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Antidiabetic Potential of Andrographis Echioides in Streptozotocin-Induced Diabetic Rats

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ABSTRACT

The present study was designed to investigate the hypoglycemic effect of the methanol extract of Andrographis echioides (MEAE) in streptozotocin (STZ)-induced diabetic Wistar rats. Diabetes was induced via a single intraperitoneal injection of STZ at a dose of 55 mg/kg body weight. After three days of induction, hyperglycemic rats were orally administered MEAE at doses of 200, 500, and 800 mg/kg body weight daily for 21 days. Glibenclamide (1 mg/kg, orally) was used as the reference standard. Fasting blood glucose levels were measured on days 7, 14, and 21, along with the evaluation of serum biochemical parameters, including lipid profile. TMEAE treatment resulted in a significant ($P < 0.01$) and dose-dependent reduction in fasting blood glucose levels, the dose 800 mg/kg being the most potent showing complete normalization of blood glucose levels. Also, MEAE significantly ($P < 0.01$) restored the diabetic rats' unusual lipid profiles and other serum biochemical markers to normal. In STZ-induced diabetic rats, Andrographis echioides showed promising hypoglycemic action, supporting its ethnomedical use, according to the results.

Keywords: *Andrographis echioides, hypoglycemic, fasting blood glucose, lipid profiles, streptozotocin*

1. INTRODUCTION

The most common feature of diabetes mellitus, a chronic metabolic disease, is persistent hyperglycemia based on by abnormalities in either insulin action or secretion, or both. The global prevalence of diabetes has been on the rise, with the International Diabetes Federation reporting that approximately 537 million adults were living with the disease in 2021, a number expected to reach 643 million by 2030 [1]. Even with advancements in synthetic hypoglycemic medications, hypoglycemia, liver damage, and gastrointestinal distress are common side effects of long-term use [2]. The investigation of medicinal plants as safer substitutes for diabetic treatment is therefore receiving attention.

One such plant is Andrographis echioides, which belongs to the Acanthaceae family and has long been used in Southeast Asian and Indian medicine to cure a variety of conditions, such as liver problems, fever, and inflammation. Bioactive substances with anti-inflammatory and antioxidant qualities, including diterpenoids, flavonoids, and tannins, have been detected in A. echioides based on preliminary phytochemical screenings [3]. These substances might have an impact on glucose metabolism and insulin sensitivity.

In view of its selective cytotoxicity to pancreatic β-cells, streptozotocin (STZ), a naturally occurring nitrosourea, is frequently used to induce experimental diabetes in animal models [4]. Preclinical screening of possible antidiabetic drugs is often carried out using the STZ-induced diabetic rat model, which closely resembles the pathophysiology of Type 1 diabetes.

Andrographis echioides is a species of Andrographis Known as kalmegh in Hindi,that belongs to the Acanthaceae family. It is a thick herb that grows in wastelands and plains and bears fruit all year round. Anti-inflammatory, antimicrobial, anthelmintic, antioxidant, and larvicidal activities have been described for Andrographis echioides [5-8]. It has been reported that Andrographis panniculata has anti-diabetic properties [9]. the current study is to examine Andrographis echioides' hypoglycemic effect in rats with diabetes caused by STZ.

The objective is to evaluate its efficacy in lowering blood glucose levels and to assess its impact on biochemical parameters associated with diabetes, thereby providing a scientific basis for its traditional use in managing hyperglycemia. The plant selected for this present work is locally available in the Erode district and has been used for long a time in local folklore

medicine for the treatment of diabetes.

2. MATERIALS AND METHODS

Drugs and chemicals

STZ was from Sigma Chemical Co., USA. Glibenclamide was from Hoechst, India. All other reagents used were of analytical grade obtained commercially.

Collection and extraction

The fresh aerial parts of Andrographis echioides were collected from SKM Siddha and Ayurvedic medicines India Pvt. Ltd., Erode Dist., Tamilnadu, India,in the month of August 2013 and identified by GVS Murthy, Botanical Survey of India, Coimbatore, India. . For future use, a voucher specimen has been placed in the lab (BSI/SC/5/23/13-14/TECH.835). The plant's aerial portions have been ground up and shade-dried. Petroleum ether was used to defatten the powder. It had subsequently undergone continuous hot extraction in a Soxhlet system using 95% aqueous methanol. After being vacuum-concentrated, the extract (MEAE) was dried in desiccators, yielding 71 gm, 7.1%w/w. Before its use, the dried extract was stored in vacuum desiccators. Preliminary phytochemical analysis [10] revealed the presence of flavonoids, alkaloids, and steroids in MEAE Plant material.

Animals

Adult male Wistar albino rats weighing 150–200gm were purchased from Venkateshwara Enterprises, Bangalore, Karnataka, India and used throughout the study. All the animals were under the age of 8–12 weeks. They had been kept under standard laboratory settings (temperature 25 ± 2°C with a 12/12 hour dark/light cycle) in a very clean polypropylene cage. They were given a regular pellet diet and adequate supply of water. The animals were acclimatized to laboratory conditions for one week before experiment.. Experiments were performed complied with the rulings of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) New Delhi, India. (Registration No: 1135/a/07/CPCSEA) , and the Institutional Animal Ethics Committee (IAEC) approved the study.

Acute toxicity

By OECD-423 standards, acute toxicity tests were conducted [11]. The study used male Wistar albino rats chosen using a random selection approach. The animals were fasted for 4hrs with free access to water only. For three days, the plant extract was given orally at a dose of 5 mg/kg, and any mortality was noted. The dose was considered toxic if it was determined that two of the three animals had died. To validate the harmful impact, the same dose was given again if the mortality was only determined in one of the three animals. Higher doses of extract (50, 300, and 2000 mg/kg) were used for additional toxicity tests if no death was determined.

Oral glucose tolerance test (OGTT)

Normal rats that had been fasted for the whole night were used for the OGTT. There were five groups of rats (n = 6). Group I was given distilled water (5 ml/kg b.w., p.o.) as a normal control (NC), while groups II, III, and IV were given MEAE at dosages of 200, 500, and 800 mg/kg b.w., p.o., respectively. Glibenclamide 1 mg/kg b.w. p.o. was administered to Group V. Following these treatments, all groups were given oral glucose (4 g/kgb.w.) 30 minutes later. Just before, 30, 60, and 120 minutes after the oral glucose delivery, blood was extracted from the tail vein [12, 13]. A portable glucometer (Accu Sure blood glucose monitoring device) and glucoseoxidase-peroxidase reactive strips were used to measure blood glucose levels.

Induction of experimental diabetes mellitus

The rats were rendered diabetic by a single intraperitoneal dose of 55 mg/kg b.w. STZ freshly dissolved in ice cold 0.1 M citrate buffer (pH 4.5). Fasting blood glucose (FBG) levels were assessed after 72 hours, and only animals with blood glucose levels ≥ 225 mg/dl were employed in the next study. The day on which hyperglycemia had been confirmed was designated as day 0[14, 15].

Treatment schedule and estimation of FBG level

Normal and hyperglycemic rats were divided into seven groups (n = 6) receiving the following treatment [16]:

Group I: non-diabetic individuals received 5 ml/kg b.w., p.o. (NC) of the vehicle (distilled water).

Group II: MEAE 500 mg/kgb.w., p.o., was given to the non-diabetic control group.

Group III: Diabetic control received 5 ml/kg b.w., p.o. (DC) of the vehicle, which is distilled water.

Group IV received MEAE 200 mg/kg b.w., p.o. during the course of their diabetic treatment.

Group V: MEAE 500 mg/kg b.w., p.o., was given during the course of diabetic treatment.

Group VI received MEAE 800 mg/kg b.w., p.o. as part of their diabetic treatment.

Group VII: Glibenclamide 1 mg/kg b.w., p.o. has been given during the course of the diabetic treatment.

For 21 days, the mentioned treatment was used every day. On days 0, 7, 14, and 21, fasting blood glucose levels were measured using a portable glucometer (Accu Sure blood glucose monitoring device).

Body weight

The body weights of rats of each group were recorded on 1st, 7th, and 15th day of MEAE treatment.

Estimation of serum biochemical parameters

After twenty-one days of treatment, blood samples were drawn from overnight fasted rats by retroorbital vein puncture technique anesthetized animals. After allowing the nonheparinized blood to coagulate, the blood serum was separated by centrifuging it for 20 minutes at 4000 rpm. The following blood serum levels were measured enzymatically using commercially available reagent kits (Erba Diagnostics and Span diagnostics Ltd.): total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDLC), high-density lipoprotein cholesterol (HDLC), glycosylated haemoglobin (HbA1C), aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP).

Statistical analysis

The mean ± standard error of mean (SEM) was used to express the data. Graph Pad (Instat) software version 5 was used to analyse statistical significance using one-way analysis of variance (ANOVA) and Dunnett's posthoc test of significance. P values of < 0.05 were considered as statistically significant.

3. RESULTS AND DISCUSSION

Pharmacological treatment with of diabetes is based on oral hypoglycaemic agents and insulin. Long-term use of these medications, however, is costly and can have fatal side effects. The medical community still faces the issue of managing diabetes without causing any negative side effects [17]. The hunt for safe plant-based diabetes control medicines continues, despite significant advancements in traditional anti-diabetic treatment techniques [18]. Globally, medical academia is accepting phytotherapy as a treatment for diabetes mellitus.

. In this work, MEAE's hypoglycemic activity was assessed in rats with STZ-induced diabetic. After pilot research to determine the ideal dosage for raising blood glucose levels above 250 mg/dl, STZ was administered intraperitoneally (i.p.) at a dose of 55 mg/kg to cause hyperglycemia. Even though the rats developed chronic diabetes, the application of a lower dose of STZ (55 mg/kg) resulted in an incomplete loss of pancreatic β cells [19].

Acute toxicity

The MEAE did not show any toxic effect or death up to the dose of 2000 mg/kg, b.w., p.o. in mice.

Oral glucose tolerance (OGTT)

Fig. 1 shows the MEAE's effects on rats administered glucose. The OGTT results demonstrated that MEAE and glibenclamide treatment enhanced tolerance to glucose. The baseline blood glucose concentrations (0 min) did not differ significantly between the groups. Even though loading with glucose raised plasma glucose levels, animals given 500 and 800 mg/kg of MEAE at 30, 60, and 120 minutes during OGTT showed a slight increase in comparison to the NC group. The increase in blood glucose levels following glucose delivery at 120 minutes was significantly ($P < 0.01$) reduced by glibenclamide.

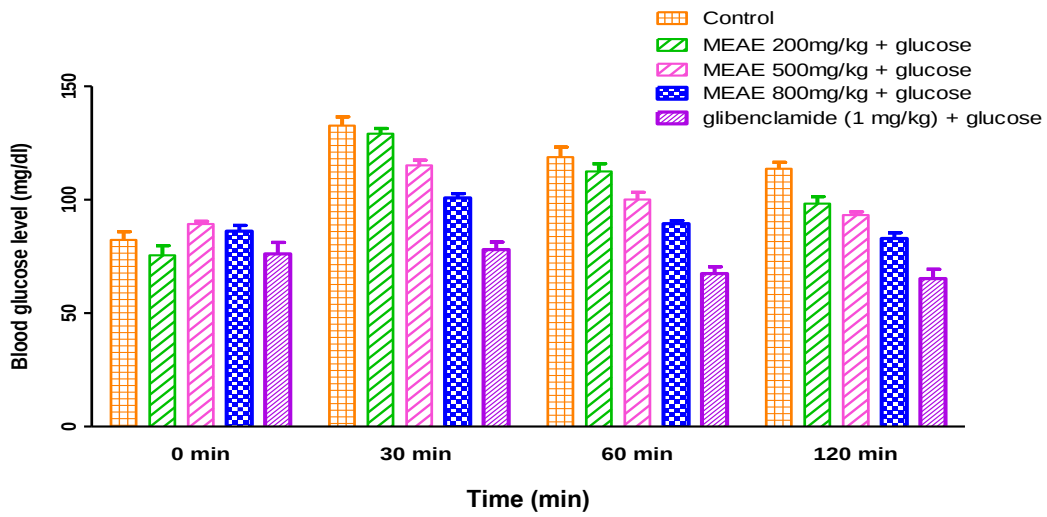

Fig 1: Effect of methanol extract of *Andrographis Echioides* (MEAE) on oral glucose tolerance in normal rats.

In diabetic rats, MEAE significantly reduced blood sugar levels at 200, 500, and 800 mg/kg. While MEAE at 200 and 500 mg/kg considerably decreased hyperglycemia as compared to the DC group, it was unable to return the FBG level to the NC group. However, when MEAE was administered at 800 mg/kg, the blood sugar levels of diabetic rats were lowered down to the NC group level. Normal rats given 500 mg/kg of MEAE showed negligible differences in blood glucose levels compared to the NC group, showing that MEAE preserved glucose homeostasis. The stimulation of insulin release from the islets of Langerhans' existing β cells may possibly be the reason of MEAE's hypoglycemic effect. In order to stimulate pancreatic β cells, the plasma glucose lowering activity was compared with that of glibenclamide, the standard oral hypoglycemic that has been used for several decades to treat diabetes [20].

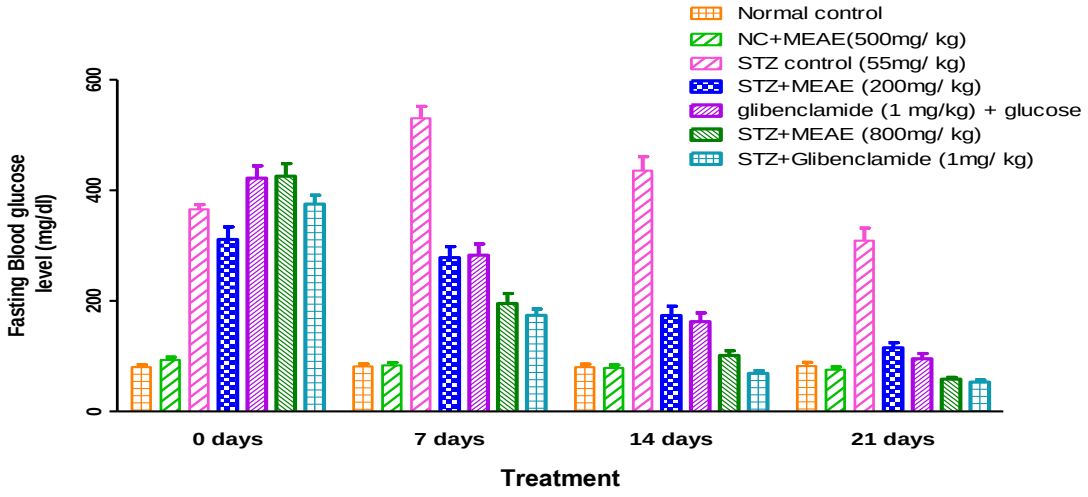

Fig 2: Effect of methanol extract of *Andrographis Echioides* (MEAE) on fasting blood glucose levels in normal and streptozotocin (STZ) - induced diabetic rats.

FBG levels

Fasting blood glucose levels determined in normal and STZ-induced diabetic rats after a single day and at the end of 7, 14, and 21 days of treatment are shown in Fig 2. Here, diabetic rats had a significant effect on blood sugar response after treat for 21 days. NC rats did not show any significant variation in the blood sugar throughout the experimental time.

When STZ (55 mg/kg, i.p.) was administered, blood glucose levels increased several times higher than in the NC group, showing sustained hyperglycemia throughout the course of the study. The FBG levels of the NC group and the normal animals treated with 500 mg/kg of MEAE (Group II) did not vary much. While glibenclamide (1 mg/kg) or MEAE at 800 mg/kg significantly ($P < 0.01$) reduced blood glucose levels near the NC group level, MEAE at 200 and 500 mg/kg

significantly (P < 0.01) reduced hyperglycemia when compared to the diabetic control (DC) group, but it was unable to restore the level to that of the NC group [21].

Effect on body weight

Figure 3 shows how MEAE affects the body weight of both normal and diabetic mice. The body weight of NC animals was found to be constant, however diabetic rats' body weight decreased significantly over the course of 21 days. MEAE treatment significantly (P < 0.01) reversed the body weight decrease caused by STZ.

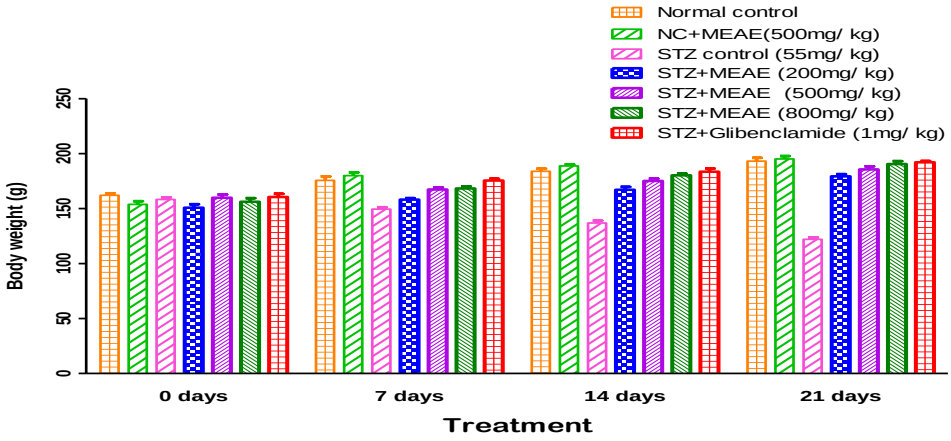

Fig 3: Effect of methanol extract of *Andrographis Echioides* (MEAE) on body weight in normal and streptozotocin (STZ)-induced diabetic rats

When compared to the STZ control animals, diabetic rats administered with MEAE showed a notable improvement in body weight; hence, MEAE showed an important role in regulating the diabetic rats' body weight loss. When MEAE was taken orally, the HbA1C level decreased. The increased level of HbA1C in diabetic rats may be the source of the lower levels of total haemoglobin seen in these animals. Throughout the circulatory life of red blood cells (RBCs), glucose is added to the N-terminal of the haemoglobin β chain to create glycohemoglobin. The average exposure of haemoglobin to glucose over a long period of time is reflected in this nonenzymatic mechanism.

Serum biochemical parameters

Fig. 4 shows the biochemical parameter results. HbA1C was significantly (P < 0.01) reduced with MEAE. When compared to the NC group, the effect of MEAE on groups II, VI, and VII was not significantly different after 21 days. In the diabetic rats, treatment with glibenclamide (1 mg/kg) plus MEAE at 500 and 800 mg/kg resulted in a significant (P < 0.01) decrease in HbA1C. When compared to NC rats, diabetic rats had significantly higher levels of TC, LDLC, and TGs and considerably lower levels of blood HDL-cholesterol (P < 0.01). Glibenclamide (1 mg/kg) and MEAE at 500 and 800 mg/kg significantly (P < 0.01) returned their levels to baseline.

Fig. 4 illustrates the biochemical parameter results. HbA1C substantially (P < 0.01) decreased with MEAE. When compared to normal rats, diabetic rats showed significantly (P < 0.01) higher levels of the blood enzymes AST, ALT, and ALP. In diabetic rats, oral treatment of glibenclamide at 1 mg/kg and MEAE at 500 and 800 mg/kg for 21 days significantly (P < 0.01) restored normal enzymatic activity[22].

The pathophysiology of diabetes mellitus is significantly influenced by lipids. Uncontrolled diabetic mellitus has been shown to increase blood TC, which may be a contributing factor to coronary artery disease [23]. In those with diabetes, hypertriglyceridemia and hypercholesterolaemia are the most prevalent lipid abnormalities. Diabetic rats in this study had higher levels of blood lipids, including TC, LDLC, and TGs. Because insulin inhibits HMG-CoA reductase, a crucial enzyme that acts as a rate limiting factor in the metabolism of cholesterol-rich LDL particles, STZ produced a number of the most common signs of diabetes mellitus, including hypoinsulinemia, which is likely the cause of the elevated serum cholesterol levels [24].

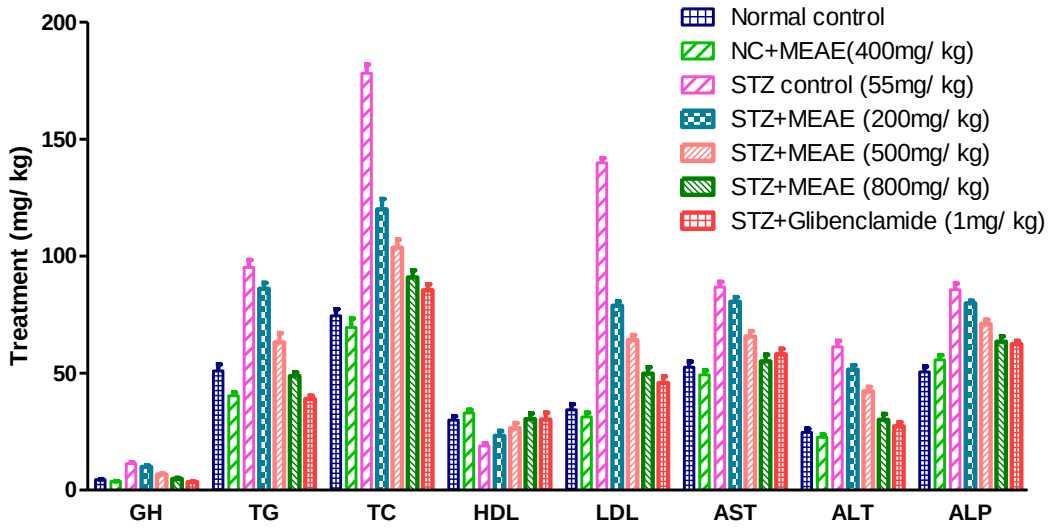

Fig 4: Effect of methanol extract of *Andrographis Echioides* (MEAE) on serum biochemical parameters in normal and streptozotocin (STZ)-induced diabetic rats.

When the state of balance of the free fatty acid esterification-TG lipolysis cycle is shifted in favour of lipolysis, free fatty acid outflow from fat depots causes an increase in blood fatty acid concentration in insulin-deficient diabetes. An antiatherogenic lipoprotein is high-density lipoprotein (HDL). It serves as a preventative measure against coronary cardiovascular disease by moving cholesterol from peripheral tissues into the liver. The rise in HDLC amounts following MEAE treatment might be the result of increased lecithin cholesterol acyl transferase (LCAT) activity, which might help control blood lipid levels [25]. In diabetic rats, oral MEAE treatment brought high blood lipids like TC, LDLC, and TGs closer to normal. Rats with diabetes showed elevated levels of serum biomarker enzymes such SGOT, SGPT, and SALP, indicating decreased liver function that was clearly caused by hepatocellular necrosis. Liver necrosis has been observed in rats with STZ-induced diabetes [26,27]. Therefore, a rise in AST, ALT, and ALP activity indicates the hepatotoxic action of STZ. The liver damage brought on by STZ-induced diabetes decreased after 21 days of MEAE treatment, which independently restored all of the above serum hepatic biochemical markers to normal levels.

4. CONCLUSION

When methanol extract of Andrographis echioides (MEAE) was given to STZ-induced hyperglycaemic Wistar rats in this study, blood glucose levels significantly decreased and serum biochemical parameters, such as lipid profiles, were standardised in comparison to the STZ control group. These results confirm MEAE's traditional therapeutic use by showing that it has potent antidiabetic action. Andrographis echioides shows potential as a complementary and alternative medicine treatment for diabetes because of its significant oral hypoglycemic impact.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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