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Antidiabetic, Hypolipidemic and Hepatoprotective Potential of Edible Leaves Extract from the Plant *Chenopodium album* (Linn) in Streptozotocin-Induced Diabetic Mice

Tripti Rani Paul[1*], Monalisa Monowar[1], A. K. M. Shafiur Rahman[1], Md. Shahriar Kobir[1], Murshida Mun Liza[1], Most. Sheuti Akter[1], Tanbin Islam[1], Ashik Mosaddik[2], Mir Imam Ibne Wahed[3]

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ABSTRACT

Diabetes is a long-term illness that affects a large number of people globally. It increases a patient's risk of morbidity and death, especially from cardiovascular disease. The current study aims to assess the antidiabetic and hypolipidemic potentials of *C. album* leaves extract in streptozotocin-induced diabetic mice. Acute toxicity tests and oral glucose tolerance tests were carried out. Streptozotocin (45 mg/kg) was given intraperitoneally to Swiss albino mice to cause diabetes. Diabetic mice subjected to oral administration of *C. album* extracts (CAL 200 and 400 mg/kg), metformin as standard (DS, 150mg/kg) and/or vehicle (DC) once daily for 15 days and age-matched healthy mice were used as normal control (NC). Blood glucose level and body weight of mice were measured on 0 day before and 5, 10 and 15 days of treatment. To measure serum glutamate-pyruvate transaminase (SGPT), serum glutamate-oxaloacetate transaminase (SGOT), low-density lipoproteins (LDL), high-density lipoproteins (HDL), total cholesterol (TC), and triglycerides (TG), mice were eventually killed, and blood samples were taken. The *C. album* extract improved glucose tolerance and no sign of toxicity was noticed in mice treated with the extract. Diabetic mice treated with *C. album* extract showed significant attenuation in blood glucose level and lipid profile. Moreover, oral treatment with *C. album* extracts significantly reduced SGPT and SGOT levels; and improved body weights in mice. The *C. album* extract was considered to be both safe and beneficial in terms of glucose and lipids reducing effectiveness, and might be used to protect liver function in diabetic mice.

INTRODUCTION

Chronically elevated blood sugar levels are an indicator of diabetes, is a metabolic disorder characterized by poor carbohydrate, protein, and lipid metabolism (Ahmed, 2002). Type 2 diabetes (T2DM) is linked to insulin resistance and causes hypertension, dyslipidemia, and glucose intolerance (Patlak, 2002). About 80% people in countries with moderate to low incomes have diabetes mellitus (DM), a condition whose incidence has been steadily increasing worldwide (Baynes, 2015). About 783 million people will have diabetes mellitus (DM) by 2045, with 152 million of those cases occurring in Southeast Asia, according to the International Diabetes Federation (IDF, 2018). T2DM has recently been diagnosed in individuals under the age of 20, and the biggest risk factor for T2DM in both adults and children is obesity (Guyton, 2006). According to Anbarasi *et al.* (2012) and Hahm *et al.* (2011), insulin resistance and decrease insulin synthesis and release from pancreatic β-cells are the primary reasons of type 2 diabetes. Furthermore, it is thought that a combination of biological/genetic and environmental variables, such as obesity, a stressful lifestyle, alcohol use, smoking, and poor nutrition, might contribute to type 2 diabetes (T2DM) (Ozougwu *et al.*, 2013). Elevated production of reactive oxygen species (ROS) is frequently linked to hyperglycemia (Brownlee, 2001), which can result in retinopathy, nephropathy, neuropathy, ketoacidosis, and other problems (Nakamura *et al.*, 2015; Merecz *et al.*, 2015). Additionally, a lack of insulin causes lipolysis, which may be the cause of fatty liver and hyperlipidemia. Morbidity and mortality in individuals with type 2 diabetes is primarily caused by hyperlipidemia (Reiner *et al.*, 2006, Simons *et al.*, 2002, Yokozawa *et al.*, 2003). Insulin and synthetic medicines are currently the primary means of DM treatment. According to Kasetti *et al.* (2010), thiazolidinedione, biguanide, and sulfonylureas are the most often prescribed oral hypoglycemic drugs for the management of type 2 diabetes. Moreover, α-glucosidase inhibitors are useful in delaying the intestinal absorption of glucose. Oral hypoglycemic medications are actually linked to negative side effects including obstructive jaundice, hypoglycemia shock, weight gain, gastrointestinal problems, nausea, vomiting, hematological, and dermatological reactions (Gandhi *et al.*, 2016, UKPDS, 1998). Over 800 plants have historically been shown to have antidiabetic potential (Rizvi *et al.*, 2013) and be useful in the cure of diabetes mellitus (Arumugam *et al.*, 2013). The World Health Organization (WHO) advised using local plants to treat diabetes and associated consequences, especially in underdeveloped nations. Therefore, in order to find new bioactive compounds, scientists are mostly focused on screening natural products (Bhandari *et al.*, 2008). Flavonoids, alkaloids, glycosides, and saponins are among

[1] Department of Pharmacy, School of Science and Technology, Varendra University, Rajshahi, Bangladesh
[2] East West University, Dhaka-1212, Bangladesh
[3] Department of Pharmacy, Faculty of Science, University of Rajshahi, Rajshahi, Bangladesh
[*] Corresponding author's e-mail: triptipaul.ph@gmail.com

the many chemical constituents found in medicinal plants. These constituents have been shown to have antioxidant, hypoglycemic, and hypolipidemic characteristics (Juárez-Reyes *et al.*, 2015) and may offer protection against β-cell destruction brought on by oxidative stress (Coskun *et al.*, 2005; Molina *et al.*, 2003).

The plant Chenopodium album Linn indigenously known as Bathu Sag (Hindi), Chandan bethu (Bengali) belongs to Chenopodiaceae family and universally grown in Asia, Europe, Africa and North America. According to Bonner-Weir (1988), the plant *C. album* has been adopted in traditional medicine as a diuretic, laxative, analgesic, sedative, hepatoprotective, antidiabetic, cardiotonic, anthelmintic, and antiparasitic. Alkaloids, saponins, glycosides, flavonoids, proteins, and amino acids were all tested by phytochemical analysis of the methanolic extract of *C. album* root (Kant, 2018). The ethanolic extract from *C. album* fruits prevented mice from scratching when 5-HT was administered. It has been reported that the extract from *C. album* leaves has analgesic, anti-inflammatory, gastroprotective, hepatoprotective, antioxidant, antimicrobial activities. It also contains alkaloids, flavonoids, phenols, phytic acid, saponin, phytate phosphorus, proteins, and trace elements. (Suleman *et al.*, 2021). As far as the author has learned, no prior research has been done on the extract from *C. album* leaves' hypoglycemic and antihyperlipidemic properties. Thus, the objective of the current research was to assess the antidiabetic and hypolipidemic potentials of methanolic extract from *C. album* leaves in streptozotocin (STZ) induced diabetic mice.

MATERIALS AND METHODS

Drugs and Chemicals

Team Pharmaceuticals Ltd. Rajshahi, Bangladesh generously donated metformin hydrochloride. The supplier of streptozotocin was Sisco Research Laboratories in India. A standard glucometer (Origin, Taiwan) was utilized to monitor the blood glucose level. A commercial kit from Human, Germany, was used to measure serum triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), serum glutamate oxaloacetate transaminase (SGOT), and serum glutamate pyruvic transaminase (SGPT).

Plant Materials

In February 2022, the entire plant *C. album* was collected from the roadside of Puthia, Rajshahi, Bangladesh. A taxonomist verified the plant's authenticity, and a voucher specimen (No. 72, 10/02/2022) was stored in the herbarium, Department of Botany, University of Rajshahi, Bangladesh.

Preparation of Leaves Extract

After being separated, the *C. album* leaves were sun-dried for a few days in the shade. The leaves were then processed into a coarse powder using a grinding mill after being dried for 24 hours at 40°C in an oven. For seven days, the ground-up leaves of *C. album* were soaked in w/v methanol and stored in a dark area with periodic shaking and stirring. The resulting filtrate was then run through Whatman No. 1 filter paper and cotton. Using a rotary evaporator set to 40-45°C, the filtrate was allowed to evaporate at lower pressure. The concentrated semisolid methanol extract (% yield) was so produced, allowed to air dry, and then stored.

Phytochemical Screening Tests

The phytochemical analysis was done by the use of standard methods (Pollock & Stevens, 1965; Trease & Evans, 1996; Plummer, 1985).

Animals

The animal house of the Department of Zoology, Rajshahi University in Rajshahi, Bangladesh, provided the six-week-old male Swiss albino mice, whose weighed between 30 and 40 grams. The animals were kept in cages and under normal environments (temperature 25°C, humidity 75±5%, 12-hour cycle of light and darkness). The mice were given rodent chow with water ad. libitum during the acclimatization period. The mice were treated in according to our institution's animal experimentation protocols. Following approval from the Varendra University Institutional Ethics Committee, the animal study was conducted in the pharmacy department at Varendra University in Rajshahi, Bangladesh (Ref. VU/ERC/2021-2022/004).

Acute Toxicity Study

The OECD recommendations were applied when carrying out the oral acute toxicity test (Jonsson *et al.*, 2013). The animals were split up into five groups, with three animals (n=5) in each group. Following an overnight five, mice were given various doses of methanol extract from *C. album* leaves (100, 250, 500, 1000, and 2000 mg/kg). The behavior and mortality of mice were monitored for the first two hours, the next 24 hours, and then every day for 14 days (Schlede, 2002).

Oral Glucose Tolerance Test (OGTT)

Normal mice were fasted overnight and separated into four groups randomly, each of which consisted of three mice (n=3) for oral glucose tolerance test. After 30 minutes of oral intake of *C. album* extract (200 & 400 mg/kg), metformin (150 mg/kg), and/or vehicle (0.5% MC), a glucose load (2 g/kg) was administered to the mice. A glucometer was used to monitor the fasting blood glucose (FBG) level at 0 minutes, before and after 30, 60, 90, and 120 minutes of glucose loading (Bergmeyer, 2012).

Induction of Diabetes

Mice were given a single intraperitoneal injection of STZ (45 mg/kg) dissolved in 0.1M citrate buffer (pH=4.5) to induce diabetes. In order to counter the hypoglycemic effect of STZ, mice were given a 10% glucose solution for 24 hours. Blood glucose levels were measured using a

glucometer after 96 hours, and mice with fasting glucose levels greater than 10.5 mmol/L were thought to be diabetic (Kumar *et al.*, 2013).

Experimental Protocol

After inducing diabetes, mice were separated into five groups each comprising of three mice and subjected to oral ingestion of *C. album* extract (CAL 200 & 400 mg/kg), standard (DS, metformin 150mg/kg) and/or vehicle (DC, 0.5% MC) once daily for 15 days using gastric tube. Age-matched healthy mice received vehicle were used as normal control (NC, 0.5% MC).

Determination of Blood Glucose Levels and Changes in Body Weight

FBG levels and body weight of mice were measured on day 0, before therapy, and then on days 5, 10, and 15 following treatments. Blood samples were taken from mice's tail veins and FBG levels were evaluated (Reddy *et al.*, 2012; Khatune *et al.*, 2016).

Estimation of Lipid Profile

At the completion of the experiment, mice were sedated with diethyl ether and sacrificed. Blood samples were collected from the aorta and stored in blood collection containers at room temperature. Finally, blood samples were centrifuged for 15 minutes at 4000 rpm. The serum collected was isolated and stored at -80°C for biochemical analysis. The levels of TG, TC, and HDL were determined using commercial kits (Human, Germany) and the spectrophotometric technique. The formulas VLDL=TG/5 and LDL=TC-(HDL+VLDL) were used to compute the levels of LDL and VLDL. The LDL/HDL cholesterol ratio was determined (Asati *et al.*, 2021).

Determination of Liver Enzymes

The SGOT and SGPT level of serum were measured in accordance with the manufacturer's instructions using wet reagent diagnostic kits (Human, Germany) (Schumann *et al.*, 2002, Nakano *et al.*, 1994).

Statistical Analysis

The data was expressed as a standard error mean (SEM). Following the one-way analysis of variance (ANOVA), Dunnett's multiple comparison tests were done. P-values < 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Results

Acute Toxicity

After 14 days of oral ingestion of *C album* leaves extract, mice did not show any sign of autonomic or behavioral changes irrespective of doses. None of the mice died taking different doses of *C. album* extracts except 2000 mg/kg, where 20% mice died between 7 to 14 days. Therefore, 1/5th and 1/10th of the toxic dose of *C. album* that is 400 and 200 mg/kg were considered for further study (Table 1).

Table 1: Effect of *C. album* leaves extract after 14 days of oral ingestion in normal mice

Extract Doses (mg/kg)	Total	Survivor	Death	Survival Rate (%)
100	5	5	0	100
250	5	5	0	100
500	5	5	0	100
1000	5	5	0	100
2000	5	4	1	80

Data expressed in percentages (%)

Oral Glucose Tolerance Test (OGTT)

After 30 min of glucose loading, mice from all groups exhibited high blood glucose level which was decreased in mice pretreated with *C. album* extracts (200 and 400 mg/kg) and metformin but in vehicle-treated mice remained steady at 60 min. Further, *C. album* extracts

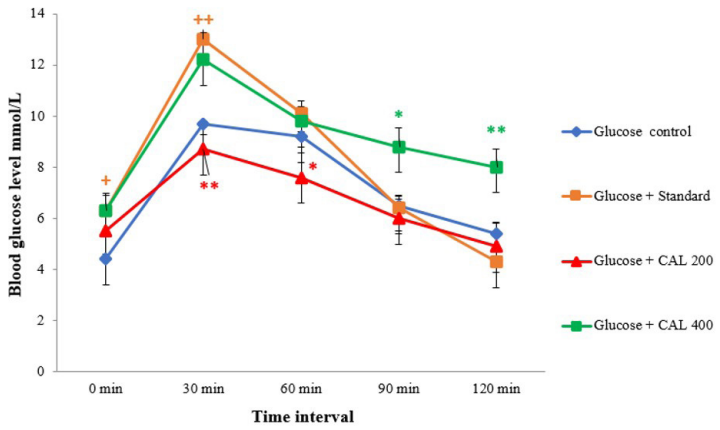

Figure 1: Effect of *C. album* extract on oral glucose tolerance test (OGTT). ***p < 0.001, **p < 0.01, *p < 0.05 vs. standard, ++p < 0.01 vs. glucose control

showed significant reduction in blood glucose levels at 90 and 120 min. However, CAL400 was comparable to the standard and demonstrated a higher improvement in glucose tolerance ($p < 0.001$).

Clinical Course

Neither of the mice passed away during the period of treatment. As a result, all treatment groups survived.

Changes in FBG Level in Diabetic Mice

Figure 2 showed the efficacy of CAL extract on FBG levels in diabetic mice. The FBG levels were significantly increased in diabetic mice than that of NC mice. Diabetic mice treated with CAL200, CAL400 extracts and DS demonstrated a gradual decrease in FBG levels on 5, 10 and 15 days. Furthermore, CAL extracts exhibited a dose-dependent attenuation of FBG levels; and their hypoglycemic effects were comparable to that of DS.

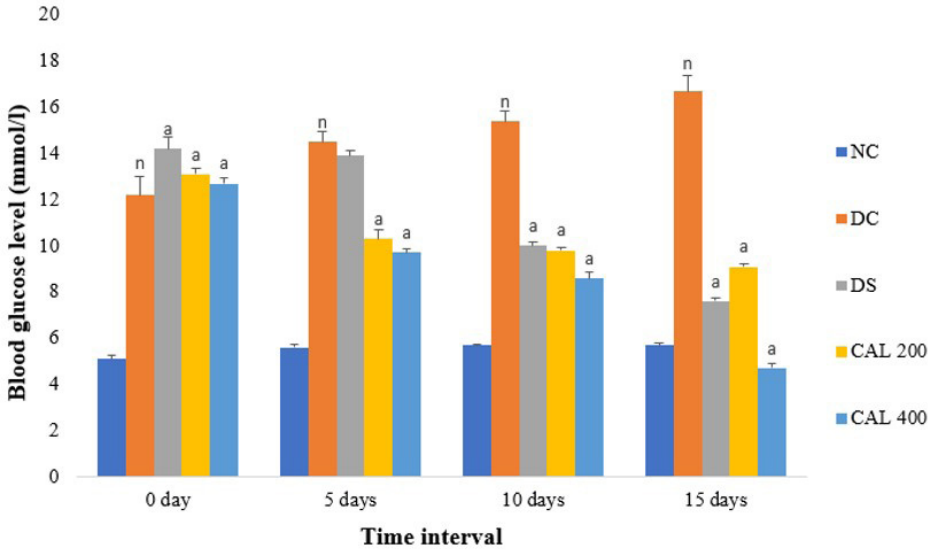

Figure 2: Effect of *C. album* leaves extract on fasting blood glucose level in diabetic mice. $^{n}p < 0.001$ vs. NC, $^{a}p < 0.001$, $^{b}p < 0.01$, $^{c}p < 0.05$ vs. DC

Body Weight Changes in Diabetic Mice

Changes in body weights after 15 days of treatment were shown in Figure 3. On 0 day, before the initiation of the treatment body weight did not differ. The body weight of DC mice tends to be decreased throughout the treatment period. Oral administration of CAL200 and CAL400 extracts exhibited a dose-dependent increment in body weights; and the effect was comparable to those of NC and DC mice.

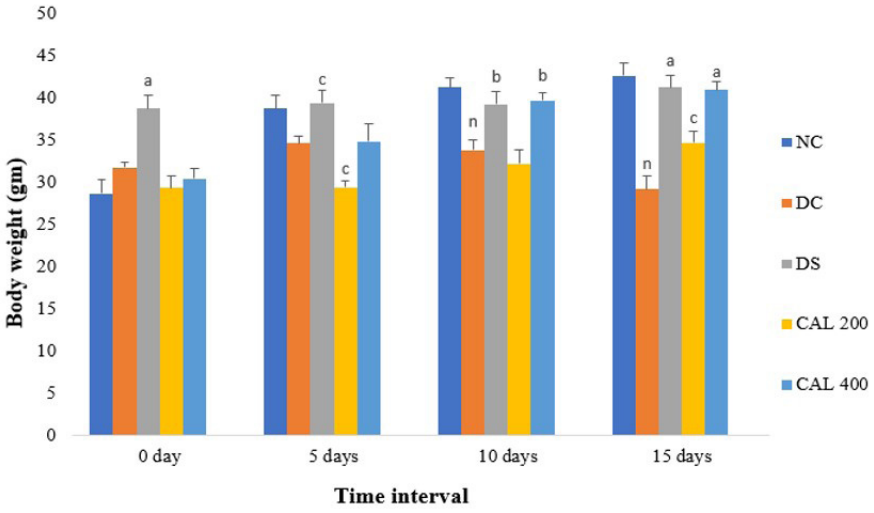

Figure 3: Effect of *C. album* leaves extract on body weight changes in diabetic mice. $^{n}p < 0.001$ vs. NC, $^{a}p < 0.001$, $^{b}p < 0.01$, $^{c}p < 0.05$ vs. DC

Alteration of Lipid Profile in Diabetic Mice

Table 2 represented the result of extract on lipid profile in diabetic mice. The TC, TG and LDL levels were significantly increased and HDL level was significantly reduced in diabetic mice in contrast to NC. Treatment with CAL extracts significantly decreased the higher TC, TG and LDL levels and slightly enhanced the low HDL level in comparison with DC mice ($p < 0.001$, $p<0.01$, $p<0.05$). The CAL 400 expressed notable improvement in lipid profile which was comparable to DS.

Table 2: Effect of *C. album* leaves extract on lipid profile in STZ-induced diabetic mice

Groups (n=3)	Lipid Profile (mg/dl)					
	TC	TG	LDL	VLDL	HDL	LDL/HDL
NC	174.33 ± 1.33	153 ± 1.73	111 ± 1.15	30.6±0.35	81± 1	1.37 ± 0.01
DC	220 ± 2.89+++	192 ± 3.06+++	133 ± 1.14+++	38.4 ± 0.61+++	43 ± 2.65+++	3.12 ± 0.20
DS	179 ± 1.15***	161.67 ± 1.20***	107.66 ± 1.33***	32.33 ± 0.24***	51± 1.15***	2.14 ± 0.08
CAL 200	202 ± 1.53***	160 ± 2.64***	132 ± 1.73	30.6 ± 0.34***	34 ± 1.15***	3.89 ± 0.17
CAL 400	190.66 ± 2.60***	159 ± 0.58***	127 ± 1.15**	31.8 ± 0.12***	37 ± 1.14**	3.44 ± 0.01

*Data expressed as SEM. +++p < 0.001 vs. NC; ***p < 0.001, **p < 0.01, *p < 0.05 vs. DC*

Liver Function in Diabetic Mice

The liver enzymes SGPT and SGOT levels were greater in DC mice ($p < 0.001$). Oral ingestion of CAL extract significantly reduced both SGPT and SGOT levels ($p < 0.001$, $p<0.01$) and was comparable to NC.

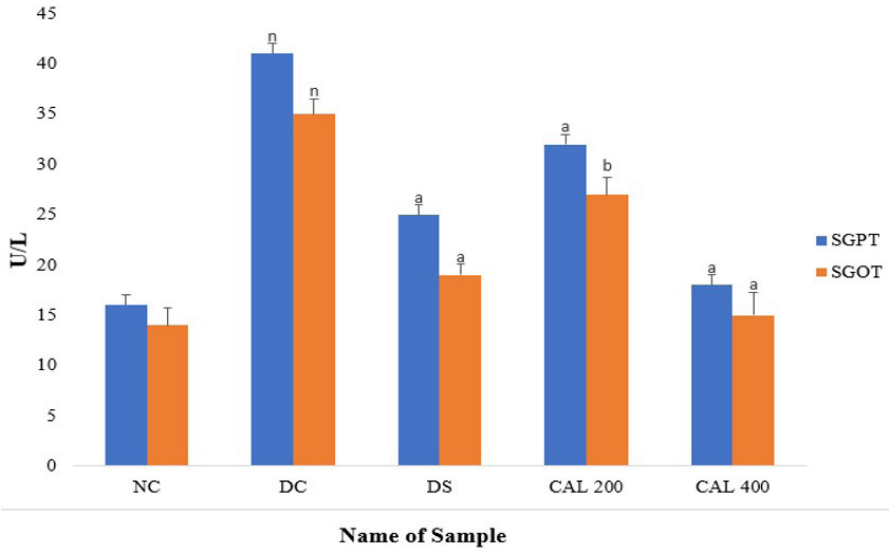

Figure 4: Effect of *C. album* leaves extract on SGOT and SGPT in diabetic mice. $^{n}p < 0.001$ compared to NC, $^{a}p < 0.001$, $^{b}p < 0.01$ compared to DC

Table 3: Phytochemicals of *C. album* leaves extract

Extract	Steroid	Alkaloid	Glycoside	Tannin	Triterpene	Saponin	Flavonoid
C album leaves	-	+	+	+	+	+	+

+ indicates present and − indicates absent

Discussion

According to Li *et al.* (2004) and Lyra *et al.* (2006), Diabetes is the third greatest cause of mortality, especially when it comes to organ failure and chronically high blood glucose levels. Furthermore, hyperlipidemia increased the risk of cardiovascular disease, coronary artery disease, and peripheral vascular disease. Around the world, currently, the primary treatment is metformin, an oral hypoglycemic drug for type 2 diabetes. Furthermore, sulfonylureas or dipeptidylpeptidase-4 inhibitors are advised in conjunction with metformin for diabetic patients (Gomes *et al.*, 2019). There is an increasing interest in complementary and alternative therapies due to the increasing incidence of diabetes and related healthcare costs. Many plant or plant-derived medications have been scientifically evaluated in diabetic people and animal models in over a decade, but many more need to be established. So, we investigated the glucose and lipid lowering effects of *C. album* leaves extract in STZ-induced diabetic mice. The study found that CAL extracts significantly improved FBG levels, lipid profiles, and liver enzymes in mice.

In acute toxicity study, the methanol extracts of *C. album* leave in mice were found to be safe and no sign of autonomic and/or behavioral changes were observed in mice at dose ranges 100-2000 mg/kg. Thus, it gives the basis for the selection of doses of extract i.e.200 mg/kg & 400 mg/kg for further animal study. In, OGTT, mice treated with extract and/or metformin significantly counteracted the glucose induced hyperglycemia in normal mice. Oral ingestion of CAL200 and CAL400 extract was effective in lowering FBG levels. When

carbohydrates are insufficient to be used as an energy source, weight loss in diabetic mice may be the result of muscle wasting and loss of structural protein (Jacobson, 2007). As previously reported (Pari & Venkateswaran, 2004; Ruzaidi *et al*., 2005), the STZ-induced diabetic rats developed significant hypertriglyceridemia in addition to substantial hyperglycemia. Treatment significantly attenuate TC, TG, and LDL while increasing HDL cholesterol, which is necessary for the body to eliminate excess cholesterol and lower the risk of cardiovascular events. Patients with diabetes are associated with the impairment of liver function as evident by the expression of higher levels of SGPT and SGOT (Ghosh *et al*., 2001). SGPT and SGOT levels were abnormally high in STZ-induced diabetic mice, which may have been brought on by hepatotoxicity. The CAL200 and CAL400 extract significantly reduced both SGOT and SGPT levels. So, the CAL extracts exerted prominent effects on body weight, lipid profile, glycemic index and liver functions in diabetic mice. The study found out that, CAL400 extracts showed pronounced reduction in lipid profile and attenuation of FBG levels and the effects was comparable to metformin. It is currently unclear how the extract from *C. album* leaves lowers blood sugar, although it does not include stimulating the release of insulin from the pancreatic β-cells. In the animal model caused by STZ, the pancreatic β-cells are selectively destroyed, and in moderate cases, part of the β-cells can still secrete insulin (El-Hilaly and Lyoussi, 2002). Both metformin and/or the extract in this study significantly decreased the FBG levels in diabetic mice. The mechanism of increasing peripheral glucose utilization via insulin sensitization, which has been observed with metformin, can help to explain the hypoglycemic effects of the *C. album* extract (Nandhini *et al*., 2004). The antihyperglycemic potential of the fractions of *C. cordifolia* were probably mediated by an enhanced secretion of insulin, like biguanides. The extracts of *C. album* exerted prominent effects on lipid profiles and they had a greater effect on serum TG than that of TC levels. Although metformin exhibited pronounced reduction in serum TC and LDL, the effects of *C. album* leave extract on TG and HDL were found higher than metformin. By inhibiting hormone-sensitive lipogenic enzymes (Pari and Venkateswaran 2004) and/or activating lipoprotein lipase (Ahmed *et al*., 2001, Sharma *et al*., 1997), *C. album* may have hypolipidemic effects that are comparable to those of metformin.

The pathophysiology of diabetes is significantly influenced by oxidative stress, which is the cause of the death of pancreatic β-cells. According to Robertson (2010) and Takayanagi *et al.* (2010), plants with antioxidant capacity demonstrated free radical scavenging activity and could be helpful in lowering oxidative stress caused by hyperglycemia. Therefore, according to previous study, medicinal plants have the capacity to reduce blood glucose levels. This glucose lowering potential may be caused due to the existence of bioactive components such as flavonoids, alkaloids, triterpenes, tannins, and saponins etc. (Robertson, 2010). The phytochemical screening of *C. album* leaves extract confirmed the existence of alkaloid, glycoside, tannin, triterpenes, saponin and flavonoids. The presence of flavonoids and triterpenes in the *C. album* extract may be the cause of its hypoglycemic potential, which can be explained by the antioxidant action of phytochemicals. In addition to phytic acids, the extract from *C. album* leaves provides a good source of lipids, phosphorus, protein, oxalates, and trace elements (Suleman *et al*., 2021).). The leaves of *C. album* seem to have a promising therapeutic value which can be useful in the therapy of diabetes.

CONCLUSION

Diabetic mice treated with *C. album* extract showed significant attenuation in blood glucose level and lipid profile. Moreover, oral treatment with *C. album* extracts significantly reduced SGPT and SGOT levels; and improved body weights in mice. The *C. album* extract was considered as safe and effective in terms of glucose and lipid lowering efficacy; and might be used to protect liver function in diabetic mice. The findings provide scientific evidence in favor of utilizing the plant in conventional medicine to cure diabetes and its related problems. However, to determine how this plant has an antidiabetogenic impact and which bioactive components are responsible for it, more research is needed.

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