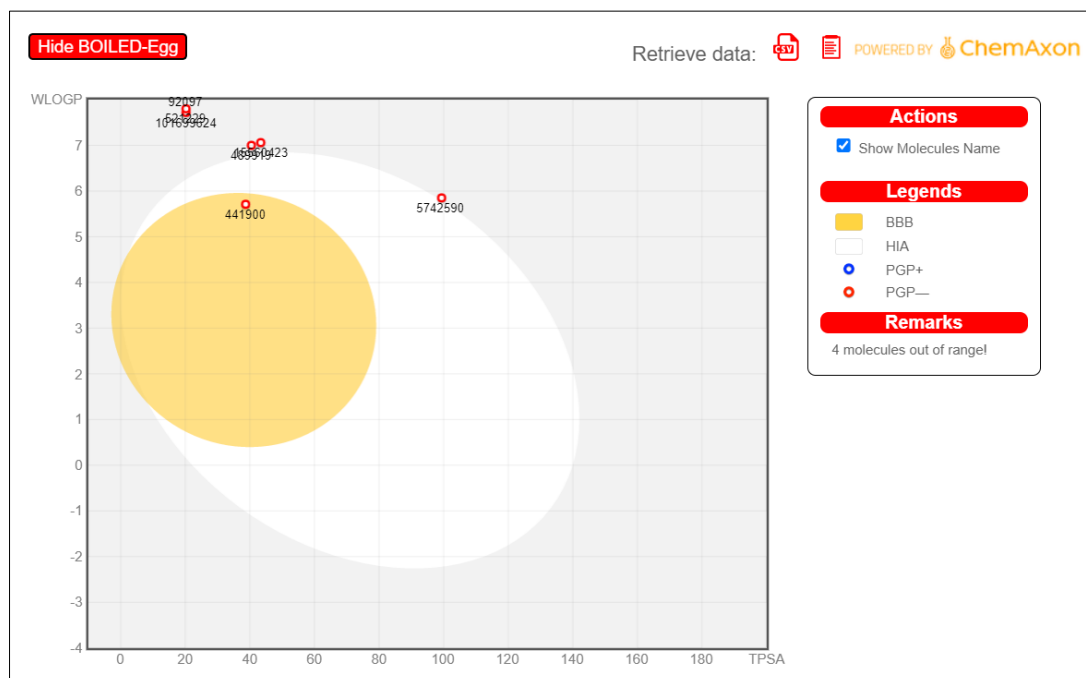


Figure 10: ADMET - Boiled Egg image of the best phytochemicals.

Note: through the blood-brain barrier.

BBB: Points located in BOILED-Egg's yolk are molecules predicted to passively permeate

HIA: Points located in BOILED-Egg's white are molecules predicted to be passively

absorbed by the gastrointestinal tract.

PGP+: Blue dots are for molecules predicted to be effluated from the central nervous system by the P-glycoprotein.

PGP-: Red dots are for molecules predicted not to be effluated from the central nervous system by the P-glycoprotein.

CONCLUSION

In the present study, the phytochemicals from the different Indian medicinal plants and the target protein PPAR γ were subjected for *in silico* docking analysis to find the bioactive compounds for treating Diabetes mellitus. For this, around 430 phytochemicals were selected and all the compounds were subjected to check the Lipinski Rule of Five. Of which, 363 compounds obeyed Lipinski Rule of Five and these compounds were taken for further docking and ADMET study. Further, the Synthetic drug Rosiglitazone was also taken and subjected to docking studies.

From the results, 54 compounds showed better results than the Synthetic drug Rosiglitazone. Among them, ten compounds showed very good binding affinity with the target protein. Of which, the phytochemicals Taraxerol, Obtusifoliol and Kulactone showed highest binding affinity with the target protein PPAR γ . Toxicity studies were also done for the ten best-interacted phytochemicals and the results showed that the compounds had very less toxicity.

Hence, the present study concludes that the phytochemical Taraxerol from *Coccinia grandis*, Obtusifoliol and Kulactone from *Azadirachta indica* and may have a potential ability in the treatment of Diabetes mellitus.

Acknowledgement

The authors would like to thank the Management, the Principal and the Head of the Department of Biochemistry, Dr. N.G.P. Arts and Science College, Coimbatore – 641 048, Tamil Nadu, India for their support to complete this work successfully.

Conflict of Interest

The authors declare that there is no conflict of interest.

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HOW TO CITE THIS ARTICLE

Mala K, Logeshwaran A, Kathiravan S, Umabarathi V, Ravikumar P. Virtual screening, Docking and ADMET analysis of bioactive compounds from the Indian medicinal plants for the treatment of Diabetes Mellitus. *J Ayu Herb Med* 2023;9(2):89-97. DOI: 10.31254/jahm.2023.9207

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