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Research Article

Predicting ADME and Molecular Docking Analysis of Murraya paniculata Chemical Constituents against Antidiabetic Molecular Targets

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Abstract

The goal of this study is to carry out potential binding affinities of Murraya paniculata phytochemicals. The computer-based drug design methodology has led to the effective disclosure of diabetic agents. In the field of computer-based drug design, molecular docking and ADMET analysis continue to provide an exceptional guarantee. A wide range of docking score to select a potent drug compound identified by molecular docking and ADMET review. Overall results indicate that in antidiabetic studies, all phytochemicals are promising compounds leading to the production of selective insulin receptor inhibition.

Keywords: Antidiabetic, Docking, Murraya paniculata, ADMET, Insulin Receptor

Introduction

Diabetes mellitus is a common and very widespread disease that affects both developed and developing countries' citizens [1]. This is a complex chronic condition associated with a state of elevated blood glucose or hyperglycemia arising from insulin secretion, intervention, or both deficiencies. 25 percent of the global population is estimated to be affected by this disease. It is estimated by the World Health Organization (WHO) that about 200 million people worldwide suffer from diabetes and this number is expected to double by 2030[2]. The WHO says that in middle-income countries, about 80 percent of deaths occur every year due to diabetes. Diabetes mellitus is caused by carbohydrate metabolism disorders associated with low blood insulin levels or insensitivity of the target organs to insulin. In India, 62.4 million people with type 2 diabetes (T2DM) and 77 million people with prediabetes have been identified in the recently published Indian Council for Medical Research-India diabetes (ICMR-INDIAB) national survey. By 2030, this will be raised to 100 million [3]. Diabetes is a metabolic disorder where insulin, a hormone that is needed to turn sugar, starches, and other foods into energy, is not developed or properly produced in the human body. Constant elevated blood glucose levels are indicative of diabetes mellitus. It includes various conditions such as hyperglycemia, glycosuria, lipid, carbohydrate and protein irregular metabolism. T2DM is a genetically heterogeneous, polygenic disorder caused by genetic predisposition and environmental factors and associated with hypertension and dyslipidemia, with a complex inheritance pattern. Type 1 diabetes leads to a low rate of glucose absorption into adipose tissue due to the inability to release insulin. The human body needs to maintain a very limited range of blood glucose levels, which is accomplished with insulin and glucagon. The action of glucagon allows the liver to release glucose into the blood or extract energy from its cells.

Different types of antidiabetic medicines that include insulin secretagogues, such as sulfonylureas and meglitinides, are available on the market. Stimulating the production of insulin from the pancreas or increasing the sensitivity of the body's cells to insulin is the fundamental mechanism of antidiabetic drugs and is widely used along with insulin. Insulin sensitizers include biguanides, thiazolidinediones and metformin, and alpha-

glucosidase inhibitors are important inhibitors, including acarbose and miglitol, etc. Extreme hypoglycemia, liver cell damage, lactic acidosis, intestinal pain, permanent cognitive deficit, headache, dizziness and even death are the side effects of these drugs. Maintaining blood glucose levels near to normal levels is a fundamental obstacle in curing diabetes. For optimum regulation of glycemia, these therapies are used as monotherapy or in combination. As described before, these medications are typically costly and have side effects.

Protein-ligand interaction (docking) is analogous to the concept of lock-and key, in which the protein is encoded by the lock and the key is grouped with the ligand. Hydrophobic interaction tends to be the main driving force for binding. Silico methods help to classify the drug target by bioinformatics. This study has been carried out in order to identify the binding affinity of 1,3-Pentadine, 5,7-Dimethoxy-8-(2-oxo-3-methylbutyl) coumarin, 7-Methoxycoumarin, Auraptene, Coumarin, Coumurrayin, Methyl 2,5-dihydroxycinnamate, Methyl 4-hydroxycinnamate, murralongin, murrayatin, Omphamurrayone, osthol, Paniculacin, Scopolin) from *Murraya paniculata (L.) (M. paniculata)*. ChemDraw, Accelry Discovery Studio 3.5 [6] were used for studying molecular docking and ligand–protein interactions, respectively.

2. Materials and methods

In our present study, *in silico* molecular docking studies were carried out using BIOVIA Discovery Studio (DS) 2017 software.

2.1. Preparation of protein

The X-ray crystal structure of insulin receptor 1IR3 for in this anti-diabetes mellitus study was retrieved from RCSB Protein Data Bank (http:// www.rcsb.org/pdb). Hydrogen's were added to the protein 1IR3 by applied the Forcefield algorithm subsequently the energy of protein was minimized using CHARM forcefield in DS.

2.2. Ligand preparation

In this molecular docking analysis and toxicity studies, the most active phytochemicals (1,3-Pentadine, 5,7-Dimethoxy-8-(2-oxo-3-methylbutyl)coumarin, 7-Methoxycoumarin, Auraptene, Coumarin, Coumurrayin, Methyl 2,5-dihydroxycinnamate, Methyl 4-hydroxycinnamate, murralongin, murrayatin, Omphamurrayone, osthol, Paniculacin, Scopolin) from *M. paniculata* were used. All the chemical structures were drawn in chemdraw software, subsequently energy minimized and saved in SDF file format for docking studies. The standard Glibenclamide was used as standard drug for comparison study.

2.3. Docking studies

Molecular docking research was conducted to determine the most preferred protein-ligand complex geometry. The computer docking analysis was used to analyze 1IR3 structural complexes with the drug Glibenclamide and the most active phytochemicals of M. To recognize the structural basis of this target protein, paniculata. The CDOCKER (CHARMm-based DOCKER) protocol integrated within DS has examined potential binding modes between the ligands and these target proteins. The CDOCKER parameter to be run was tabulated in Table 1. The algorithm flexibly provides complete ligand and employs fields of CHARMm power. Using CDOCKER energy, CDOCKER Interaction energy, Hydrogen bonds, binding energies, protein energy and ligand protein complex energy, ligand binding affinity was measured. The energy of CDOCKER is stated in negative values. More negative value energy was seen as the higher binding affinity of the target protein ligands [7].

Table 1. Parameter of CDOCKER protocol

Input Receptor	Input/1ir3.dsv
Input Ligands	/Input/Total_min_ligands.sd
Input Site Sphere	-23.9454, 29.2003, 7.29961, 9
Top Hits	1

Random Conformations	10
Random Conformations Dynamics Steps	1000
Random Conformations Dynamics Target Temperature	1000
Include Electrostatic Interactions	True
Orientations to Refine	10
Maximum Bad Orientations	800
Orientation vdW Energy Threshold	300
Simulated Annealing	True
Heating Steps	2000
Heating Target Temperature	700
Cooling Steps	5000
Cooling Target Temperature	300
Forcefield	CHARMm
Use Full Potential	Yes
Grid Extension	8.0
Ligand Partial Charge Method	CHARMm
Random Number Seed	314159
Final Minimization	Full Potential
Final Minimization Gradient Tolerance	0
Parallel Processing	False
Parallel Processing Batch Size	25
Parallel Processing Server	localhost
Parallel Processing Server Processes	2
Parallel Processing Preserve Order	True
Random Dynamics Time Step	0.002

2.4. ADMET Prediction

Properties of absorption, distribution, metabolism, elimination, and toxicity (ADMET) were predicted in Discovery Studio using ADMET descriptors (Accelrys, San Diego, CA, USA). Six mathematical models are used to quantitatively predict the properties of the module by means of a set of rules/keys (Table 2) defining the threshold characteristics of ADMET for the chemical structure of the molecules on the basis of available drug information: ADMET absorption predicts oral human intestinal absorption (HIA). The model was developed based on AlogP (ADMET AlogP98) and 2D polar surface area measurements, using 199 compounds in the training set (PSA 2D). 95% and 99% confidence ellipses in the ADMET PSA 2D, ADMET AlogP98 circles are described by the absorption levels of the HIA model. [8]. The regions where well-absorbed compounds are anticipated to be found are represented by these ellipses. The upper limit of the 95 percent confidence ellipsoid PSA 2D value is 131.62, while the upper limit of the 99 percent confidence ellipsoid PSA 2D value is 148.12. The solubility of each compound in water at 25^0C is predicted by ADMET aqueous solubility. The model is based on the genetic partial least square approach and is based on a training collection of 784 experimentally determined solubility compounds [9]. The ADMET blood brain barrier model estimates the blood brain barrier (BBB) penetration of a molecule following oral administration. This model was derived from the quantitative linear regression model of the ADMET PSA 2D, ADMET AlogP98 aircraft for the estimation of blood-brain penetration as well as 95 and 99 percent confidence ellipses (analogous to that of HIA). They were collected from over 800 compounds that are known to reach the CNS after oral administration [10]. The plasma protein binding model of ADMET predicts whether a compound is likely to be strongly linked in the blood to carrier proteins. The predictions are based on the similarity of AlogP98 and 1D to two sets of "marker" molecules. One set of markers is used at a level of 90 percent or greater for flag binding, and the other set is used at a level of 95 percent or greater for flag binding. The binding levels predicted by the marker similarities are updated according to the measured logP conditions. [11]. Using 2D chemical structure as data, ADMET CYP2D6 binding predicts

cytochrome P450 2D6 enzyme inhibition as well as a probability estimate for the prediction. ADMET hepatotoxicity predicts possible human hepatotoxicity for a wide range of structurally diverse compounds based on a training set of 100 compounds with proven CYP2D6 inhibitions [12]. The predictions are based on an ensemble recursive partitioning model of 382 training compounds known to exhibit liver toxicity (i.e. positive hepatocellular, cholestatic, neoplastic, dose-dependent, etc.) or to induce elevated dose-related aminotransferase levels in more than 10% of the human population [13]

Result and Discussion

X-ray crystallography of a 1.9 (Å) homo sapiens insulin receptor 1IR3 protein containing 306 amino acids. Figure 1 indicates the secondary structure of the target protein with the active site sphere (radius 9). By extracting water molecules and repeating coordinates, the crystal structures have been refined. Atoms of hydrogen were added and charges were assigned to the atoms of proteins.

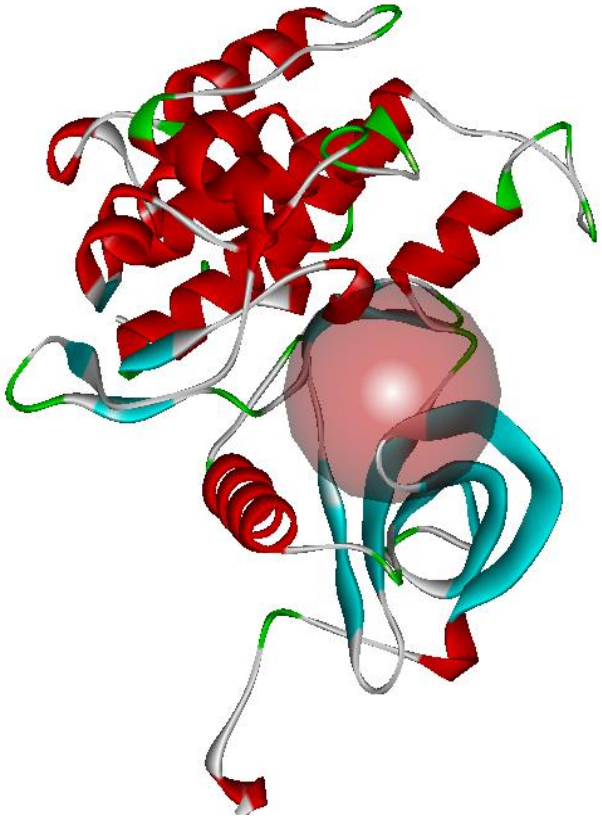

Figure 1. The secondary structure of the target insulin receptor 1IR3 with active site sphere

In this docking analysis, all photochemical molecules with standard Glibenclamide molecules formed good interactions with the 1IR3 receptor cavity site. (Figure 2).

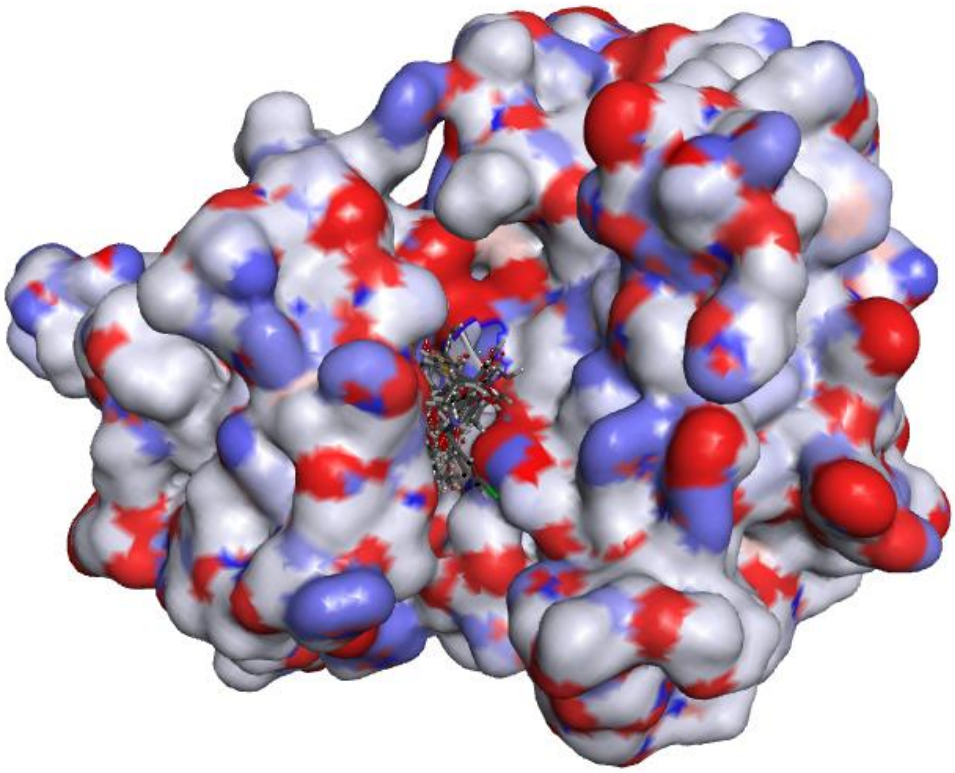

Figure 2. Surface area of receptor 1IR3 with ligands

The docking score of each molecule are listed out in table 2. From the docking result the molecule Murrayatin shows higher binding affinity in receptor 1IR3 (CDOCKER energy is - 49.0841 Kcal/mol^{-1}). The Murrayatin molecules forms strong hydrogen bond with Lys 1030 residue. Further, Met 1076, Met 1139, Val 1010, Ala 1028 forms alkyl interaction with alkyl group of the Murrayatin molecule (Figure 3). The aromatic benzene group of the molecules has forms strong Pi-anion interaction Asp 1083. Notably, the Mg metal of the receptor forms metal acceptor interaction with ketone group of the molecules. Finally, the above interactions shows more binding affinity in the receptor of 1IR3 compared to standard drug Glibenclamide (Figure 4). Similar interactions also found in the Glibenclamide drug in insulin receptor. The other best compound's Omphamurrayone and 5,7-Dimethoxy-8-(2-oxo-3-methylbutyl) coumarin shown in figure 5 and 6 respectively.

Table 2. The involved energies of the docking study of 1IR3 protein

Molecule Name	-CDOCKER Energy
Murrayatin	49.0841
Omphamurrayone	46.2212
5_7-Dimethoxy-8-(2-oxo-3-methylbutyl)coumarin	43.7855
Glibenclamide	38.7493
Methyl_2_5-dihydroxycinnamate	31.7169
Methyl_4-hydroxycinnamate	30.3077
7-Methoxycoumarin	25.0113
Coumarin	23.6605
Scopolin	18.3907
murralongin	13.7753

osthol	12.9561
Coumurrayin	10.8395
1_3-Pentadiene	3.0138
Auraptene	-10.9909

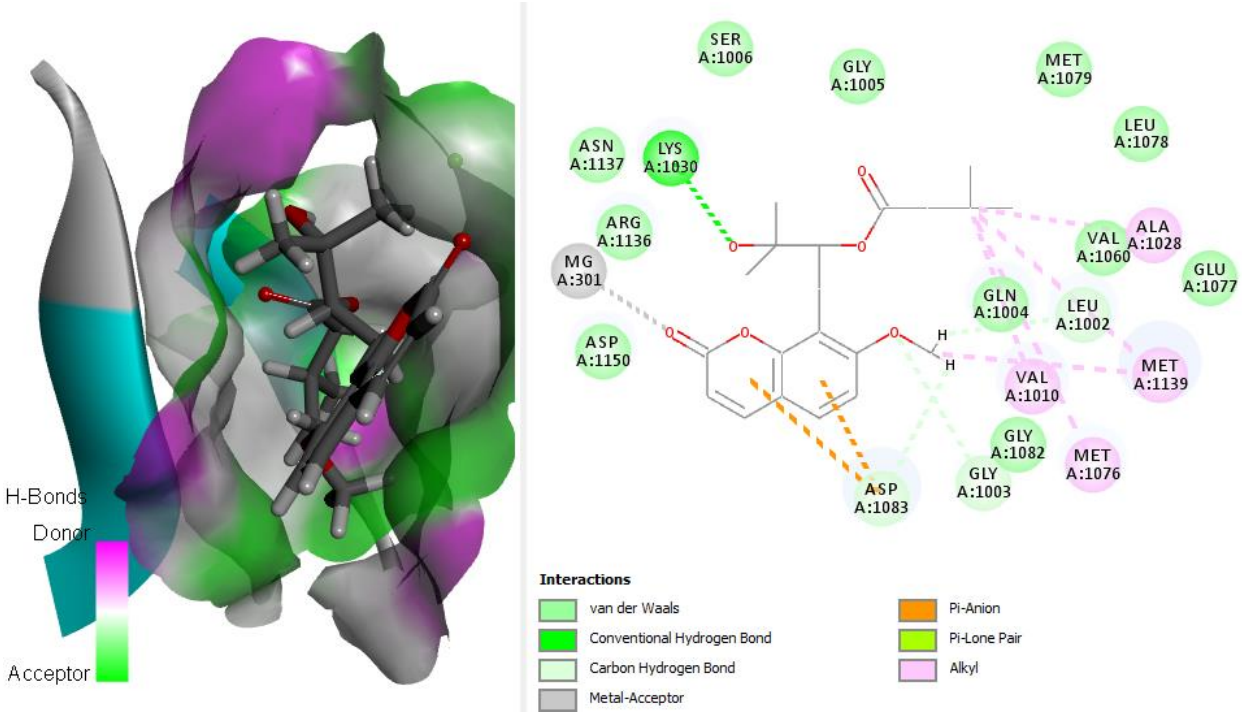

Figure 3. Interaction of Murrayatin in receptor 1IR3

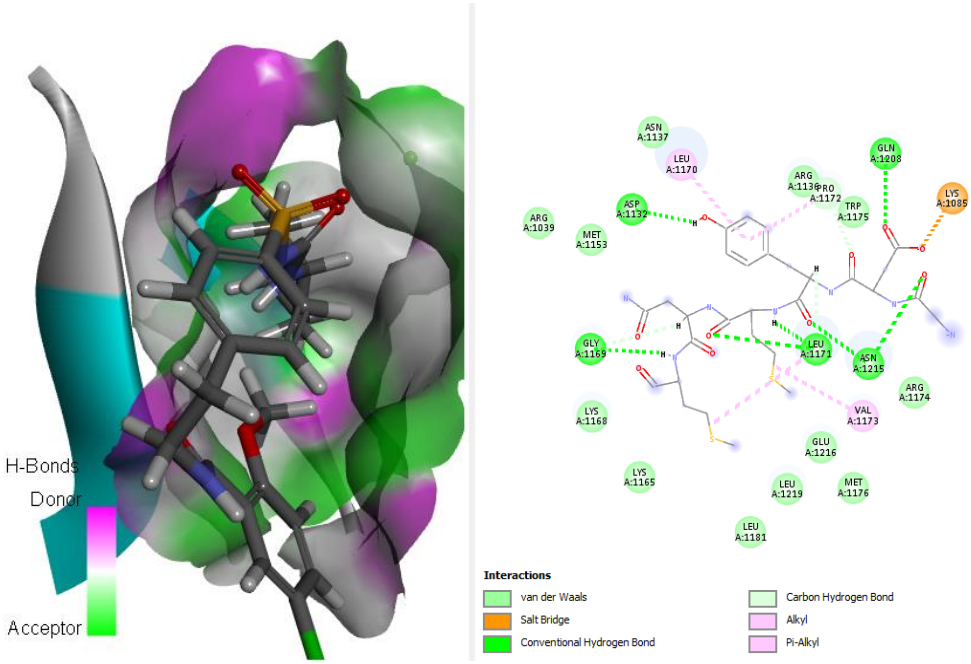

Figure 4. Glibenclamide interaction analysis in insulin receptor 1IR3.

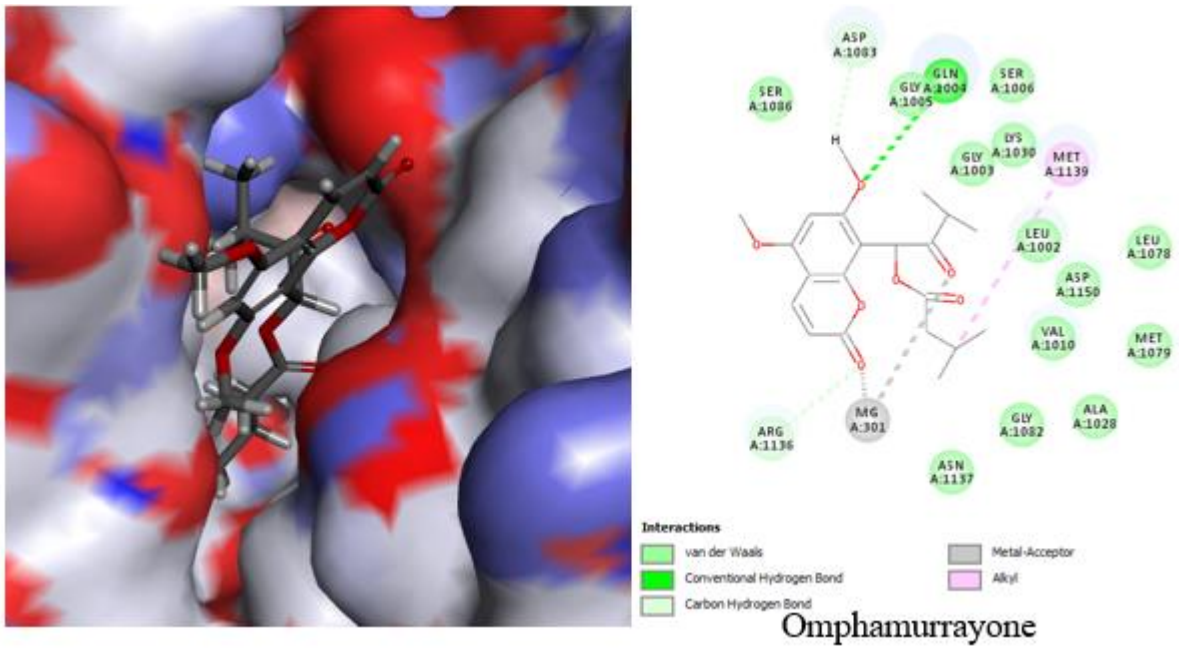

Figure 5. Omphamurrayone interaction in receptor 1IR3

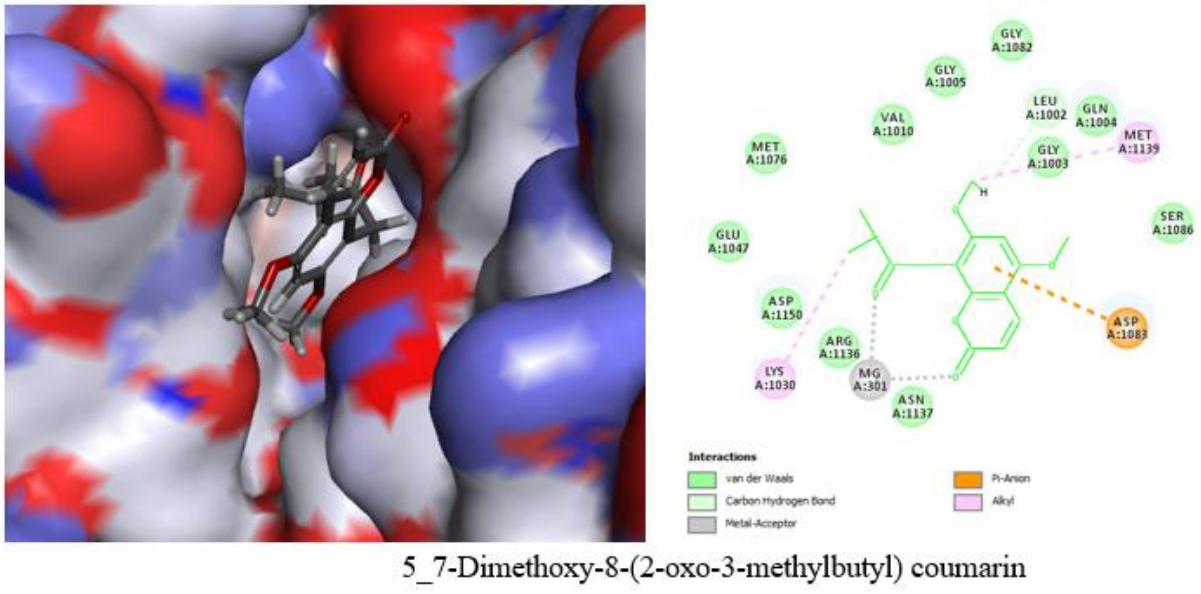

Figure 6. 5, 7-Dimethoxy-8-(2-oxo-3-methylbutyl)coumarin interactions in recptor 1IR3

ADMET analysis

The product of ADMET for all active compounds of M. Table 3 lists paniculata and glibenclamide. The results obtained were cross-checked with the standard levels listed in Table 4. Figure 7 shows the plot of polar surface area (2D PSA) and AlogP for these compounds. 2D PSA and AlogP, which involve 95% and 99% confidence ellipses, were predicted for intestinal absorption and blood barrier penetration in the ADMET study [14-19]. It determines the region of ellipses where the compounds are supposed to be well-absorbed. The level of absorption (human intestinal absorption-HIA) of all molecules demonstrates excellent absorption (value 0 as good absorption). 95% and 99% confidence ellipses in the ADMET model describe the absorption levels of the HIA model.

Similarly, the aqueous solubility rating is 4, meaning that all the compounds in aqueous media have a strong solubility nature. In addition, both ligands are adequate with respect to the liver of CYP2D6, indicating that non-inhibitors of CYP2D6 are PA. The model orders either "toxic" or "nontoxic" and offers a certainty level pointer to the likelihood of prescient accuracy of the models (Table 2). Our findings show that all compounds are non-toxic to the liver (level 0) and therefore have a substantial first-pass effect. The parameters should be met according to the model for all substances with optimum cell permeability. (PSA < 140 $Å^2$ and AlogP98 < 5) [7]. All the compounds showed polar surface area (PSA) < 140 $Å^2$. Since the AlogP98 criteria, all the compounds had AlogP98 value <5As a result of ADMET, we find that the molecules have drug-like properties and would also be useful as a powerful new diabetes mellitus drug.

Table 3. ADMET properties of the molecule.

Name	Absorption level	Solubility level	BBB level	PPB level	Hepatotoxic level	CYP 2D6	PSA 2D	AlogP98
Murrayatin	0	3	4	0	0	0	64.27	4.46
Omphamurrayone	0	3	4	0	0	0	35.16	4
5_7-Dimethoxy-8-(2-oxo-3-methylbutyl)coumarin	0	3	4	0	0	0	52.46	4
Glibenclamide	0	3	4	0	0	0	52.46	4.66
Methyl_2_5-dihydroxycinnamate	0	3	4	1	0	0	59.49	5.48
Methyl_4-hydroxycinnamate	0	3	4	0	0	0	59.49	4.53
7-Methoxycoumarin	0	3	4	1	0	0	58.21	4.49
Coumarin	0	3	4	0	0	0	56.23	4.34
Scopolin	0	3	4	1	0	0	55.61	4.71
murralongin	0	3	4	1	0	0	59.87	4.74
osthol	0	3	4	1	0	0	59.32	5.14
Coumurrayin	0	3	4	0	0	0	44.91	5.23
1_3-Pentadiene	0	3	4	0	0	0	56.87	4.92
Auraptene	0	4	4	0	0	0	56.34	4.77

Table 4. Standard levels of ADMET descriptors

Aqueous Solubility		BBB		CYP450		Hepatotoxicity		Intestinal absorption	
Level	Intensity	Level	Intensity	Level	Value	Level	Value	Level	Value
0	Extremely low	0	Very High	0	Non inhibitor	0	Non toxic	0	Good
1	No, Very	1	High	1	Inhibitor	1	toxic	1	Moderate

	Low								
2	Yes, Low	2	Medium	PPB				2	Low
3	Yes, good	3	Low	Level		% of Binding		3	Very Low
4	Yes, Optimal	4	Very Low	0		<90%			
5	No, Too soluble			1		>90%			
6	Unknown			2		>95%			

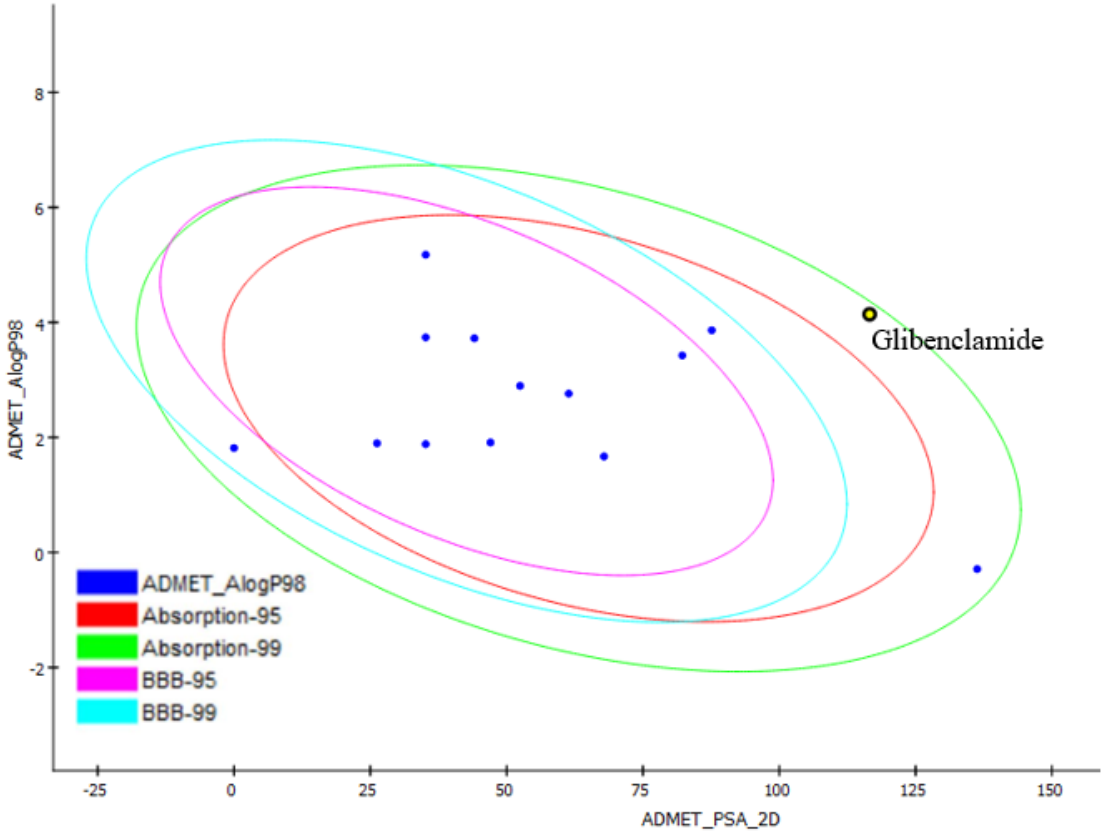

Figure 7. Plot of polar surface area (PSA) versus ALogP for capsazepine and its derivatives showing the 95% and 99% confidence limit ellipses corresponding to the blood brain barrier (BBB) and intestinal absorption.

Conclusion

The objective of the current study was to determine the antidiabetic activity of *M. paniculata* active phytochemicals by means of computational approaches. The in silico docking studies revealed that the compounds can mimic the action of insulin and activate insulin receptors as insulin mimetics. In addition, the ADMET findings indicate that compounds have drug-like properties. This study therefore indicates that the compounds of *M. paniculata* have a potent anti-diabetic rather than an effect that could be efficiently used instead of Glibenclamide medication for the treatment of diabetes.

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