# ANTI-DIABETIC ACTIVITY OF *ABUTILON INDICUM*IN GLUCOCORTICOID INDUCED INSULIN RESISTANT MALE ALBINO WISTAR RATS

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## ABSTRACT

Antidiabetic activity of ethanolic and aqueous extracts of Abutilon indicum (AI) was investigated in glucocorticoid (dexamethasone 8 mg/kg b. wt.,) injected male wistar rats. The AI leaf extracts at a dose of 400mg/kg b. wt., and reference standard drug pioglitazone (PIO) 45mg/kg b. wt., injected to the respective groups for 21 days was able to significantly regulate the serum glucose, insulin, cholesterol, and triglycerides in the glucocorticoids injected. Quite interestingly the results attained with the treatment of AI extract were comparable with the results of PIO treated rats. Anti-hyperglycemic effects attributed with the treatment of AI extract may be due to the presence of one or more Phyto-constituents that were identified in the AI which is involved in the regulates the glucose and effects on insulin. Our study supports the traditional usage of the whole plant of AI by Ayurvedic physicians for the control of diabetes. Hence it might help in preventing the complications of diabetes and serves as a good adjuvant in the present armamentarium of anti-diabetic drugs.

**Keywords:** *Abutilon Indicum, Antidiabetic activity, Glucocorticoids, Dexamethasone*

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## INTRODUCTION

Diabetes mellitus (DM) is a syndrome characterized by chronic hyperglycemia and disturbances of carbohydrate, fat and protein metabolism associated with absolute or relative deficiencies in insulin secretion and/or insulin action when fully express diabetes is characterized by fasting hyperglycemia. DM may be suspected or recognized clinically by the presence of characteristic symptoms such as excessive thirst, polyuria, pruritus, unexplained weight loss or one or more of the many complications associated with or attributable to the disease.[1-6]

The most characteristic feature in DM is persistently high level of glucose in the blood. When glucose cannot be metabolized by the cells then it remains in the bloodstream. A person with diabetes therefore has constantly high blood glucose levels[2-4]. As the glucose level becomes sufficiently high, some of the glucose is excreted in the urine. Hence, the name 'diabetes' which means 'to run through' and 'mellitus' means sweet or with a taste of honey.

DM is taken into consideration as one of the five leading reasons of loss of life globally. About a hundred and fifty million human beings are suffering from diabetes worldwide, which is sort of 5 times more than the estimates ten years ago and this will double by the year 2030[7]. India leads the manner with its biggest range of diabetic topics in any given country. It's been anticipated that the range of diabetes in India will increment57.2 million continually by the year 2025[8].Plants have played a major role in the introduction of new therapeutic agents. Herbs have provided us some of the very important lifesaving drugs used in the armamentarium of modern medicine. Among estimated 250000-400000 plant species only 6% have been studied for biological activity and 15% have been investigated scientifically[9]. This shows a need for planned activity guided phytopharmacological evaluation of herbal drugs[10].

AI(L) sweet belongs to family Malvaceae, is a cog-like fruits, and is found abundantly in wastelands[11]. It is a perennial shrub, softly tomentose and up to 3m in height. The leaves are evergreen, Base-cordate, stipulate, filiform, ovate, acuminate, toothed, rarely sub trilobite and 1.9-2.5 cm long. Petiole1.5 -1.70cm lengthy, cylindrical, yellowish in colour, stellate and bushy. The flowers are yellow in colour; peduncle jointed above the middle. The petioles are 3.8 - 7.5cm lengthy; stipules 9mm lengthy; pedicels often 2.5-5mm long, axillary solitary, jointed very close to to pinnacle and the seeds are three-5mm, kidney formed, and reniform, tubercled or minutely stellate hairy, black or darkish brown. It is used as Anthelmintic, antiemetic, anti-inflammatory, and also used for urinary or uterine discharge, piles, and antidote. It is used in the treatment of fever, dry cough; bronchitis, Gonorrhea and leprosy. This plant has a long history of being used medicinally as an antidiabetic remedy, and phytochemical screening of the plant revealed that it contained alkaloids, flavonoids, tannins, saponins and glycosides.[11-12]

AI is a hairy herb or underneath shrub observed within the outer Himalayan tracts from Jammu to Bhutan as much as an altitude of 1500 m and lengthening thru the entire of northern and central India. It could grow in dry and terrible soil and require hot conditions. In India after rainy season develop it's miles on roadsides and waste locations.

Many traditional herbal treatments for diabetes also are used however maximum of the proof

for their useful effects is anecdotal. Traditional anti-diabetic flora may offer new oral hypoglycemic compounds, which can counter the high fee and poor availability of the contemporary medicines / modern drugs for rural populations in growing nations. India is widely known for its herbal wealth. Medicinal flowers like Trigonella foenum graecum, AI, Allium Sativum, Gymnema slyvestre and Syzygium cumini have been studied for remedy of DM. Within the indigenous Indian gadget of drugs precise numbers of plant life had been stated for the remedy of diabetes and some of them had been experimentally evaluated and active principle had been isolated. WHO (1980) has also suggested the evaluation of the effective of plants in circumstances' wherein there are not any safe current dose[13]. The ethnobotanical facts report nation that about 800 plant life can also own anti-diabetic capability. Lately the medicinal values of various vegetation extracts have been studied through many scientists inside the field of diabetic studies[14].

The abutilon genus of the Malvaceae family contains about a hundred and fifty plant species; those are extensively distributed in tropical and subtropical nations of Asia, Africa, Australia and United States of America.

## MATERIALS AND METHODS

**Collection and authentication of plant material:** Whole plant of AI was collected from less polluted field areas of Karimnagar, Telangana state of India and authenticated by Dr. Praveen Reddy (Botanist), Vivekananda Degree and PG College, Karimnagar, Telangana.

**Preparation of AI extracts:**

Leaves of AI were rinsed in tap water to remove any dust particles. After completely wiped of the water droplets, the leaves were dried under shade and coarsely powdered. The Aqueous extract of AI leaves (AEAIL) was prepared by macerating the leaf powder in sterile distilled water for 72 hr. After 72 hr, the aqueous extract was carefully drained off and filtered using masculine clothe to remove any coarse or bulky leave material and was evaporated to obtain a semisolid mass. The prepared semi-solid mass of plant extract was stored in desiccators till further processes. Ethanolic extract of AI leaves (EEAIL) was prepared by using Soxhlet extraction method. The extract was filtered using masculine cloth and evaporated to dryness to obtain a semi-solid mass. The prepared semi-solid mass of the extracted material was stored indesiccators until further use.

**Qualitative Screening of Phyto-constituents:** Preliminary phytochemical screening of both the AEAIL and EEAIL were performed by employing the standard qualitative assays to detect the presence of alkaloids, phenolics, flavonoids, saponins, carbohydrates, steroids and Terpenoids.

**Animals used in the study:** Male albino rats of wistar strain weighing approximately 250g ± 30 g body weigh were procured from the animal house of Pratima Institute of Medical Sciences, Karimnagar, and Telangana. The animal usage protocol was strictly adhered as per the regulations of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). The animals were housed in well ventilated poly-propylene rat cages, maintained under normal temperature and light: dark (12:12) cycle with free access to commercial pelted rat chow and water ad libitum throughout the study. The animals were acclimatized for at least one week before the start of the study and were used to determine the acute toxicity, anti-hyperglycemic and anti-hyperlipidemic effects of AEAIL and EEAIL in the current study.

**Determination of acute toxicity of AI extracts in rats:**

Acute toxicity study was performed according to Organization for Economic Co-operation and Developmentguideline 423. Animals were fasted overnight prior to dosing without interruption in

water supply. On the next day morning body weight of the animals were weighed and randomly grouped into nine containing six animals in each group. Four ml of ethanol was used as solvent to dissolve different concentrations of AEAIL and EEAIL to obtain the respective dosages namely 500 mg $kg^{-1}$ b. wt., 1000 mg $kg^{-1}$ b. wt., 1500 mg $kg^{-1}$ b. wt., and 2000 mg $kg^{-1}$ b. wt.

Group 1 : Normal Control

Group 2 : Animals received a single oral dose of AEAIL 500 mg $kg^{-1}$ b. wt.

Group 3 : Animals received a single oral dose of AEAIL 1000 mg $kg^{-1}$ b. wt.

Group 4 : Animals received a single oral dose of AEAIL 1500 mg $kg^{-1}$ b. wt.

Group 5 : Animals received a single oral dose of AEAIL 2000 mg $kg^{-1}$ b. wt.

Group 6 : Animals received a single oral dose of EEAIL 500 mg $kg^{-1}$ b. wt.

Group 7 : Animals received a single oral dose of EEAIL 1000 mg $kg^{-1}$ b. wt.

Group 8 : Animals received a single oral dose of EEAIL 1500 mg $kg^{-1}$ b. wt.

Group 9 : Animals received a single oral dose of EEAIL 2000 mg $kg^{-1}$ b. wt.

After administration of test samples both the AEAIL and EEAIL, the animals were observed continuously for the first 4 hr and at two hours interval for a period of 24 hrs for any behavioral changes. Mortality rate of rats were also recorded at the end of 24 hr[15].

**Determination of anti-hyperglycemic and anti-hyperlipidemic effects of AI extracts in rats:**

To determine the anti-hyperglycemic and anti-hyperlipidemic effects of the extracts of AI leaves, the animals were randomly dived into five groups containing six animals in each group.

Group I: Normal control animals – Received only the same volume of the vehicle used to dissolve the AI extracts

Group II : Diabetic control (DC) rats received oral dose of 2% gum acacia for a period of 21 days (from day $0^{th}$ to $21^{st}$ day of the study) and received intraperitoneal injections of Dexamethasone (8mg $kg^{-1}$ b. wt.,) once a day from the $8^{th}$to $21^{st}$ day

Group III: EEAIL treated + DC received EEAIL (p.o) 400mg $kg^{-1}$ b. wt., (selected based on the observed acute toxicity study result of the present study) from day 0 to day 21, additionally the animals have also received intraperitoneal injections of Dexamethasone (8mg $kg^{-1}$ b. wt.,) once daily from $8^{th}$to $21^{st}$ day.

Group IV: AEAIL treated + DC received AEAIL (p.o) 400mg $kg^{-1}$ b. wt., (selected based on the observed acute toxicity study result of the present study) from day 0 to day 21, additionally the animals have also received intraperitoneal injections of Dexamethasone (8mg $kg^{-1}$ b. wt.,) once daily from $8^{th}$to $21^{st}$ day.

Group V: Standard drug (Piooglitazone) treated + DC received 45mg $kg^{-1}$ b. wt., oral dose of PIO[16](p.o) from day 0 to day 21, additionally the animals have also received intraperitoneal injections of Dexamethasone (8mg $kg^{-1}$ b. wt.,) once daily from $8^{th}$to $21^{st}$ day.

On days 0, 8 and 22 of the study period, fasting blood samples were collected through retro-orbital sinus puncture under Ketamine (50 mg/kg/i.p.) anesthesia. On day $22^{nd}$ animals were sacrificed by cervical dislocation, blood samples were collected and allowed for clotting to separate the serum.

The blood samples were centrifuged for 20 minutes at 1500 rpm for 10 minutes. Serum was used for estimation of serum glucose, insulin and lipid levels. Body weight of animals have been recorded on weekly basis throughout the study[17-20].

Liver was dissected out, perfused with physiological saline, weighed and a portion was stored in 10% formalin solution and used for histopathological investigations.

**Statistical Analysis:** The results have been tabulated and represented as mean±SD for six rats in each group. Statistically significant differences between the mean were calculated by employing the one-way analysis of variance

(ANOVA), followed by Dunnett test. P values <0.05 were considered significantly different. Statistical Package for Social Studies version (SPSS) was used for the analysis in the present study.

## RESULTS

**Table 1:** Presence/absence of selected phytochemical constituents in the EEAIL and AEAIL

| Test | EEAIL | AEAIL |
|---|---|---|
| **Alkaloids** | + | + |
| **Carbohydrates** | - | - |
| **Flavonoids** | + | + |
| **Resins** | + | + |
| **Phenols** | + | + |
| **Triterpenoids** | + | + |
| **Steroids** | - | - |
| **Quinones** | - | - |
| **Saponins** | + | + |
| **Tannins** | + | + |
| **Amino acids** | - | - |

The ethanolic and aqueous extract prepared and used in the present study was subjected to determine the presence/absence of some of the selected phyto-constituents, those have been reported to have anti-diabetic and hypolipidemic effects in several studies.[21-22] The results observed in our present study, based on the qualitative assays, the presence/absence of the phyto-constituents have been shown in Table 1. In our study we were able to determine the presence of alkaloids, flavonoids, resins, phenols, triterpenoids, saponins, and tannins in both the extracts, ethanolic and aqueous, prepared from AI leaves that the ethanolic extract of AI leaves, whereas it shows negative for the presence of carbohydrates, steroids, quinones and amino acids.

**Acute Toxicity**

Acute toxicity examination of the both the extracts of AI leaves, EEAIL and AEAIL, with different doses, 500 mg $kg^{-1}$ b. wt., 1000 mg $kg^{-1}$ b. wt., 1500 mg $kg^{-1}$ b. wt., and 2000 mg $kg^{-1}$ b. wt., in the present study revealed no significant behavioral changes up to 4 hrs and no mortality was observed until up to 48 hrs even with the maximum dose level of 2000mg/kg b. wt.

**Table 2:** Regulatory effects of EAIL and AEAIL against Dexamethasone induced alteration in blood glucose levels in rats

| **Blood sugar in mg/dl** | | | |
|---|---|---|---|
| **Groups/Days** | **Day 0** | **Day 8** | **Day 21** |
| **Group I** | 99.50±0.73 | 98.82±0.55 | 99.34±0.67$^{s}$ |
| **Group II** | 102.58±0.40 | 103.61±0.82 | 267.96±1.51$^{NS}$ |
| **Group III** | 99.60±0.54 | 98.89±0.53 | 141.71±6.32$^{NS}$ |
| **Group IV** | 98.82±0.55 | 99.59±0.64 | 161.22±0.64$^{s}$ |
| **Group V** | 101.50±0.73 | 97.82±0.55 | 131.63±2.08$^{NS}$ |

NS-Not significant
S- Significant

Values are expressed as mean±SD (n=6). Group I-normal control; Group II diabetic control; Group III Ethanolic extract Abutilon indicum (400 mg/kg); Group IV Aqueous extract Abutilon indicum (400 mg/kg); Group V pioglitazone (45mg/kg). Comparisons made: [a] Day 0 vs Day 8; [b]Day 8 vs Day 21; [c]Day 0 vs Day 21; [d]Group I vs Group II, Group III, Group IV, Group V on day 21; [e]Group II vs Group III, Group IV and Group V on day 21; Group V vs Group III and Group IV on day 21; [g]Group III vs Group IV on day 21. *p<0.05; NS-Not significant

Dexamethasone at the given dose (8 mg $kg^{-1}$b.wt.,) once daily from day 8to day 21 has significantly increased the blood glucose (table 2). On the other hand, it was observed from the

results of the present study, oral treatment of rats with the extracts of AI leaves namely, EEAIL and AEAIL at a dose of 400 mg $kg^{-1}$b.wt., for a period of 21 days (7 days prior to Dexamethasone doses and continued till the end of the experimental period) was able to regulate the blood glucose levels. Comparison of the results group III and Group IV with group II, DC rats (table 2), showed a significant regulation in levels of glucose that was found significantly elevated due to dexamethasone injections.

**Effect of AI extract against insulin resistance and hyperglycemia**

**Table 3:** Protective effect of EAIL and AEAILagainst Dexamethasone induced hyperglycemia and insulin resistance

| Groups | Treatment | Glucose (mg/dl) | insulin µU/ml |
|---|---|---|---|
| **Group I** | **Normal Control** | 99.34±0.67 | 78.31±1.44$^{S}$ |
| **Group II** | **Dexamethasone Control** | 267.96±1.51 | 370.03±4.64$^{NS}$ |
| **Group III** | **Ethanol EXT +Dexamethasone** | 141.71±6.32 | 156.26±1.89$^{S}$ |
| **Group IV** | **Aquas EXT + Dexamethasone** | 161.22±0.64 | 191.16±1.1$^{NS}$ |
| **Group V** | **STD PIO +Dexamethasone** | 131.63±2.08 | 137.60±3.69$^{S}$ |

NS-Not significant
S- Significant

Values are expressed as mean±SD (n=6). Group I-normal control; Group II diabetic control; Group III Ethanolic extract Abutilon indicum (400 mg/kg); Group IV Aqueous extract Abutilon indicum (400 mg/kg); Group V pioglitazone (45mg/kg). Comparisons made: [a]Group I vs Groups II, III, IV & V; [b]Group II vs Groups III, IV & V; [c]Group V vs Groups III & IV; *p<0.05; NS-not significant

**Serum insulin and glucose levels:** As shown in Table 3 Dexamethasone administration significantly (p<0.05) elevated serum glucose and insulin levels in DEX treated group compared to control group of rats in the present study. Administration of Ethanolic and Aqueous extract of Abutilon indicum (400 mg/kg) significantly (p<0.05) regulated the elevation of serum glucose and insulin levels, those were found significantly elevated with the DEX injection. The reference standard drug Pioglitazone also significantly (p<0.05) regulated the blood glucose and insulin levels compared to diabetic control group.

**Histopathology examination:** Isolated liver tissues were fixed in 10% formalin solution. Tissues were sliced to 5 µmthickness by using microtome and sections were stained with H&E stain. Further these sections were analyzed for histopathological changes under the microscope (40X).

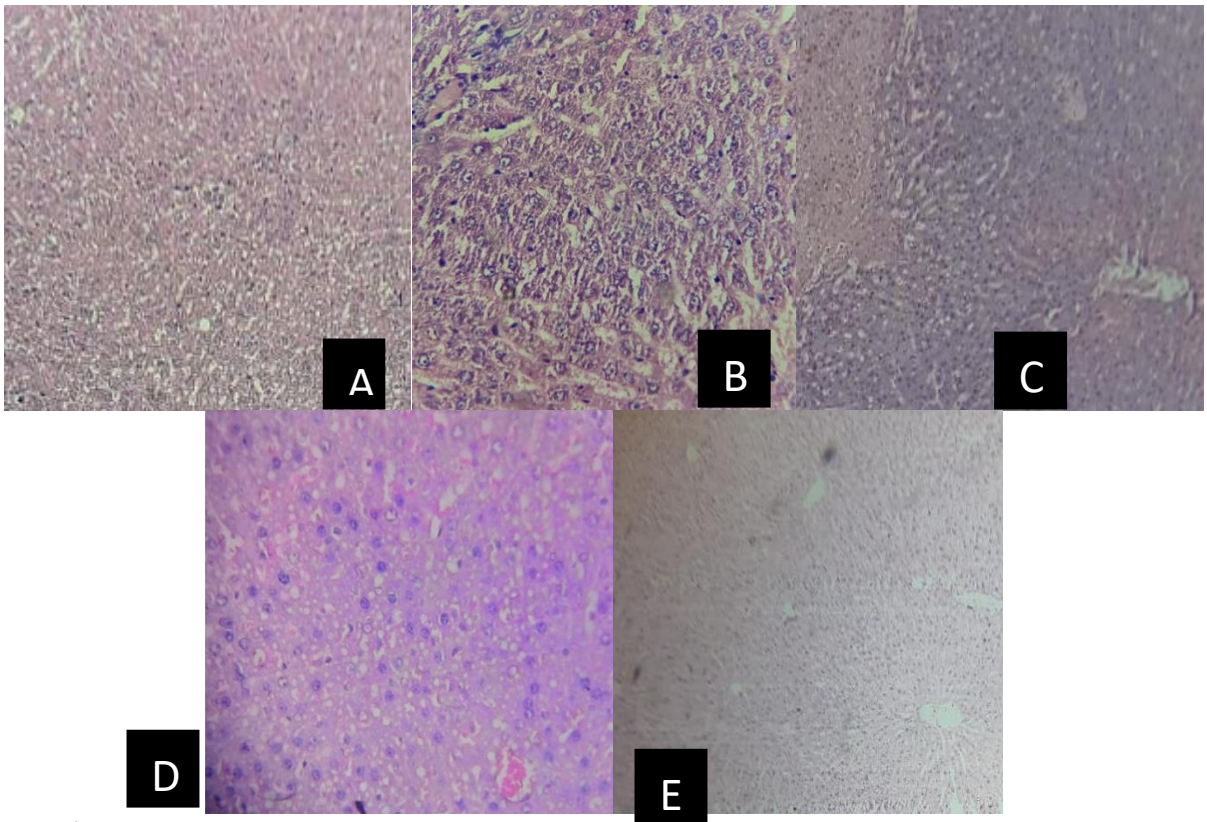




Fig-1: A) Normal control rat liver showed normal hepatocytes: Centrally placed nucleus: cytoplasm is pink and vesicular. (H&E, 40X); B) Dexamethasone treated rat liver showed loss of liver architecture; Hepatocytes showed fatty vacuoles in cytoplasm; Nucleus is pushed to periphery. (H&E, 40X); C) Ethanolic extract of AI treated rat liver exhibited an improvement in architecture; restored fatty changes induced by dexamethasone. (H&E, 40X); D) Aqueous extract of AI treated rat liver exhibited an mild improvement in architecture; Restored fatty changes induced by dexamethasone E) Pioglitazone treated rat liver showed partial improvement in hepatic parenchyma; Mild fatty changes were seen in cytoplasm. (H&E, 40X).

**DISCUSSION**

The hypoglycaemic activity of leaves was studied on rats by using oxidase-peroxidase method. The alcoholic & aqueous extract after oral administration of 400 mg/kg p.o. were shown to exhibit significant regulation in the blood glucose levels in our study. Our findings are in agreement with several other studies where various extracts of plants leaves have been shown to have the ability of regulating the blood glucose levels in experimentally induced hyperglycemia (Ref).[23-26]Normoglycemic studies revealed its capacity to lower blood glucose levels. Diabetic rats treated with the CF revealed a significant reduction in blood sugar levels compared with the diabetic control group at the end of a 21-day experimental period.

This decrease in the blood sugar levels may be attributed to the stimulation of the residual pancreatic mechanism or to a probable increase in the peripheral utilization of glucose.[27] Treated diabetic rats showed a marked increase in serum insulin levels thereby suggesting that the hypoglycemic activity of Abutilon indicum is related to insulin secretion. Results of our present study are in agreement with the findings of Nikkila and Kekki[28]. The most common

abnormalities in diabetes are hypertriglyceridemia and hypercholesterolemia.[29] Hypertriglyceridemia is also associated with the metabolic consequences of hypercoagulability, hyperinsulinemia, insulin resistance, and insulin intolerance[30].

In our study, insulin levels in all animal groups, Normal Control group showing insulin level 78.31±1.44, Dexamethasone Control group showing insulin level 370.03±4.64, Ethanol EXT + Dexamethasone - group showing insulin level 156.26±1.89, Aqueous EXT + Dexamethasone-group showing insulin level 191.16±1.11STD PIO +Dexamethasone - group showing insulin level 137.60±3.69*.

In our study, high level of insulin in Dexamethasone Control group when compare with the other groups. Low level of insulin in Normal Control group when compare with the other groups. In treatment with extract group's insulin secretion is observed due to the regeneration β-islets in pancreatic tissue. Insulin is involved in not only Type-I Diabetes and also acts on Type-II Diabetes, insulin always reduces glucose levels in blood to reduce the complications of Diabetes Mellitus.

Molecular mechanisms supporting the antidiabetic effect was studied to evaluate whether extract of the plant improves insulin sensitivity. These results suggested that the plant extract may be beneficial for reducing insulin resistance through its potency in regulating adipocyte differentiation

The promotion of the extract on insulin secretion was confirmed by incubating β cell of pancreatic islets and INS-1E insulinoma cells with the extract at 1 to 1000 μg/mL. These observations suggest that the aqueous extract from the A indicum plant has antidiabetic properties, which inhibited glucose absorption and stimulated insulin secretion. Phytochemical screening also revealed that the extract contained alkaloids, flavonoids, tannins, glycosides, and saponins that could account for the observed pharmacologic effects of the plant extract.

The phytochemical analysis by the Spectrophotometric methods of AI is useful traditional medicine. The leaves of AI Shown positive for the presence of alkaloids, flavonoids, resins, phenols, triterpenoids, saponins, and tannins whereas it shows negative for the presence of carbohydrates, steroids, quinones and amino acids (Table 1). Phytochemicals play important role by combining with nutrients and dietary fiber to us against diseases though some have bitter taste. Alkaloids have been shown to have antioxidative and antimicrobial effect in many plants. Hypoglycemic activity of AI leaf extracts in rats known from previews study[23]. The ethanolic extracts of AI exhibited significant reduction in the blood glucose levels ($p<0.05$) (group III) compared with diabetic control rats ($p<0.05$) (group II). Flavonoids are known to regenerate the damaged pancreatic β-cells and glycosides stimulate the secretion of insulin in β -cells of pancreas. The observations suggested that the ethanolic extracts from the AI has antidiabetic properties, which inhibited glucose absorption and stimulated insulin utilization and thereby decreased the blood glucose level. The extract changed into evaluated for in-vivo antidiabetic pastime using glucocorticoids at a dose of 16mg/kg frame weight. Inside the gift study it became determined that there is a marked elevation inside the blood glucose stage after management of glucocorticoids. This is in accordance with the reviews posted with the aid of diverse authors in which the growth in glucose stages has been attributed to the destruction of beta-cells via glucocorticoids. Damage to the beta-cells is associated with the liberation of saved insulin and then the insulin synthesis is stopped leading to a continual diabetic country. Due to the fact that insulin not be available, glucose absorption is impaired leading to hyperglycemia. There has been a large rise in blood glucose stage in group II, group III and group IV after glucocorticoids

management in comparison to everyday organization I. After the treatment of animals with the ethanolic leaf extract of Abutilon indicum for 21 days, it turned into found that the improved blood glucose degrees decreased substantially. Those results have been tabulated and represented with the aid of a graph the usage of ANOVA observed by using Dunnett test. The present study provides evidence of glucocorticoids induced insulin resistant in Wister rats (group II), it is observed that administration of ethanolic leaf extract of AI (group III) at dosage of 400 mg/kg b.Wt., helps in narrowing the blood glucose levels. Dexamethasone treated rats in our current study showed a marked increase in serum insulin levels thereby suggesting that the hypoglycemic activity of AI is related to insulin secretion.

**CONCLUSION**

Thus, it can be concluded that ethanolic leaf extract of AI has protective effect on type 2 diabetes mellitus. However, the molecular mechanism of the study needs to be carried out. Our study supports the traditional usage of the whole plant of AI by Ayurvedic physicians for the control of diabetes. Hence it might helpful in preventing the complications of insulin resistant diabetes and serves as a good adjuvant in the present armamentarium for insulin receptor sensitizing anti-diabetic drugs.

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