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Anti-Diabetic Activity Assessment Of Justicia Adhatoda L. Whole Plant Extract

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ABSTRACT
Objective: The objective of this experiment was to assess the antidiabetic efficacy of Justicia adhatoda L.The entire port ion of the methanol extract (JAWME) was tested for its effects on rats with Alloxan-induced hyperglycemia.
Methods: Hyperglycemia was provoked by administering a dose of 150mg/kg (intraperitoneally) of alloxan monohydrat e, which had been recently dissolved in distilled water.After a period of 72 hours, the rats with a Blood Glucose Level (BGL) higher than 150 mg/dl were chosen for the study. These rats were then separated into seven groups (I-VII), each consisting of six rats.
The vehicle and reference medication metformin (at a dosage of 250 mg/kg) were orally delivered to animals in group I and group II, respectively. Group III, which served as the control, received just alloxan.Groups IV, V, VI, and VII were administered methanolic extracts at doses of 100mg/kg, 200mg/kg, 300mg/kg, and 400mg/kg for 12 consecutive days. T he subjects were then observed after 1, 3, 6, and 12 days.
Outcome: The ingestion of a methanolic extract at a dosage of 400mg/kg body weight demonstrated a noteworthy (*p< 0.01, **p<0.05) antihyperglycemic effect in rats with diabetes caused by alloxan.The phytochemical screening result ind icated the existence of saponins, flavonoids, alkaloids, and other compounds.
Conclusion: The methanolic extract of Justicia adhatoda L demonstrates a decrease in blood glucose levels compared to the standard medication Metformin.Justicia adhatoda L has been shown to have anti-diabetic properties, according to the results.

Key terms: Alloxan monohydrate, Diabetes mellitus, Justicia adhatoda L

1. INTRODUCTION

Diabetes mellitus (DN) is a condition characterized by impaired pancreatic cells and an increased susceptibility to vascu lar disease consequences. It is caused by a complex combination of genetic and environmental factors.Diabetes is a prev alent chronic illness worldwide.The user's text is "[1]".These are a group of metabolic disorders that are characterized by high levels of sugar in the blood, as well as changes in the way the body processes fats, carbohydrates, and proteins.The symptoms may be attributed to the inadequacies in insulin secretion, action, or both.The user's text is enclosed in tags.T ype 2 diabetes mellitus is the most widespread form of the disease worldwide, with emerging nations seldom being at th e forefront of the pandemic [3].Type 1 diabetes is managed by exogenous insulin, whereas type 2 diabetes is treated usin g artificial oral hypoglycemic medicines and/or insulin.The user's text is "[4]".Despite the availability of several oral hy poglycemic drugs and insulin for treating diabetes mellitus, patients are increasingly expressing a desire to employ natur al substances that have the ability to reduce blood glucose levels.The user's text consists of two references, [5] and [6].T he primary causes of postprandial hyperglycemia are the carbohydrate hydrolyzing enzymes alpha-amylase and alpha-glucosidase. Alpha-amylase initiates carbohydrate digestion by hydrolyzing the 1,4glycosidic bonds of polysaccharides such as starch and g lycogen, resulting in the formation of disaccharides.
The user did not provide any text.Glucosidase facilitates the transformation of disaccharides into monosaccharides, leadi ng to an increase in blood sugar levels after a meal [7].
Ethnobotanicals have been used in traditional medicine for a long time to treat abnormal blood glucose levels.Conseque ntly, scientists continue to explore natural hypoglycemic agents that are both safer and more efficient.The user's text is " [8].The Acanthaceae family consists of small, lowgrowing plants that are always green and have the characteristic of bei ng herbaceous. One member of this family is the Malabar nut, scientifically known as Justicia adhatoda L.The Ayurveda and Unani medicinal schools acknowledge this plant as a renowned medicine because of its unique phytochemistry.It h as a global distribution, but is particularly prevalent in tropical places such as Burma, Malaysia, Sri Lanka, India, and so utheast Asia.This plant flourishes in arid regions with infertile soil and usually receives limited amounts of rainfall.Vasi cine and vasicinone are the two main chemical components of Justicia adhatoda, together with an essential oil.The prima ry constituents of Justicia adhatoda are quinazoline alkaloids, with vasicine being the principal alkaloid.Additionally, it i

ncludes polyphenols, glycosides, and phytosterols.
A comprehensive analysis of the essential oil extracted from Justicia adhatoda leaves identified various chemical compo nents such as phytosterols, anthraquinones, alkaloids, polyphenols, flavonoids, saponins, and triterpenoids. Notably, the oil also contained N-
oxides of vasicine, vasicine, maiontone, and deoxyvasicine.This plant displays a range of biological characteristics due t o its chemical compounds, such as antidiabetic, antibacterial, antiinflammatory, antimalarial, antioxidant, antimutagenic, respiratory stimulant, and bronchodilatory activities. Additionally, it has cardioprotective, antiulcer, insecticidal, allopat hic, hepatoprotective, and anticholinesterase properties. As a result, it is utilized in various commercial products [9, 10].

2. METHODOLOGY

2.1 Gathering and processing of plants

The plant material was collected from the medicinal garden of Veer Bahadur Singh Purvanchal University in Jaunpur, In dia, with the postal code 222003.Scientist E. Arti Grag from the Central Regional Centre of the Botanical Survey of Indi a in Praygraj, Uttar Prades, conducted the process of identifying and verifying the specimen.The samples are stored in th e institutional herbarium for future use, and they are assigned the accession number Justicia adhatoda L. 104530 [11].

2.2 Plant material extraction process

The plant samples were collected, cleaned, rinsed, and dried prior to extracting the plant material using the cold macerati on method.The plant sample's powder form was extracted using several organic solvents, including petroleum ether, eth yl acetate, and methanol. The extraction process involved letting the solvents to stand with the plant sample for a duratio n of 45 days.Filter paper was employed to eliminate any nonextractable constituents from the extract, such as cellular co mponents and other insoluble substances in the extraction solvent.The extract was dehydrated by moving it to a beaker a nd allowing evaporation to occur before storing it in an airtight container.A qualitative examination of extracts from diff erent solvents was conducted to identify the presence of certain phytoconstituents [11].
The extraction yield of all extracts was determined using the equation shown below:

Percentage Yield = Actual yield × 100
Theoretical yield

•Quantitative analysis of phytochemical compounds in the extracts

The phytochemical content of the extracts was assessed using established procedures, including the determination of car bohydrates, alkaloids, flavonoids, tannins, phenol, saponins, protein, and glycosides.

2.3 Animals and Experimental Design

The PBRI research facility in Bhopal, India supplied SpragueDawley rats weighing between 150200g, which were either male or female and about of the same age.The animals were housed under controlled environmental conditions, with co nsistent temperature and access to water at all times. They were provided with a standard pellet diet from Hindustan Lev er Ltd., Bangalore.
All the animals were kept in polypropylene cages.The animals were confined in enclosures that lternated between period s of darkness and light, each lasting 12 hours.Prior to the commencement of the experiment, the animals underwent a we eklong period of acclimation to the laboratory environment.The animals had a fasting period of at least 12 hours prior to the commencement of each workout.The Institutional Animal Ethics Committee (1337/PO/Re/S/10/CPCSEA) granted a uthorization for the experimental protocols.The induction of hyperglycemia was achieved by administering Alloxan mo nohydrate at a dosage of 150 mg/kg body weight via intraperitoneal injection. The Alloxan monohydrate utilized was ob tained from Sigma Chem. Co., located in St. Louis, MO, USA.They were divided into seven groups, each consisting of s ix animals.[12]
Group I: The normal control group got only normal saline.
Group II consisted of rats that were administered with a standard dose of Metformin HCL at a concentration of 250 mg per kilogram of body weight. These rats had previously been treated with Alloxan.
Group III consisted of rats that were administered with Alloxan (150 mg/kg i.p) to induce diabetes and manage their bl ood sugar levels.
Group IV: The methanol extract of the dried whole portion of Justicia adhatoda L (100 mg/kg) was administered to rats treated with Alloxan.
Group V: The methanol extract of the dried whole portion of Justicia adhatoda L (200 mg/kg) was administered to rats t reated with Alloxan.
Group VI: The methanol extract of the whole plant of Justicia adhatoda L (300 mg/kg) was administered to rats treated with Alloxan.

Group VII: The methanol extract of the dried whole portion of Justicia adhatoda L (at a dosage of 400 mg/kg) was adm inistered to rats treated with Alloxan.
The version number is

2.3.1. Diabetes caused by alloxan
Mice were subjected to an 18hour period of not eating, followed by an injection of 150 mg/kg of alloxan monohydrate i nto their abdominal cavity to induce high blood sugar levels.After one hour of administering alloxan, the animals were p rovided with regular pellets and unrestricted access to water.The blood glucose level was assessed by obtaining samples by the tailtipping method while the patient was under local anesthesia. The blood glucose level was then evaluated using an autoanalyzer and the Accu Check Advantage II glucose kit.After a period of 72 hours, rats with blood glucose levels (BGL) above 150 mg/dl were selected for the investigation. These rats were then separated into seven groups (I through VI), each consisting of six rats.Animals in groups I and II were administered oral dosages of the reference medicine met formin (250 mg/kg). Group III, which served as the control group, received just alloxan without any further treatment. [13,14]Over a period of 12 consecutive days, Groups No. IV, V, VI, and VII were administered dosages of 100 mg/kg, 2 00 mg/kg, 300 mg/kg, and 400 mg/kg of methanolic extracts, respectively.
Blood glucose levels (BGL) were tested after 1, 3, and 12 days. (Refer to Table)
Table 1 presents the impact of the methanol extract of Justicia adhatoda L on the blood glucose levels of both normal an d experimental animals throughout a 12-day treatment period.

2.3.2 Histopathological investigations
• Activity of alpha amylase
The αamylase inhibitory activity of the extract and fractions was assessed using a conventional technique with some mo difications. [14,15]The reaction mixture consisted of 20 liters of extract
and fractions with varying concentrations (0.1, 0.2, 0.3, 0.4, and 0.5 mg/ml) and 50 liters of phosphate buffer (100 mM, pH = 6.8). The mixture was preincubated at 37°C for 20 minutes.Next, the substrate, namely 20 l of 1% soluble starch in a 100 mM phosphate buffer with a pH of 6.8, was introduced. The mixture was then placed in an incubator and kept at a temperature of 37 °C for an additional 30 minutes.Next, 100 liters of the DNS color reagent were introduced, and the m ixture was subjected to a 10minute heating process.The absorbance of the combination was measured at 540 nm using a Multiplate Reader (Multiska thermo scientific, version 1.00.40).Acarbose was used as a reference substance at various c oncentrations (0.10.5 mg/ml).The experiment was conducted in triplicates, and the control material (extract and fraction s) was set up simultaneously.
The results were quantified as the percentage of inhibition, which was determined using the following Formula.
% α-amylase inhibition = Absorbance (blank) -Absorbance (test/standard) X 100
Absorbance (blank)
% = (1-As/Ac) × 100
Were
As is the absorbance in the presence of test substance and Ac is the absorbance of control.

- **Alpha glucosidase activity**

The αglucosidase inhibitory activity of the extract and fractions was assessed using a conventional technique with some modifications.[14,15].The experiment involved preincubating alphaglucosidase (1 U/ml), phosphate buffer (100 mM, p H = 6.8), and a reaction mixture containing 20 l of different extract concentrations (0.1, 0.2, 0.3, 0.4, and 0.5 mg/ml) at 3 7°C for 15 minutes.Next, the substrate was introduced into a solution containing 20 liters of P-
NPG at a concentration of 5 millimolar. The reaction proceeded for an additional 20 minutes at a temperature of 37 degr ees Celsius.The addition of 50 liters of Na2 CO3 halted the reaction, which had a concentration of 0.1 M.
The Multiplate Reader was utilized to determine the p-
absorbance of nitrophenol at a wavelength of 405 nm.Acarbose was used as a reference substance at various concentrati ons (0.10.5 mg/ml).Every experiment was conducted three times, and a control group without the test medication was es tablished simultaneously.The findings were quantified as the percentage of inhibition, determined by applying the follo wing formula:
% α-glucosidase inhibition = Absorbance (blank) -Absorbance (test/standard) X 100
Absorbance (blank)
% = (1-As/Ac) × 100
Were
As is the absorbance in the presence of test substance and Ac is the absorbance of control.

2.4 Statistical Analysis
The software Graph Pad Prism 5 version 5.01 was utilized to calculate the IC50 values and conduct all measurements in triplicate.The results are provided as the mean standard deviation using GraphPad software, Inc., located in La Jolla, CA

, USA. This program is used for data analysis.
The present study utilized the invitro method to evaluate the inhibitory impact of the methanolic extract of the whole par t of Justicia adhatoda L on α-amylase and α-glucosidase enzymes.
The methanolic extract of the whole Justicia adhatoda L. shown inhibitory effects against amylase and glucosidase at a c oncentration of 0.5 mg/ml, with inhibitory values of 1.670 and 1.431, respectively.The primary medicine used as a refer ence was acarbose, which effectively blocked the activity of amylase with an IC 50 value of 0.118 mg/ml and αglucosid ase with an IC 50 value of 0.091 mg/ml.

3. RESULTS

3.1 Phytochemical Screening

The extraction of the whole plant of Justicia adhatoda L was conducted, resulting in an extract yield of 8.1%.All extracts exhibited a dark brown hue, with the methanolic extract of the whole Justicia adhatoda L plant being in a semisolid stat e.
The methanolic extract of the entire portion of Justicia adhatoda L (JAWME) was found to include glycosides, alkaloids , amino acids, carbohydrates, phenolic compounds, tannins, saponins, flavonoids, and proteins.The bioactive compounds provide somewhat qualitative information on the active components of the extract.An examination of the phytochemica ls in PAMW revealed that the methanolic extract had the greatest quantities of phytoconstituents, as shown in Table 1. Consequently, JAWME underwent further in-vivo investigation.

Table 1 displays the outcomes of the phytochemical screening test.

S. No.	Experiment	Result		
		Pet. Ether Extract	**Ethyl Acetate**	**Methanol**
Test for Carbohydrates				
+1.	Molisch's Test	-ve	-ve	+ve
2.	Fehling's Test	-ve	-ve	+ve
3.	Benedict's Test	-ve	-ve	+ve
4.	Bareford's Test	-ve	-ve	+ve
Test for Alkaloids				
1.	Mayer's Test	-ve	+ve	+ve
2.	Hager's Test	-ve	+ve	+ve
3.	Wagner's Test	-ve	+ve	+ve
4.	Dragendroff's Test	-ve	+ve	+ve
Test for Terpenoids				
1.	Salkowski Test	-ve	-ve	+ve
2.	Libermann-Burchard's Test	-ve	-ve	+ve
Test for Flavonoids				
1.	Lead Acetate Test	-ve	+ve	+ve
2.	Alkaline Reagent Test	-ve	+ve	+ve
3.	Shinoda Test	-ve	+ve	+ve
1.	$FeCl_3$ Test	-ve	+ve	+ve
2.	Lead Acetate Test	-ve	+ve	+ve
3.	Gelatine Test	-ve	+ve	+ve
4.	Dilute Iodine Solution Test	-ve	+ve	+ve
Test for Saponins				
1.	Froth Test	+	-ve	-ve
Test for Protein and Amino acids				
1.	Ninhydrin Test	-ve	-ve	+ve
2.	Biuret's Test	-ve	-ve	+ve
3.	Million's Test	-ve	-ve	+ve
Test for Glycosides				
1.	Legal's Test	-ve	-ve	+ve
2.	Keller Killani Test	-ve	-ve	+ve
3.	Borntrager's Test	-ve	-ve	+ve

+ = Components present

- = Components absent

Table 2: α-amylase and α-glucosidase inhibitory effects of *Justicia adhatoda* L extract

SUBSTANCE	IC50 Values of α- amylase (mg/ml)	IC50 Values of α- glucosidase(mg/ml)
Acarbose	0.118	0.91
Extract	1.670	1.431

3.2 In-vivo studies

Table 3: Effect of *Justicia adhatoda L* methanol extract on blood glucose level of normal and experimental animals during 12 days treatment

Group	Treatment	Dose mg/kg	Blood glucose level mg/dl				
			initial	1st day	3rd day	6th day	12th day
I.	Normal control	_	80.5±5.47	79.73±6.30	78.00±4.73	78.63±4.83	80.00±5.37
	Standard treated metformin +alloxan	251+160	288.5±6.93*	263.5±6.86*	188.65±7.65*	131.83±6.19*	94.74±9.70*
	Diabetic control alloxan only	150	280.91±10.18**	284.31±10.23**	285.82±11.62**	290.15±10.15**	294.65±9.14**
	Methanol extract +alloxan	100+150	287.64±6.22*	246.63±10.60*	175.14±6.02*	138.02±9.13*	130.63±10.25*
	Methanol extract +alloxan	200+150	296.64±9.07*	241.32±8.91*	166.5±5.36*	164.83±8.30*	156.33±15.17*
	Methanol extract +alloxan	300+150	292.18±9.52*	244.30±9.31*	171.51±5.52*	178.33±4.51*	180.63±5.60*
	Methanol extract +alloxan	400+150	291.32±5.27*	259.61±6.11*	180.81±6.03*	187.67±3.00*	191.63±6.18*

Values are expressed in mean ± S.D ,Each group contain 6 animals (n=6)
One way ANOVA followed by Dunnett's test (P< 0.05) is used. ∗P < 0.01 and ∗∗P< 0.05 vs. Normal control

3.2.1 Histopathology Study

Using conventional micro method,pancreatic slices that had been immersed in bovine solution for 12 hours were prepared for paraffin embedding.A 0.5 micrometer sample of the pancreas, which had been coarsely pulverized with alum and stained with hematoxylin and eosin, was subsequently anal yzed under a microscope to observe any histological alterations.
Below are the precise details of the pathology studies, along by their respective descriptions[16,17].

3.2.2 Samples of the pancreas

Group I: Normal control: - The section displays the pancreas. The islets are in a regular state. The architectural integrity is maintained. The acini are covered with circular to elliptical cells with a modest amount of cytoplasm and tiny circular to elliptical nuclei. (Figure 01: Pancreas)
Group II: Standard treatment: This section displays the pancreatic.The islets have normal characteristics.The architectu ral integrity is maintained.The acini are covered with circular to elliptical cells with a modest amount of cytoplasm and t iny circular to elliptical nuclei.(Fig 02: Pancreas)
Group III: Diabetic control: - This section displays the pancreas. The islets are in a regular state. The architectural integrity is maintained.There is little accumulation of lymphocytes at some areas.The acini are covered with circular to elliptical cells with a modest amount of cytoplasm and tiny circular to elliptical nuclei.(Figure 03: Pancr eas)
Group IV: Methanol extract administered at a dosage of 100 mg/kg resulted in the visualization of the pancreas in the s ection.The stroma contains a high concentration of lymphocytes that are spread out and not concentrated in one area.The acinar cells exhibit normal morphology and function.(Figure 04: Pancre as)
Group V: Administration of methanol extract at a dosage of 200 mg/kg:The section displays the pancreatic. The architecture is typical.The islets are in a regular state.The acinar cells exhibit a considerable amount of cytoplasm and have nuclei that are circular to oval in shape. (Figure 05: Pancreas)
Group VI: Administration of a methanolic extract at a dose of 300 mg/kg resulted in the observation of the pancreas in t he section. The islets are in a regular state. The architectural integrity is maintained. The acini are covered with circular to elliptical cells with a modest amount of

cytoplasm and tiny circular to elliptical nuclei. (Figure 06: Pancreas)
Group VII was administered a methanolic extract at a dosage of 400 mg/kg. The section displays the pancreatic. The islets are in a regular state.The architectural integrity is maintained.
The acini are covered with circular to elliptical cells with a modest amount of cytoplasm and tiny circular to elliptical nu clei. (Figure 07: Pancreas)

3.3.1 Histopathology of Pancreases

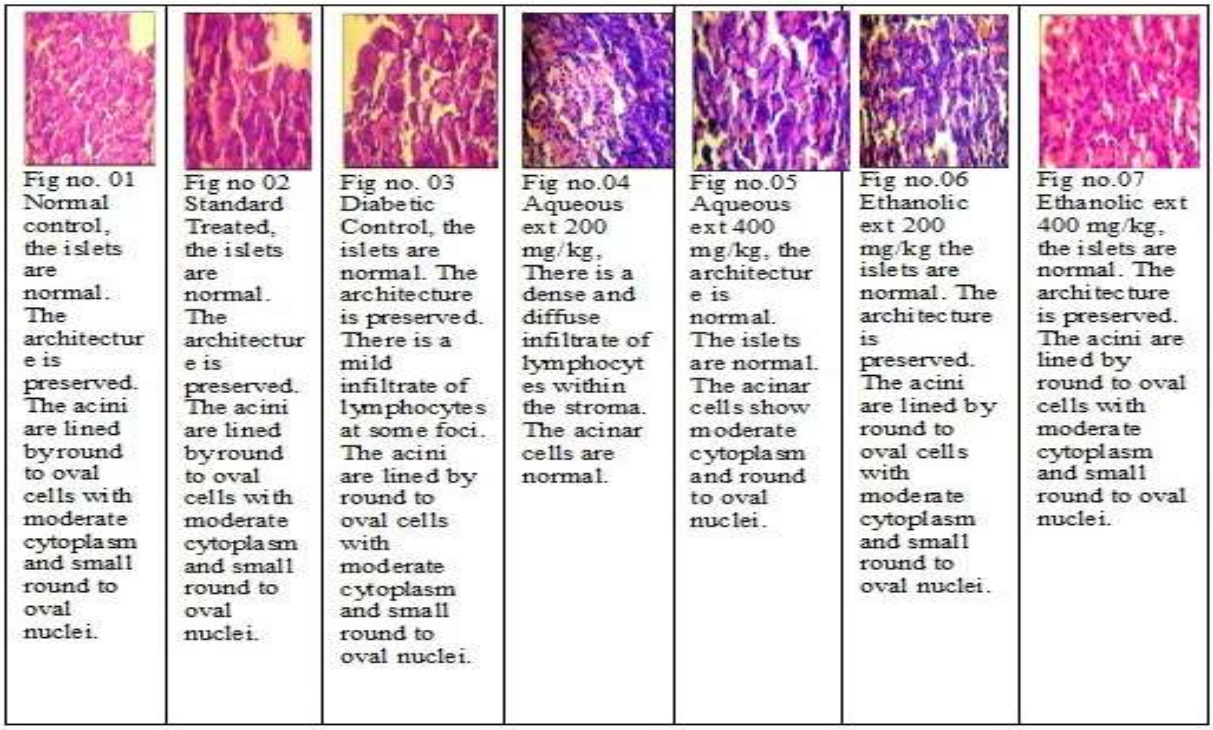

Figure 2: Histopathology of Pancreases

1. DISCUSSION

The phytochemical study of the extracts from the Justicia adhatoda plant identified several components, such as alkaloid s, glycosides, flavonoids, saponins, carbohydrates, fixed oil & fat, and tannins, among others. Please refer to Table 1 for more details.The histopathology of pancreases is depicted in Figure 2.Alloxan is a cytotoxin that specifically targets and kills the pancreatic islet of Langerhans cells in animals. This results in a decrease in the production of insulin and an incr ease in blood sugar levels.The user's text is "[18]".During the study, diabetic rats that were given the methanolic extract of the whole part of Justicia adhatoda L experienced a significant decrease in their blood glucose levels.
[19]The Methanolic extract of the whole Justicia adhatoda L plant was given to subjects at doses of 100 mg/kg, 200 mg/ kg, and 300 mg/kg.After 12 days of treatment with a 400 mg/kg dosage of methanolic extract, the Blood Glucose Level (BGL) of alloxaninduced diabetic rats decreased from 296.64±9.07 to 130.63±10.25 mg/dl (see Table 3).These data sug gest that both extracts significantly contribute to the decrease in blood glucose levels (BGL).
The methanolic extract of the whole plant of Justicia adhatoda L exhibited significant antiamylase and antiglucosidase a ctivities.Alkaloids, phenolics, triterpenoids, flavonoids, and steroids were detected in the initial phytochemical examinat ion of the whole section of Justicia adhatoda L.Based on the data, it was discovered that JAWME had the highest level o f inhibitory potential.[20]
Several bioactive chemicals derived from various plants have been scientifically demonstrated to possess hypoglycemic properties. Among these compounds, flavonoids and phenolics such as oleanane, ursane, and lupane have the most pote nt anti-diabetic effects.
The αenzyme inhibitory characteristics of this plant may be attributed to the triterpenoids present in it. Furthermore, JAWME has been shown to contain polyphenolic chemicals that have the potential to bind with or inhibit certain enzyme sites, hence reducing the activity of α-amylase and α-glucosidase.[21]
One potential method that bioactive substances (such as alkaloids, vasicinone, vasicinol, adhatodine, adhatonine, adhava

sinone, anisotine, and peganine) may use to regulate blood glucose levels is by inhibiting the activities of αamylase and αglucosidase in the gut.These plants have encouraged the beta cells to enhance the production of insulin, hence promoti ng the absorption and use of glucose by other tissues. "[22,23,24]"

1. CONCLUSION:

JAWME, when administered orally, significantly reduces blood sugar levels. However, its effectiveness is weaker or lo wer compared to metformin, a standard medicine for this purpose.The key chemicals responsible for inhibiting the activi ty of amylase and glucosidase, and potentially useful in reducing postprandial glucose levels, are referred to.Utilizing in digenous plant resources to create novel antidiabetic medications might be beneficial. Consequently, further investigatio n was necessary to ascertain the probable mechanism of action.

DECLARATION OF INTERESTS

The authors affirm that they do not possess any recognized conflicting financial interests or personal ties that might have potentially influenced the findings presented in this research.

AUTHOR'S CONTRIBUTIONS

Author 1: S. P. Singh
He executed the tasks of conceptualizing, formulating the methodology, collecting data, and authoring the research.
Author 2: Dr. Alok Kumar Dash He analyzed the dataset and conceptualized the project.

CONFLICTS OF INTEREST

The writers affirm that they do not have any conflict of interest.

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