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# *In-vitro* **and** *In-silico* **Inhibitory Action of Methanol Extract of** *Rhynchosia beddomei* **Whole Plant on** *α***-Glucosidase and** *α***-Amylase**

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## *Authors' contributions*

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## **ABSTRACT**

The goal of the current study was to identify potential bioactive components that may be responsible for *Rhynchosia beddomei's* antidiabetic activity through in silico docking study and to investigate potential mechanisms by which *Rhynchosia beddomei* may be helpful in managing diabetes and its associated complications. *In vitro* anti-diabetic assays showed that this plant's high efficiency to inhibit α-amylase (62.13%) and α-glucosidase (59.9%) enzymatic activity, which are well-established targets for the management of diabetes, is responsible for its antihyperglycaemic activity. Soxhlet extraction produced an extractive yield of 35.43%. Additionally,

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we hypothesised that flavonoids including rutin, lucenin, orientin, rhynchosin, and isooreintin contained in this plant may be accountable for the antidiabetic characteristics through docking experiments. The traditional usage of this herb as an antidiabetic is supported scientifically by these findings. By reducing dietary glucose intake, it may help slow the course of diabetic complications and control diabetes. The therapy of hyperglycaemia requires further screening of predicted antidiabetic compounds.

*Keywords: Rhynchosia beddomei; anti-diabetic; docking; α-glucosidase; α-amylase.*

## **1. INTRODUCTION**

A chronic hyperglycemic state is a hallmark of diabetes mellitus (DM), a complicated metabolic condition. Even though diabetes therapeutics are developing quickly, the prevalence of DM is alarmingly rising and is projected to double by 2040 [1]. As a result of diabetes, the eyes, kidneys, hearts, and nerves are all commonly affected by a number of problems, including neuropathy, nephropathy, retinopathy, cardiovascular issues, etc. [2]. Aside from having a number of adverse effects and the requirement to take lifelong medicine, the available anti-diabetic medications are concentrated on removing excessive glucose from the blood and have little impact on the mechanisms that give rise to various issues. A significant portion of patients will eventually need insulin therapy to maintain long-term glycaemic control, either as monotherapy or in conjunction with oral antidiabetic therapy, because the majority of patients are overweight or obese at diagnosis and cannot achieve or sustain near normoglycaemia without oral antidiabetic agents [3].

In order to effectively treat diabetes, it would be wise to combine anti-diabetic medications with particular additives that block the pathways that lead to various issues. Since the beginning of human civilization, natural resources have been utilised for the treatment and prevention of numerous diseases. Recent times have seen a shift in the research's attention towards traditional medicinal herbs, and a sizable body of evidence has accumulated that supports the use of these plants in traditional ways. Its impact on diabetes complications has received relatively little attention, and none of the important research illustrates potential mechanisms by which it might be helpful in preventing diabetic complications [4]. The goal of the current study was to get a preliminary understanding of the mechanism by which *in vitro* and *in silico* technologies can help in treating diabetes and its consequences. We assessed the ability of the

methanolic extract of *R. beddomei* to counteract oxidative stress, which is a key factor in the emergence and progression of diabetic problems, on the basis of this. Additionally, this plant's putative antidiabetic mechanisms were tested experimentally using *in vitro* tests, and bioactive anti-diabetic ingredients that may be in charge of the anti-diabetic activity were anticipated using *in silico* docking studies.

## **2. RESOURCES AND PROCEDURES**

The companies Sigma-Aldrich, Loba Chemie, Merck, Sdfine-Chem, Himedia, and Spectrochem provided all of the chemicals employed in the current investigation.

## **2.1 Plant Gathering and Drying**

Dr. K. Madhava Chetty, a botanist at S.V. University in Tirupati, confirmed the *Rhynchosia beddomei* whole plant's procurement, preparation, and referral for certification. The entire plant was washed in running water to remove debris, then dried in the shade. After being ground into a coarse powder, the dried plant material underwent one more process.

## **2.2 Preparation of Plant Extract**

Plant material was suspended in a roundbottomed flask containing the extraction solvent as the powdered plant material was progressively extracted in 500 ml of methanol using the Soxhlet method. The flask was then heated after being fitted with a condenser, allowing the extract's active ingredients to enter the fluid. The source was filtered at the end of the extraction procedure. Extracts were maintained in airtight ampoules at 4°C until use after the excess was vaporised and placed in desiccators to eliminate any remaining moisture, if any [5].

## **2.3 Initial Screening of the Phytochemicals**

The methanolic whole plant extract of *R. beddomei* (MERB) was preliminary phytochemical screened for the presence of phytochemical elements such alkaloids, flavonoids, terpenoids, phenols, tannins, etc. [6].

### **2.4** *In-vitro* **Anti-diabetic Activity**

#### **2.4.1 α-amylase inhibitory activity**

Starch (2 mg) was added to 0.2 mL of 0.5 M Tris-HCl buffer (pH 6.9) and 0.01 M calcium chloride (substrate) in a test tube. The test tube was then pre-incubated at 37 °C for 5 minutes and boiled for 5 minutes. To dissolve 1 mg of dried MERB extract, 1 mL of 0.1% gum acacia was employed. Following the addition of 0.2 ml of MERB extract, 0.1 mL of porcine pancreatic amylase in Tris-HCl buffer (2 units/mL) was added to the tube containing the substrate solution. The operation was then carried out at 37 °C for 10 minutes. 0.5 mL of 50% acetic acid was added to each tube to stop the reaction, and the reaction mixture was centrifuged at 3000 rpm for 5 minutes at 4 °C. A UV spectrophotometer was used to detect the absorbance at 595 nm [7].

#### **2.4.2 α-glucosidase inhibitory activity**

MESA's glucosidase inhibitory activity was assessed by incubating 0.1 mL of an enzyme solution with 1.0 mL of 0.2 M Tris buffer, pH 8.0 (1.0 mL) containing various concentrations of MERB extract at 37 °C for 60 min. The mixture used in the reaction was boiled for two minutes in a water bath to terminate the process, and the amount of freed glucose was calculated using the glucose oxidation method. (Assay condition 3ºC±0.1ºC, pH-8.0; optical density at 540 nm). The same approach was applied three times [8].

## **2.5** *In-silico* **Analysis**

## **2.5.1 Docking studies for molecules**

For the purpose of logical drug discovery and design, molecular docking is a useful scaffold for comprehending drug-drug interactions. A scoring algorithm in the programme is used to rank and categorise the various potential adduct structures that are generated by molecular docking. Molecular docking's primary goal is to create ligand-receptor complexes with optimised conformations and the idea of reducing the binding free energy [9]. Molecular docking performed with mCule online tool.

#### **2.5.2 Designing drugs based on structure**

The protein was initially produced in discovery studio by generating sphere properties after being downloaded in PDB format. In both chains, there are no longer any water molecules. Later molecules are drawn using Chemdraw/ Chemsketch in mol format. Protein and ligand were docked against proteins like 1B2Y, 3TOP and 3RX2. Docking indicates that some of our compounds, docked with protein α amylase inhibitor (PDB ID: 1B2Y), α glucosidase inhibitor (PDB ID: 3TOP) and Aldose reductase (PDB ID: 3RX2).

#### **2.5.3 Docking results visualization**

Discovery Studio was used to see how the docking stances appeared. Using the glide score method, we selected the best docked structures. The binding is more advantageous the lower the glide scores are. The varied ligand receptor interactions were also examined, as well as the docked ligand poses [10].

#### **2.5.4 Ramachandran plot**

The docked proteins of glucosidase inhibitor (PDB ID: 3TOP), aldose reductase (PDB ID: 3RX2), and amylase inhibitor (PDB ID: 1B2Y) were validated and evaluated using procheck by computing the Ramachandran plot to access the quality of the model by looking into the allowed and disallowed regions of the plot [11]. All ensemble residues (apart from those at the chain termini) have their phi-psi torsion angles displayed on the Ramachandran map. The various regions indicated in [12] are represented by the coloring/shading on the plot. The "core" regions, or the most advantageous combinations of phi-psi values, are represented by the darkest areas, which are here displayed in red.

#### **2.5.5 ADME analysis**

#### *2.5.5.1 Calculating molecular properties and bioactivity scores*

The drug-likeness was assessed using Lipinski's rule of five, and the molecular characteristics that are crucial for a drug's pharmacokinetics, such as ADME (absorption, distribution, metabolism, and excretion), were calculated. Certain molecular properties were obtained using the website-based Molinspiration software (www.molinspiration.com). Using a technique created by molinspiration, the values of miLogP, as (octanol/water partition coefficient), and TPSA of the examined cytosolic PLA2 were calculated. Based on contributions and correction factors, drug-likeness ratings were computed to represent the number of fragments [13].

The tool Molinspiration Chem Informatics Server (http://www.molinspiration.com) was used to assess the bioactivity score of a few selected compounds. In this method of computational chemistry, massive chemical databases are evaluated to find potential novel drug candidates [14]. By tracking the activity scores of GPCR (Gprotein coupled receptors ligand), KI (kinase inhibitor), PI (protease inhibitor), EI (enzyme inhibitor), ICM (ion channel modulator), and NRL (nuclear receptor ligand), the prediction of bioactivity scores of these MERB drugs was determined.

#### **3. RESULTS AND DISCUSSION**

#### **3.1 Preparation of** *Rhynchosia beddomei*  **Methanolic Extract**

The soxhlation process was used to create the methanolic extract of *Rhynchosia beddomei*. The following formula was used to get the extract's yield %.

% yield= (Quantity obtained (grams)/ Quantity used (grams)) ×100 35.43%. w/w

#### **3.2 Preliminary Phytochemical Screening**

Phytochemical analysis of the crude extract revealed the presence of alkaloids,

#### **3.3.2 α-Glucosidase inhibition assay**

glycosides, steroids, flavonoids, carbohydrates, proteins, and tannins. *Rhynchosia beddomei* was next tested for other phytochemicals.

#### **3.3** *In-vitro* **anti-diabetic Activity**

#### **3.3.1 α- Amylase inhibition assay**

In order to break down the -1-4-glycosidic bonds in starch, an enzyme called -amylase is present in the saliva, intestinal mucosa, and pancreatic secretions. As a result, the bioavailability of glucose in the blood is increased by this enzyme. A medication must be able to lower blood glucose levels or inhibit α-amylase in order to be considered an anti-diabetic. According to Table 1's results on the percent inhibition and IC<sup>50</sup> of *Rhynchosia beddomei's*  methanolic extracts, the percentage inhibition rises with dose (for plant extracts), but the responses are not linear for the three dose levels. The inhibition data is additionally processed for relative inhibition in comparison to standard. The value of the amylase inhibition assay increases with increasing relative inhibition.

Acarbose is the benchmark substance. Acarbose produced inhibition at lower doses (10–50 µg/mL), as was expected.

A slower rate of glucose absorption and a subsequent reduction in the postprandial plasma glucose rise were induced by the inhibition of -glucosidase, which delays carbohydrate digestion [15]. One helpful strategy for lowering postprandial hyperglycemia is α-glucosidase inhibition [8]. Comparison is made between the  $IC_{50}$  values of the test and standard extracts. Alternatively said, the plant extract has almost one-fourth the activity of acarbose. Higher doses result in a decrease in relative% inhibition, indicating that the full dose is not necessary to trigger the reaction. As the dose of the standard is increased, there is an increased % inhibition.



#### **Table 1. α-Amylase inhibitory activity of MERB**

<b>Test extract</b>	<b>Dose</b> $(\mu g/mL)$	Percent inhibition, $AM±SEM (n=3)$	<b>Relative</b> inhibition	$IC_{50}$ $(\mu g/mL)$
Methanolic	10	$16.14 \pm 0.0606$	34.10	
extract of	25	$44.71 \pm 0.2810$	25.65	33
Rhynchosia beddomei	50	71.84 ±0.4081	22.78	
Acarbose	2.5	$11.83 \pm 0.05292$	100	9.22
	5	$34.85 \pm 0.0688$	100	
	10	$63.06 + 0.1386$	100	

**Table 2. α-Glucosidase inhibitory activity of MERB**

## **3.4** *In-silico* **Analysis**

## **3.4.1 Molecular docking studies**





*G score = glide score, the binding is more beneficial the more negative the Glide score*

## **PDB ID: 1B2Y:**







**c) 5,7,3,4 tetrahydroxy 6-C-β-D glucopyransyl flavone -7.2 d) Acarbose -5.6**

**PDB ID: 3TOP:**



**a) Rutin -8.1 b) 5,7,3,4 tetrahydroxy 6-C-β-D glucopyransyl flavone -7.8**











#### **a) Rhynchosin -7.7 b)Apigenin -8.7**





**c) Quercetin -9.4 d) Acarbose -3.9**

## **Fig. 1. Compounds showing interactions with the binding site (PDB ID)**

#### **3.4.2 Ramachandran plot analysis**

Proteins were evaluated using a Ramachandran plot to determine which amino acids were present in which sections of the corresponding protein. The results are shown in Table 4 and in the picture.

#### **3.4.3 ADME analysis**

*3.4.3.1 Calculating the characteristics of molecules*

The compounds derived through MERB were docked with proteins, chosen for their ADME characteristics, and drug-likeness (according to Lipinski's rule of five), and the results are shown in Table 5 (MWT ≤500).

#### **Table 4. Ramachandran plot status with protein with 1B2Y, 3TOP and 3RX2**





**c) 3RX2**

**Fig. 2. Ramachandran plot of protein 1B2Y, 3TOP and 3RX2.**



#### **Table 5. ADME properties of α-amylase inhibitor, α-glucosidase inhibitor and aldose reducatse Inhibitor by molinspiration**

*MW = Molecular weight, nON = number of hydrogen bond acceptors, nOH = number of hydrogen bond donors, nV = number of violation of Lipinski's rule of five, nrotb = number of rotatable bonds, TPSA = Total Polar Surface Area and miLogP = Octanol-water partition coefficient logP*

#### **Table 6. Bioactivity of α-amylase inhibitor, α-glucosidase inhibitor and aldose reductase Inhibitor by molinspiration**



*GPCR = G protein coupled receptor, Ion cm = Ion channel modulator, KI = Kinase inhibitor, sNRL = Nuclear receptor ligand, PI = Protease inhibitor, EI = Enzyme inhibitor*

## **3.4.4 Prediction of Bioactivity properties**

Against six different protein architectures, drugs' bioactivity was assessed. The bioactivity score, which has three different ranges and is used to assess biological activity,

- 1. Having significant biological activity if the bioactivity score is more than 0.00.
- 2. If the bioactivity score is between -0.5 and 0, there is moderate activity.
- 3. The presence of inactivity if the bioactivity score is less than -0.50 [15].

## **4. DISCUSSION**

The present work aimed with the objective of *in vitro*, *in silico* analysis with anti-diabetic activity of *Rhynchosia beddomei* methanolic extract. The percent yield of extract was found to be 35.43%. Preliminary phytochemical investigation of CMME showed the presence of alkaloids, glycosides, steroids, flavonoids, carbohydrates, saponins and terpenoids.

The most prevalent tissue in the body, skeletal muscle, is primarily responsible for the postprandial consumption of glucose [16]. Generally speaking, the cell membrane's buildup of functional glucose transporter molecules is what causes skeletal muscles to absorb glucose. Leptocytes and/or myocytes regulate the glucose carrying molecules in response to a high level of insulin release in the blood, producing a hypoglycemic effect [17]. By delaying the digestion of carbohydrates, intestinal glucosidase and pancreatic α-amylase activity can be inhibited, which lowers postprandial hyperglycemia [18]. Inhibitors of α-glucosidase prevent the small intestine from breaking down carbohydrates as quickly, which reduces the postprandial blood glucose excursion in diabetics. Inhibiting carbohydrate-digesting enzymes like α-amylase and α-glucosidase in the gastrointestinal system reduces postprandial blood sugar levels and is one of the tactics and approaches used to treat diabetes mellitus [19].

The  $\alpha$  -glucosidase and  $\alpha$  -amylase inhibition assays were used in our investigation to test MERB for any potential anti-diabetic properties. At higher concentrations (50-200 µg/mL), the MERB also demonstrated substantial inhibition and had almost one-sixth the activity of acarbose. It has been demonstrated that in patients with non-insulin dependent diabetes mellitus (NIDDM), medications that block carbohydrate hydrolysing enzymes can reduce post-meal hyperglycemia and improve impaired glucose metabolism without increasing insulin secretion. Pentacyclic triterpenoids (PT), which are found in natural compounds, are a class of pharmacologically active and structurally rich metabolites with privileged motifs for further modifications that are reported to act on glucose metabolism. Flavanols may also cause conformational changes in structure [20] when studying the inhibitory activities of  $\alpha$  -amylase and α-glucosidases.

Acarbose and miglitol are competitive inhibitors of α-glucosidases, which decreases the

absorption of starch and disaccharide. In terms of dose levels, the extracts' α-glucosidase inhibition activities are substantially greater than those produced by -amylase inhibition activities. In fact, the  $IC_{50}$  values for  $\alpha$ -glucosidase inhibition (9.22) are twice as high as those for  $α$ amylase inhibitory action. One of the most wellknown and widely used *in vitro* anti-diabetic assays uses this method to screen plant extracts for their potential anti-diabetic activity. Both enzymes' activity was significantly and concentration-dependently inhibited after extract treatment. The methanolic extract of *Rhynchosia beddomei* was shown to have strong antidiabetic action by α-amylase inhibition assay and α glucosidase inhibition assay. To gain a deeper understanding of the mechanism of enzyme inhibition, studies on the interactions between inhibitors and enzymes are important. To discover the likely inhibitory mechanism, the molecular docking predictions were employed. By analysing how well compounds attach to the target protein, in silico docking studies, also known as molecular αdrugs. The results of docking give us information on the number of interactions, amino acids involved, and energy of the ligand-protein interaction (kcal/mol), all of which are used to predict the biological activity of diverse compounds. We screened chemicals found in *Rhynchosia beddomei* for their interaction to possess α-amylase inhibition (1B2Y), -glucosidase inhibition (3TOP), and aldose reduction (3RX2) using the *in silico* docking software mCule. The most efficient compounds were those with the lowest ligandreceptor binding energy and the greatest interactions with the receptor (6 bond lengths). Rutin, 5,7 dihydroxy-4-methoxy isoflavone, Quercetin, Apigenin, Orientin and Rhynchosin showed good docking score. Rutin shown the highest score -7.7 and -8.1 for α-amylase inhibitor protein and α- glucosidase inhibitor protein when compared to other compounds and Rhynchosin showed good score in aldose reductase protein. It was discovered that the docked chemicals share a binding site and interact via hydrogen bonds. These circumstances demonstrate that it is possible to predict non-competitive glucosidase, aldose reductase, and α-amylase inhibitor mechanisms. An enzyme called aldose reductase is responsible for catalysing the conversion of sorbitol from glucose. Due of the increased flow, considerable amounts of sorbitol are generated during diabetes-related hyperglycemia. Targeting this enzyme is therefore extremely helpful in reducing diabetes complications [21].

Ramachandran plot is analysed for protein α amylase inhibitor (PDB ID: 1B2Y), α glucosidase inhibitor (PDB ID: 3TOP) and Aldose reductase (PDB ID: 3RX2), the amino acids in the protein were 80% above in favourable region.

On the basis of Lipinski's rule and its constituent parts, molecular properties of inspiration were estimated. All docked compounds are less in weight so they may be transported, dispersed, and absorbed more readily. Quercetin, Apigenin, Rhynchosin, Biochanin, and D-pinitol all had a Lipinski rule of violation of 0; Isovetexin had a rule of violation of 1, and vitexin and other compounds had a rule of violation of >1 for all of these compounds. The intestinal absorption of each chemical was good. other Molinspiration characteristics, such as nON, nOHNH, nrotb, and the logP value of the octanol water partition coefficient, are below the permissible thresholds. Protein structure bioactivity was predicted via molecular modelling. Isovitexin, Iso orientin, Dionositol having good bioactivity score against all. Quercetin, Isovitexin, Apigenin, Vitexin, Vicenin, Orientin, Iso orientin, Lucenin, Rhynchosin, 5, 7, Dihydroxy-4-methoxy Isoflavone and 5, 7, 3, 4, tetrahydroxy-6-c-β-D Glucopyranosylflavone have having moderate bioactivity score against all receptors.

Overall results explain us that MERB might possess antidiabetic activity by alpha amylase and alpha glucosidase inhibitory actions and i*n silico* studies have proved better glide score of MERB compounds in comparison to standard acarbose. For the compounds of MERB and docked with proteins 1B2Y, 3TOP, and 3RX2, it is thought to be highly helpful to apply molecular docking studies and molinspiration calculations, as well as a practical technique to compute molecular characteristics and forecast bioactivity scores.

## **5. CONCLUSION**

These findings offer a rationale based on science for the plant's long-standing anti-diabetic use. Additionally, MERB decreased the activity of the enzymes α-glucosidase and α-amylase, which may have the effect of reducing the absorption of dietary glucose and controlling diabetes. By lowering oxidative stress, it might aid in the advancement of diabetes complications. The inclusion of Rutin, 5,7 dihydroxy-4-methoxy isoflavone, Quercetin, Apigenin, Orientin, and Rhynchosin, which was predicted by an *in silico* docking research, may be responsible for the

anti-diabetic potential of MERB and has to be further explored. The conclusion drawn from these findings is that plant extract has a sizable capacity to block the activity of these enzymes, and as a result, may be a valuable addition to diabetic treatment for controlling dietary input of glucose.

## **CONSENT AND ETHICAL APPROVAL**

It is not applicable.

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## **COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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