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Research Highlights

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Dr. Kamlesh Kumar Singh

Assistant Professor

Gaya Prasad Smarak Govt. P.G. College
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In-Silico Study of Bioactive Phytochemical Marrubiin: An Anti-diabetic Potential Inhibitor for PPAR γ

Maya*

Abstract

Oral antidiabetic drugs that agonists of the peroxisome proliferator-activated receptor (PPAR γ) have shown promise in the search for efficient treatment approaches for diabetes mellitus (DM). However, the need for new and safer options has been emphasized by the increasing incidence of side effects linked to many current treatments. A synthetic class of anti-diabetic drugs called thiazolidinediones targets the receptor PPAR γ , which is a crucial regulator of glucose and lipid balance. In order to find novel molecules that target PPAR γ , drug development efforts have increased due to its crucial role in the pathophysiology of Type II diabetes mellitus. The antidiabetic potential of Marrubiin from *Marrubium vulgare* as possible PPAR γ agonists is investigated in this study using a multifaceted method that integrates pharmacophore analysis, pharmacokinetic/toxicity evaluation, and in-silico molecular docking. Molecular docking analysis of Marrubiin exhibits superior binding affinity ($\Delta G = -7.0$ K cal/mol) and remarkably low inhibition constants ($K_i = 0.73$ μ M) compared to established thiazolidinediones—Rosiglitazone ($\Delta G = 5.7$ K cal/mol, $K_i = 66.29$ μ M). Further analysis through pharmacophore/ADMET profiling confirms drug-likeness properties of Marrubiin. This compound adheres to Lipinski's Rule of 5, demonstrating favorable drug-like characteristics and exhibiting good oral bioavailability, as illustrated in the bioavailability radar. The findings suggest that naturally derived phytochemical Marrubiin, holds promise as potential PPAR γ agonists. This compound, exhibiting robust in-silico characteristics, merit further experimental validation and may represent safer and more effective candidate for the development of novel antidiabetic agents.

Key words: Molecular docking, ADMET profiling, Bioactive phytochemicals, PPAR γ inhibitors

1.0 Introduction

In accordance with recent reports, an estimated 11.4% of Indians suffer from type 2 diabetes [1], Diabetes mellitus (DM) is a long-term metabolic condition characterized by insulin resistance, glucose tolerance, and hyperglycemia. The most common symptoms of diabetes mellitus include high blood glucose levels during fasting and after meals, which can be caused by impaired insulin secretion, action, or both [2]. At present, 463 million adults worldwide suffer from diabetes, and estimates for 2030 and 2045 indicate that number is expected to rise to 578 million and 700 million, respectively [3,4]. Insulin injections and oral hypoglycemic drugs such insulin secretagogues, incretin agonists, insulin sensitizers, dipeptidyl peptidase-4 inhibitors, and α -glucosidase inhibitors are part of the current management approaches. These strategies seek to attain a controlled blood glucose level; however, there are issues with their availability, cost, and known adverse effects, which include hypoglycemia, lactic acidosis, and gastrointestinal upset [5-7]. Both preventive and curative pharmaceutical preparations for humans heavily rely on medicinal

* Assistant Professor, Department of Botany, Dr. Shyama Prasad Mukherjee Govt. Degree College, Bhadohi. UP, India-221401 Email: mayavlms20@gmail.com

plants. The only reasonably priced medical treatment available, particularly for the most impoverished individuals, is herbal medicine [8]. Furthermore, because of their quality, safety, effectiveness, low side effects, and ease of access, herbal medications are becoming more and more well-liked in both developed and developing nations. Plant sources were used to make some of the already available medications, including aspirin, digitalis, quinine (an anti-malarial), vincristine, and vinblastine (an anti-cancerous). Phytochemicals derived from plants are useful against oxidative stress, cancer chemotherapy, blood disorders, brain disorders, cardiovascular diseases, diabetes, microorganisms, inflammation, and reproductive problems [9]. Although plant sources have the potential to be used as antidiabetic medications, the scientific community has not given them enough attention. Recent research has shown that incorporating the right herbs into our diet together with good nutritional regulation can help lower the risk of diabetes [10].

A perennial herb in the Lamiaceae family, *Marrubium vulgare* (white/common horehound/Maromba) has significant therapeutic use in its aerial parts. In the northern region of India, including the foothills of the Himalayas in the Union Territory of Jammu & Kashmir, the plant grows wild. It is said to have therapeutic properties for a number of ailments. *M. vulgare* hydroalcoholic extracts have been demonstrated to exhibit antispasmodic properties in isolated smooth muscle [11], antinociceptive action in pain models of mice [12], antidiabetic activity [13]. Extensive pharmacological studies have demonstrated that marrubiin displays a suite of activities including antinociceptive [14], antioxidant, antigenotoxic [15], cardioprotective [16] and antidiabetic properties [17]. The nuclear hormone receptor peroxisome proliferator-activated receptor γ (PPAR γ) plays a central role in adipogenesis and is the molecular target of the thiazolidinedione class of antidiabetic drugs [18-20].

In the present study, anti-diabetic, activities of this molecule has been investigated simultaneously along with the drug from the thiazolidinedione (TZD) class of compounds—rosiglitazone.

2.0 Materials and methods

2.1 Protein and Ligand preparation

The crystal structure of peroxisome proliferator-activated receptor gamma (PPAR γ) (PDB ID: 3DZY) was retrieved from Protein Data Bank (PDB) repository [21] in pdb format. Since previously docked drug rosiglitazone binds only with D chain of the protein thus only this chain was saved removing water and other part of the protein using BIOVIA Discovery Studio Visualizer software [22] and finally prepared with Autodock Tools-incorporated with PyRx Software [23]. Marrubiin and drug molecule Thiazolidinediones [Rosiglitazone (Avandia), were obtained by PubChem [24] in 3D.sdf format and further minimized and converted into PDBQT format with PyRx software. D Chain of Intact PPAR γ (PDB Id: 3DZY) and structure of Marrubiin and Rosiglitazone are shown in Fig. 1.

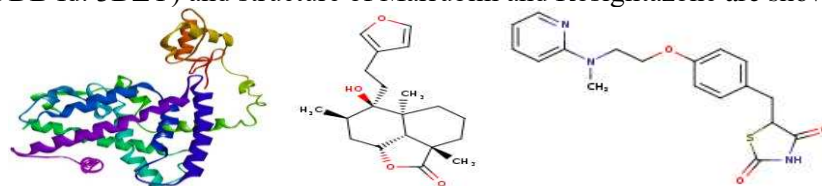


Fig. 1. D Chain of Intact PPAR γ (PDB Id: 3DZY) and structure of Marrubiin and Rosiglitazone

2.2 Protein-ligand docking

The docking calculations were performed using the AutoDock Vina software suite incorporated with PyRx. Flexible Blind docking was performed by applying a gridbox ($x=2.9750$, $y=30.9242$ and $z=11.1677$ and dimensions (in $\text{\AA}^0$) $x=65.2359$, $y=79.5085$ $z=57.9026$ to cover the whole protein with an exhaustiveness value of 9. The contributions of intramolecular hydrogen bonds, hydrophobic, ionic, and Van der Waals interactions between docked protein and ligand complexes were used to determine the free energy (ΔG) specifying affinity scoring of the binding. After docking best pose (with zero lower and upper rmsd value) was chosen for further analysis. The docked protein-ligand complexes were created and the binding sites were analyzed to construct a 2D and 3D representation of the ligand interaction for each complex using BIOVIA Discovery Studio Visualizer software.

2.3 Computation of Inhibition Constant

The molecular docking analysis predicts the inhibition constant (K_i value), which is used to evaluate the effectiveness of the interaction. It also considers changes in hydrogen bonds formed with the protein's active site residues and predicted binding energies. The inhibition constant, or K_i value of the docked enzyme-inhibitor complex' is the Dissociation constant (K_d). Lower dissociation probability and hence higher inhibition are associated with smaller K_i values. The formula $K_i = \exp(\Delta G/(RT))$ is used to calculate it, where T is the temperature (298.15 K), R is the gas constant (1.987 Kcal/K/mol), and ΔG is the free energy of binding [25].

2.4 Screening of Ligand for Pharmacokinetics and Drug-Likeness

Pharmacokinetics and Toxicity of candidate molecules decide them to be a drug molecule. In the early stages of Computer Added Drug Design (CADD), Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) of chemicals have been recognized as important considerations. The SwissADME [26] Web tool was used to evaluate the Pharmacokinetics, drug-likeness, and medicinal chemistry of these molecules. The SMILES format of the molecules was entered, and 2D structure files were generated. Several parameters were analyzed to check the ADMET properties of these molecules. Important parameters for a drug molecule include pharmacokinetics parameters like P-glycoprotein, HIA (human intestinal absorption), drug-likeness prediction Lipinski, Ghose, and Veber criteria, and the BBB (Blood-Brain Barrier penetration). In order to evaluate drug-likeness and ascertain whether a compound is likely to be bioactive, a number of additional crucial parameters were employed, including molecular weight, LogP, number of HBA and HBD, as well as the Lipinski, Ghose, and Veber guidelines. Most "drug-like" compounds have $\log P \leq 5$, molecular weight (MW) ≤ 500 , number of hydrogen bond acceptors (nHA) ≤ 10 , and number of hydrogen bond donors (nHD) ≤ 5 , according to Lipinski's "Rule of 5" [27]. If a molecule violates multiple principles, it might face issues with its bioavailability. The human intestinal absorption, bioavailability, Caco-2 (human epithelial colorectal adenocarcinoma cell line), monolayer permeability, and blood-brain barrier penetration can all be described by the ideal descriptor, LogP (octanol/water partition coefficient), Topological Polar Surface Area (TPSA). These factors play a significant role in predicting the qualities of drug.

3.0 Results and Discussion

3.1 Molecular docking and Molecular interactions (2D and 3D) analysis

Molecular docking and virtual screening, rational drug design (RDD) or computer-aided drug design (CADD), offering a swift cost-effective and dependable approach to discovering novel drugs (lead molecules) and potential druggable protein targets. In this study, we employed molecular docking-based virtual screening to pinpoint a promising target for Type 2 diabetes Mellitus (T2DM). Following a comprehensive literature review and considering available crystal structures of proteins pivotal in T2DM's biosynthetic pathways, we have selected peroxisome proliferator-activated receptor gamma (PPAR γ) (PDB ID: 3DZY). This in-silico investigation delved into the likely molecular docking interactions between Marrubiin and the PPAR γ . The findings were juxtaposed with established T2DM drug Rosiglitazone (Avandia). Marrubiin exhibited superior binding energies of -7.0 kcal/mol compared to the binding energy of drug molecule Rosiglitazone (-5.7 Kcal/mol, Table 1). The binding affinity (Kcal/mol) of the ligand or inhibitor serves as a metric to correlate and scrutinize with the corresponding protein target. Generally, a lower binding energy indicates a higher affinity (more negative) of the ligand for the receptor protein. Consequently, the ligand demonstrating the utmost affinity emerges as a promising candidate warranting further research.

This virtual screening gave us a vivid idea of the best ligands having the highest affinity for the receptor protein. Human adipogenesis, insulin sensitivity, and glucose homeostasis are all regulated by PPAR γ , a significant transcriptional factor for which the drug rosiglitazone, is an excellent sensitizer to insulin and enhances glucose absorption and reduces hyperglycemia and hyperinsulinemia [28-30]. The ineffectiveness of PPAR-gamma receptors to stimulate transcription was demonstrated by their reduced capacity to bind DNA in response to rosiglitazone and also potential therapeutic targets to treat inflammation, atherosclerosis, and hypertension. In our investigation rosiglitazone binds with D chain of PDB 3DZY with three hydrogen bonds with residues Gly284, Cys285 and Arg288 having bond lengths 3.6273, 3.11498 and 2.52131 Å⁰. Marrubiin forms one Hydrogen bonds with residue Cys285 with bond length 3.62981 Å⁰.

These whole findings are summarized in Table 1. Fig. 2a- 3b depicts the 3D and 2D diagrams of different phytochemicals showing H –bond donor and receptor regions with bindings of residues in active sites of the D chain of the protein 3DZY.

Table 1. Auto Dock Vina docking results showing binding affinities and inhibition constant of Ligands and Drug Molecules with PPAR γ protein (PDB Id: 3DZY) related to diabetes mellitus.

S. No.	Ligand name	PubChem CID	Binding Affinity (ΔG) (kcal/mol)	Inhib. Const. Ki (μM)	No. of H-Bonds	H-Bond Forming Residues	H-Bond length (Å ⁰)	Other Types of bonds within Ligand-Protein Complex (No. of Other bonds)
1	Marrubiin	73401	-7.0	0.73	1	Cys285	3.6298	Pi- (Sigma,Sulfur, and Alkyl each 1)
2	Rosiglitazone	77999	-5.7	66.29	3	Gly284 Cys285 Arg288	3.6273 3.11492.5213	C-H (1) Pi- Alkyl (2)

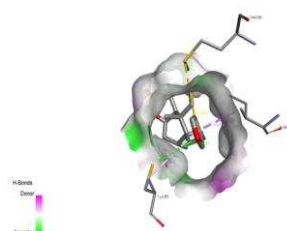


Fig. 2a

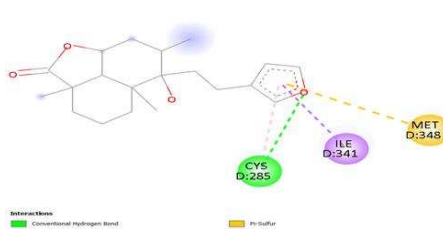


Fig. 2b

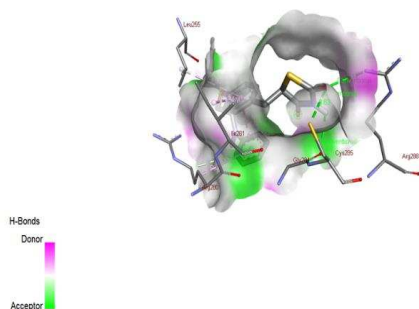


Fig. 3a

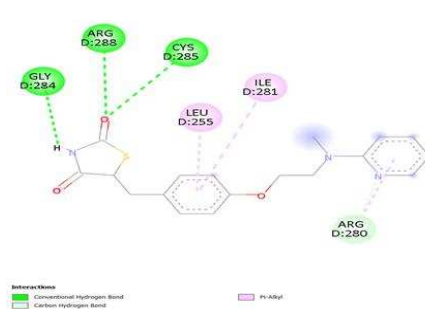


Fig. 3b

Fig 2-3. (a) The 3D image shows significant interactions with donor and acceptor H –bonds regions (b) The molecular level interactions of binding-pocket residues with the molecules are depicted in the 2D plot.

3.2 Pharmacokinetics and ADMET Evaluation of ligand and drug molecules

The Physico-chemical, pharmacokinetic and drug-likeness data are presented in Table 2 and Table 3. According to the pharmacokinetic/ADMET properties, ligand and drug molecule both showed high human intestinal absorption (HIA). Marrubiin have higher BBB permeability. Drug-likeness prediction was also performed for Lipinski, Ghose, Veber, Egan and Muegge. Both Marrubiin and Rosiglitazone follow above all drug rules (Table3, Fig 4).

Table 2. Predicted Physico-chemical and Molecular properties of ligands and drug molecules

S/N	Parameter	Marrubiin	Rosiglitazone
1	Formula	C ₂₀ H ₂₈ O ₄	C ₁₈ H ₁₉ N ₃ O ₃ S
2	Molecular weight	332.43 g/mol	357.43 g/mol
3	Num. heavy atoms	24	25
4	Num. arom. heavy atoms	5	12
5	Fraction Csp ³	0.75	0.28
6	Num. rotatable bonds	3	7
7	Num. H-bond acceptors	4	4
8	Num. H-bond donors	1	1
9	Molar Refractivity	91.40	101.63
10	TPSA	59.67 Å ²	96.83
11	Log Po/w (iLOGP)	3.16	2.41

Note: *HBA: Hydrogen Bond Acceptors (as total number of nitrogen and oxygen atoms),
 **HBD: Hydrogen Bond Donors (as total number of oxygen–hydrogen and nitrogen–hydrogen bonds)

Table 3. In silico Pharmacokinetics, and Drug-likeness of studied Molecules

S/N	Pharmacokinetics			Drug-likeness		
	Parameter	Marrubiin	Rosiglitazone	Parameter	Marrubiin	Rosiglitazone
1	GI absorption	High	High	Lipinski	Yes	Yes
2	BBB permeant	Yes	No	Ghose	Yes	Yes
3	P-gp substrate	No	No	Veber	Yes	Yes
4	CYP1A2 inhibitor	No	No	Egan	Yes	Yes
5	CYP2C19 inhibitor	No	Yes	Muegge	Yes	Yes
6	CYP2C9 inhibitor	No	Yes	Bioavailability Score	0.55	0.55
7	CYP2D6 inhibitor	Yes	Yes			
8	CYP3A4 inhibitor	No	Yes			
9	Log Kp (skin permeation)	-5.68 cm/s	-6.27 cm/s			

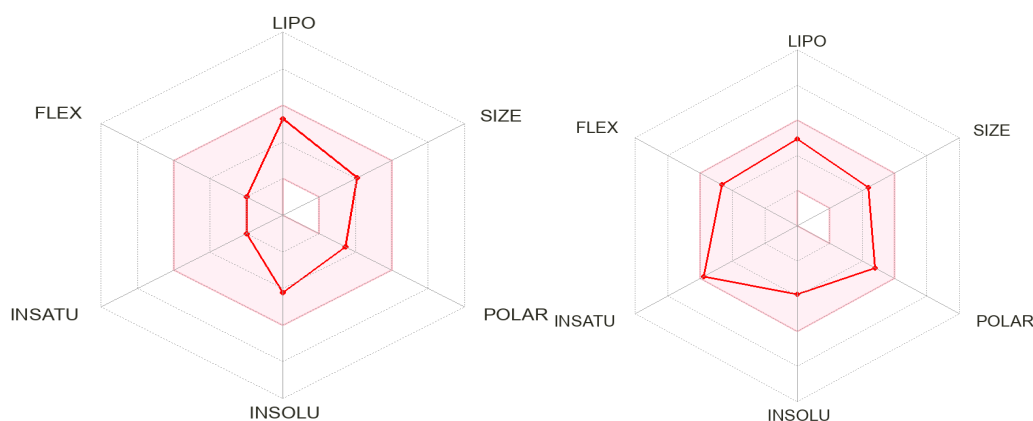


Fig. 4 Bioavailability radar of Marrubiin and Rosiglitazone. The pink zone in the bioavailability radar is the ideal physicochemical space for oral bioavailability. LIPO (lipophilicity: $-0.7 < \text{XLOGP3} < 5$); SIZE (molecular weight: $150 \text{ g/mol} < \text{mol wt} < 500 \text{ g/mol}$); POLAR (polarity: $20 \text{ \AA}^2 < \text{TPSA} < 140 \text{ \AA}^2$); INSOLU [insolubility: $0 < \text{Log S (ESOL)} < 6$]; INSATU (insaturation: $0.25 < \text{fraction C sp}^3 < 1$); and FLEX (flexibility: $0 < \text{number of rotatable bonds} < 9$).

Conclusions:

Given the seriousness of diabetes mellitus worldwide and the side effects of existing diabetes treatments, research into low-toxicity phytoconstituents appears to be a viable direction. This study delved into the screening of phytochemical Marrubiin derived from the *Marrubium vulgare* plant, specifically targeting peroxisome proliferator-activated receptors PPARs, notably PPAR γ . These receptors play a pivotal role in regulating adipogenesis, insulin sensitization, and glucose homeostasis in humans. Molecular docking analyses

uncovered Marrubiin that exhibited superior binding affinity with the target protein (PDB Id: 3DZY) compared to conventional PPAR γ agonists, such as Rosiglitazone. In light of these findings, it is plausible to anticipate that Marrubiin could emerge as promising candidate for developing a more effective and safer antidiabetic drug. The next crucial step involves subjecting this phytoconstituent to rigorous clinical trials to validate its potential therapeutic benefits and pave the way for its integration into mainstream diabetes treatment protocols. The future holds promise for harnessing the potency of this natural compound in addressing the global health challenge posed by diabetes mellitus.

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