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Identification of potential phytochemicals in *Murraya paniculata* against anti-diabetic activity

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Abstract

Diabetes mellitus, is non-communicable diseases, is still the serious problem due to leading the causes of death in the developed countries. The newer anti-diabetic drugs are continued searching because the existing synthetic drugs have several limitations. Traditional medicinal plants are used in the treatment of diabetes mellitus more than century, but only a few of these have proofed their safe and efficacy. The aim of this article is focused on *Murraya paniculata* one of the medicinal plants belongs to the family Rutaceae and is mostly distributed throughout South Asia to Australia used for anti-diabetic activities. It contains several kinds of coumarins and derivative, alkaloids, flavonoids, phenolic compounds and essential oil. Many researches have examined that these phytochemical substances have the major impact on diabetes mellitus. This Journal focus on the molecular docking studies of anti-diabetic activity of *Murraya paniculata* and the result reveals that some of the phytochemicals can act as anti-diabetic drugs.

Keywords: *Murraya paniculata*, Anti-diabetic, Protein, Phytochemicals, Molecular Docking, ADMET.

1 Introduction

Diabetes mellitus (DM) is a chronic multisystem disease characterized by hyperglycaemia related to abnormal insulin production, impaired insulin utilization, or both. DM is a serious health problem throughout the world, and its prevalence is rapidly increasing. It is also a major contributing factor to heart disease and stroke. In addition, quite half adults with diabetes have hypertension and high cholesterol levels.

The American Diabetes Association (ADA) admit four different classes of diabetes. The two commonest are type 1 DM and type 2 DM. The two other classes are gestational diabetes and other specific types of diabetes with various cause Normal Glucose and Insulin Metabolism.

Type 1: This type diabetes mellitus, formerly known as Juvenile-onset diabetes or insulin-dependent diabetes, accounts for about 5% to 10% of all people with diabetes. This eventually results in not enough insulin for a person to survive. The individual with type I diabetes requires insulin from an outside source (exogenous insulin) to sustain life.

Type 2: This type diabetes mellitus was formerly known as adult-onset diabetes (AODM) or non-insulin-dependent diabetes (NIDDM). Type 2 diabetes is, by far, the most prevalent type of diabetes, accounting for approximately 90% to 95% of patients with diabetes **[1]**. Many risk factors contribute to the development of type 2 diabetes, including being overweight or obese, being older, and having a family history of type 2 diabetes.

Murraya paniculata:

Figure 1: The Morphology of *Murraya paniculata*.

The genus ***Murraya*** (Rutaceae) is made up of about 14 species [16]. *Murraya paniculata* is also known as Chalcas exotica, Chalcas paniculata, and Camunium exoticum [19]. *Murraya paniculata* is commonly known as orange jasmine or mock orange. *Murraya paniculata* has been used as an ornamental and a medicinal plant. The extracts from bark and leaf are stimulant and astringent, anti-inflammatory, antidiarrheal [21], antidiabetic, antimalarial, antibacterial, antifungal, and antioxidant activity [22,23].

Phytocompounds in *Murraya paniculata*:

The essential oil from leaves was obtained by hydro distillation and a detailed chemical analysis was conducted by GC-MS has shown that, total of 76 volatile components were identified from the essential oil of *M. paniculata* [16]. The major components are coumarins and derivatives [2, 3, 4], alkaloids [5, 6], flavonoids [10, 9], phenolic compounds [7], and essential oil [8, 12, 11].

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Molecular docking and ADMET analysis has used to determine the Docker energy and ADMET properties of phytochemicals present in *M. paniculata* to analyse whether this phytocompounds act as antibiotic drug against diabetics.

2 Experimental

1.Materials and methods

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

1.1 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 Force field algorithm subsequently the energy of protein was minimized using CHARMm force field in DS.

1.2 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.

1.3 Docking studies

Molecular docking describes the "best-fit" orientation of a ligand that binds to a particular protein of interest. Ligand is a small molecule, which interacts with protein's binding sites. This case is known as the protein ligand interaction [25]. The computer docking analysis was used to analyse 1IR3 structural complexes with the drug Glibenclamide and the most active phytochemicals of *M. paniculata*. To recognize the structural basis of this target protein. 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[15].

1.4 ADMET Prediction

Chemical absorption, distribution, metabolism, elimination, and toxicity (ADMET) play a vital role in drug discovery and development. The ADMET properties were used to assess pharmacokinetics and toxicity properties of the drug using through Discovery Studio (Accelrys, San Diego, CA, USA). The parameters such as, hepatotoxicity levels, aqueous solubility, cytochrome CYP2D6 inhibition, BBB, PPB and HIA are quantitatively predicted by a set of rules/keys that specify threshold ADMET characteristics for the chemical structure of the molecules based on the available drug information. The absorption levels of HIA model are defined by 95% and 99% confidence ellipses in the ADMET PSA 2D, ADMET AlogP98 plane [15].

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
Force field	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

3 Results and Discussion

Molecular Docking Results:

Figure 2. depicts, the secondary structure of target insulin protein of active receptor site with sphere shape. By removing water molecules and repeating coordinates the crystal structures were refined. Hydrogen atoms were added and charges were assigned to the protein atoms. Molecular docking study reveals that all the 14 phytochemicals were interacted with the target insulin receptor

1IR3 and shows CHARMm-DOCKER binding energy (Table 2).

Among these 14 phytocompounds, which is present in the *M. panniculata*, murrayatin, Omphamurrayone, 5,7-Dimethoxy-8-(2-oxo-3-methylbutyl) coumarin and Glibenclamide have high Docker energy.

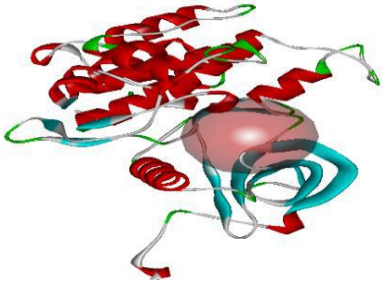

Figure 2: The secondary structure of the target insulin receptor 1IR3 with active site sphere.

a) Murrayatin: Has Docker energy of about -49.0841 kcal/mol-1. This compound experience interaction through Van der Waals, conventional hydrogen bond, carbon hydrogen bond, metal acceptor and alkyl interaction between its amino groups. The docking results shows that, the molecule forms one strong hydrogen bond interaction with LYS 1030. ALA 1028, MET 1139, VAL 1010 and MET 1076 interacted with Alkyl bond. And MG 301 get interacted with metal acceptor. Most of the groups shows only vanderwaals interaction.

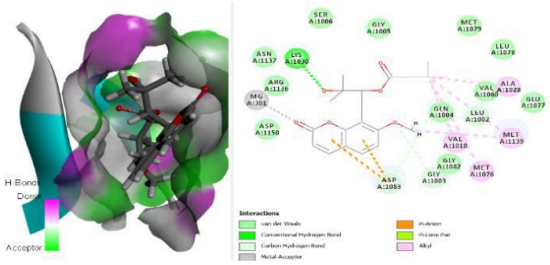

Figure 3: Interaction of Murrayatin in receptor 1IR3.

b) Omphamurrayone: It has docker energy of about -46.2212 kcal/mol-1. This compound also interacted with receptor 1IR3 through Van der Waals, conventional hydrogen bond, carbon-hydrogen bond, metal acceptor and alkyl interaction between its amino groups. The docking results shows; the molecule get interacted with GLN 1004 through hydrogen bond interaction. MET 1139 interacted with Alkyl. And MG 301 get interacted with metal acceptor. ASP 1083 and ARG 1136 get interaction with the carbon hydrogen bond and more vanderwaals interaction in receptor site.

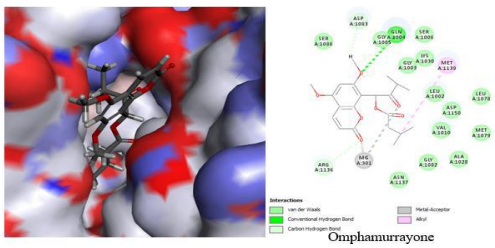

Figure 4: Omphamurrayone interaction in receptor 1IR3.

c) 5, 7-Dimethoxy-8-(2-oxo-3-methylbutyl) coumarin: The docker energy of about -43.7853 kcal/mol-1. The benzene group of this molecule shows Pi-Anion binding interaction with ASP 1083. Similarly, the two C=O group get interacted with MG 301 through metal acceptor. MET 1139 and LYS 1030. There is a carbon hydrogen bond interaction with LEU 1002.

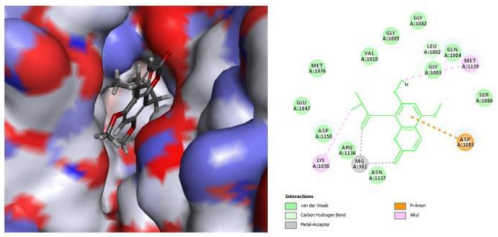

Figure 5: 5, 7-Dimethoxy-8-(2-oxo-3-methylbutyl)coumarin interactions in recptor 1IR3.

d) Glibenclamide: Has Docker energy of about -38.7493 kcal/mol-1. The standard Glibenclamide interacted with less binding energy compared to other molecules. This molecule forms hydrogen bond with GLY 1163, LEU 1171, AGN 1215, ASP 1132 and GLN 1208 residue and LYS 1085 intreact through salt bridge. The VAL 1173 and LEU 1170 intreacted as alkyl intrection.

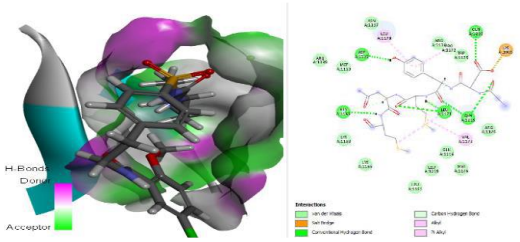

Figure 6: Glibenclamide interaction analysis in insulin receptor 1IR3.

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

Mo. No	Molecule Name	-CDOCKER Energy
1.	Murrayatin	-49.0841
2.	Omphamurrayone	-46.2212
3.	5,7-Dimethoxy-8-(2-oxo-3-methylbutyl)coumarin	-43.7855
4.	Glibenclamide (standard drug)	-38.7493
5.	Methyl-2,5-dihydroxycinnamate	-31.7169
6.	Methyl-4-hydroxycinnamate	-30.3077
7.	7-Methoxycoumarin	-25.0113
8.	Coumarin	-23.6605
9.	Scopolin	-18.3907
10.	Murralongin	-13.7753
11.	Osthol	-12.9561
12.	Coumurrayin	-10.8395
13.	1,3-Pentadiene	-3.0138
14.	Auraptene	-10.9909

ADMET Results:

Table 3 have shown the ADMET result of the active phytochemicals and the plot of polar surface area (2D PSA) versus AlogP of these compounds were depicted in Figure 7. The HIA and BBB level were predicted by 2D PSA versus AlogP that include 95% and 99% confidence ellipses in ADMET study. The absorption level of all the molecules is good, in that Mol. 2 and 4 shows extremely good value whereas Mol. 1 and 3 show good values. The absorption levels are denoted by red line and green line (figure 8). The red line shows 95% of absorption and green line shows 99% of absorption. Similarly, all molecule shows good solubility level, in that Mol. 2 and 4 shows extremely good solubility level. BBB protects against circulating toxins that could cause brain infections from drugs. The ADMET results shows that all the molecules show low BBB level. PPB capability is less than 90% for all the molecules. Plasma protein is an essential part in blood. The hepatotoxic level is nil for all molecule. And also all the molecules were non-inhibitors of the metabolic enzyme of CYP2D6 liver enzyme. All the compounds showed PSA less than 150 and AlogP98 value less than 5. This ADMET results reveals that the molecules have similar drug properties which is useful for diabetes.

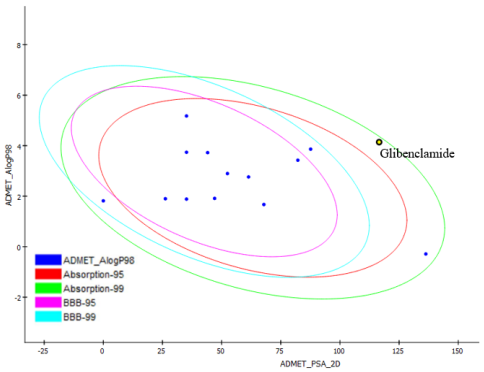

Figure 7: Plot of PSA versus AlogP for Glibenclamide and other 3 molecules which will show the 95% and 99% confidence limit ellipses corresponding to the BBB and HIA.

Table 3: ADMET properties of the molecule.

Mol. No	Absorption level	Solubility level	BBB level	PPB level	Hepatotoxic level	CYP 2D6	PSA 2D	AlogP98
1	good	good	Low	<90%	No	No	35.14	3.1
2	Extremely good	Extremely good	Low	<90%	No	No	65.19	4.8
3	good	good	Low	<90%	No	No	55.26	4.2
4	Extremely good	Extremely good	Low	<90%	No	No	74.32	3.4

4 Conclusions

To identify potential of phytochemical present in *Murraya paniculata* against anti-diabetic we performed Molecular docking and ADMET analysis. The ligands of the phytochemical present in *Murraya paniculata* binds with protein 1IR3 of diabetes. The studies conclude that, among all the phytocompounds four has high potential than others. Molecular docking study explains that CDOCKER energy of the Mol.1, 2 and 3 are greater than standard drug Glibenclamide. The ADMET result exhibits all the properties of the molecules are extremely good on comparing with standard drug.

ABBREVIATION:

The following abbreviations are used in this manuscript:
ADMET – Absorption, Distribution, Metabolism, Elimination, and Toxicity.
BBB – Blood Brain Barrier.
PPB – Plasma Protein Barrier.
PSA – Polar Surface Area.
HIA – Human Intestine Absorption.

Conflict of Interest

The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

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