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Research Article

Protective role of methanolic extract of *Cleome viscosa L. and Cleome gynandra L.* on carbohydrate metabolic enzymes in STZ - induced diabetic rats

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Abstract

Aim: This study investigates the antihyperglycemic and hepatoprotective effects of methanolic extracts of *Cleome viscosa L.* (MeCV) and *Cleome gynandra L.* (MeCG) in STZ-induced diabetic rats. Methods: Over 28 days, body weight and fasting blood glucose levels were monitored weekly. Additionally, key metabolic enzyme activities, including fructose-1,6-bisphosphatase (FBP-1,6), glucose-6-phosphatase (G-6-P), hexokinase, and glucose-6-phosphate dehydrogenase (G-6PDH), were analyzed to assess hepatoprotective effects. Results: On the 28th day, diabetic control rats exhibited severe hyperglycaemia (402±11.41 mg/dL) and significant weight loss (108.33±4.01 g). MeCV-treated rats (400 mg/kg b.w.) showed a slight weight increase (+0.92%) and a substantial reduction in fasting blood glucose levels, demonstrating better glycemic control than MeCG. Compared to diabetic controls, MeCV significantly increased hexokinase and G-6-P activity by 55.82% and 127.15%, respectively, while reducing G-6PDH and FBP-1,6 activity, supporting its role in glucose metabolism regulation. MeCV and MeCG restored total carbohydrate levels in liver tissues, counteracting STZ-induced depletion. However, MeCV was more effective, nearly matching glibenclamide in enhancing glucose uptake and glycogen synthesis. It also normalized hepatic glucose and glycogen levels more efficiently than MeCG, likely by improving insulin sensitivity and modulating key metabolic enzymes. Conclusion: These findings highlight MeCV's strong antihyperglycemic and hepatoprotective potential, making it a promising candidate for diabetes management. Further research is needed to identify its active compounds and elucidate their mechanisms of action.

Keywords: STZ, Diabetes, *Cleome viscosa* L., *Cleome gynandra* L., Antihyperglycemic activity, Carbohydrate metabolic enzymes

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Introduction

In fact, diabetes mellitus happens to be one of the most common chronic diseases of today's world, characterised by persistent hyperglycaemia. The failure of the pancreas cells to secrete enough insulin, or the body's inability to use the secreted insulin, could be the cause. However, the prevalence of diabetes is likely to rise to alarming levels in the next ten years, making it one of the most prevalent public health and economic problems in the world (1). The disease has become a significant global concern, with the WHO estimating that over 422 million people worldwide suffer from it, a number that is rapidly increasing, particularly in developing countries (2). The two types of diabetes in humans, Type 1 and Type 2, lead to chronic damage of many organs, including the eyes, kidneys, nerves, heart, and blood vessels, among others. The prevalence of diabetes and its associated complications is steadily increasing. The need for treatments that keep blood glucose normal but prevent the emergence of later complications has grown (3).

Maintaining glucose levels in the blood is critical for metabolic equilibrium. Glucose metabolism involves a series of enzymes that include hexokinase, G-6-P, FBP-1,6, and G-6PDH. Diabetes alters their activities, leading to uncontrollable glucose levels (4). In fact, medicinal plant extract application was able to reconstitute

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some of the above-mentioned enzyme levels, coupled with improved glucose metabolism, to enhance glycemic control.

Although the liver works in conjunction with supportive tissues, it also plays a critical role in maintaining blood glucose levels at the same level. Estimates suggest that this organ contributes 75% of glucose in the form of glycogen during glycogenesis (5). Under fasted conditions, the liver maintains a steady amount of glucose in the blood due to glucose production in both gluconeogenesis and glycogenolysis (6, 7). Thus, it is more active today to look for alternative treatments that can prove better.

Traditional medicinal plants, being nontoxic and free of side effects, have garnered significant attention for their potential in managing diabetes. The WHO recognized the great promise of herbal medicines for diabetes therapy and recommended further research to confirm their efficacy and safety (8). Targeting several metabolic pathways, herbal treatments help to manage glucose levels and lower diabetic complications.

Many people treat diabetes using natural medications as folk treatments. Several plant extracts show antihyperglycaemic action, and some like *Cleome viscosa L.* and *Cleome gynandra L.* have shown really remarkable effects. Both species belong to the Cleomaceae family. The antimicrobial, anti-inflammatory, and antidiabetic activities of the two species have led to their extensive use as medicinal agents (9).

Cleome species, such as *Cleome viscosa L*. and *Cleome gynandra L*., are among the medicinal plants extensively studied for their antidiabetic potential. These plants contain a variety of bioactive compounds, including saponins, alkaloids, and flavonoids, which contribute to their therapeutic effects—such as lowering blood glucose levels, reducing inflammation, and protecting cells from oxidative damage (10, 11). We intended to look at these medicinal plants, particularly with an eye toward their hepatoprotective qualities that can help cure diabetes-related problems including liver damage.

The antihyperglycaemic efficacy of MeCV and MeCG in streptozotocin-induced diabetic rats is evaluated in this work, therefore exposing the significant restrictions of current diabetes treatment strategies. It also shows the mounting amount of data in favour of using medicinal herbs. The examination of these extracts utilising pertinent carbohydrate metabolising enzymes and their effects on blood glucose levels by the study will support the conventional use of these plants in diabetes treatment. Given their safety and efficacy, the present findings might open the path for alternative treatments.

Material and Methods

Plant gathering and recognition

We collected whole plants of *Cleome viscosa L.* and *Cleome gynandra L.* from the surroundings of Dravidian University in Kuppam, Andhra Pradesh, India. Specimens identified by Prof. N. Yasodamma, a taxonomist from the Department of Botany, S.V. University, Tirupati, India.

Extract preparation

Both plant powders were successively extracted using a Soxhlet apparatus for 6 hours with methanol solvent (1:5 W/V ratio). The extraction was performed under reduced pressure at a temperature of 70–80°C. The extracts were concentrated using a rotary evaporator and subsequently freeze-dried under vacuum at 35–40°C to obtain dry powder.

Care and maintenance of experimental animals

Pathogen-free, Wistar strain male albino rats (3 months old, weighing 180-200 g) were used in the present study

Authorisation of ethical committee

Our animal study received ethical committee approval from the Institutional Animal Ethics Committee (IAEC) of Sri Krishnadevaraya University, Andhra Pradesh, India (Approval No. 1889/GO/Re/S/16/CPCSEA-SKU/ZOO/03/2018) to perform the animal work.

Induction of Diabetes

Diabetes was induced by a single intraperitoneal (I.P.) injection of freshly prepared Streptozotocin (STZ) at a dose of 45 mg/kg body weight (b.w.), following the method of Rakieten, (12). After 48 hours, rats with fasting blood glucose levels (FBGL) > 270 mg/dL were considered diabetic and included in the study. Seven days post-STZ injection, rats with confirmed hyperglycaemia were selected for further experimentation. The percentage change in blood glucose levels was calculated using the following equation:

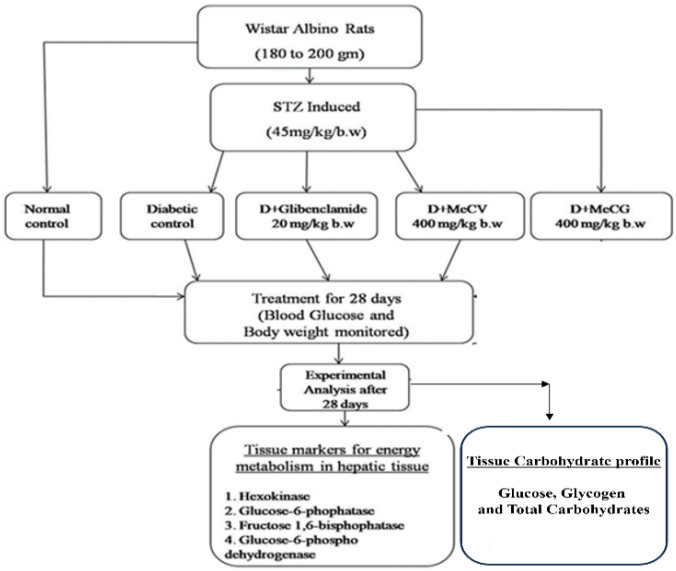
$$\text{Glycemic change level} = (Gx - Gi)/Gx \times 100$$

Whereas,

Gx= glycaemia at "7, 14, 21 and 28 day" time

Gi= glycaemia at "Zero" time

Image 1: Experimental design



Measuring blood glucose levels

Fasting blood glucose levels were estimated by Accu-check glucometer after the gathering of blood samples from 12-15hrs fasted rats tail vein of normal control, diabetic control and diabetic treated rats on 0 day (initial day), 7 day (1st week), 14 day (2nd week), 21 day (3rd week) and 28 day (4th week).

Determination of the body weight of rats

The increasing or decreasing of animal body weight in normal control, diabetic control and diabetic treated rats on 0 day (initial day), 7 day (1st week), 14 day (2nd week), 21 day (3rd week) and 28 day (4th week) were measured with electron weighing balance.

Blood collection and preparation of serum

Toward the finish of analysis period, on 29th day experimental rats were fasted for 12 to 15 hours. At that point, blood was collected from the rats by retro-orbital plexus by EDTA covered tubes. The blood was centrifuged at 3500 rpm for 15 min and the serum was stored in dry tubes at -40°C.

Preparation of tissue homogenate

Liver tissue was confined from tested and untested animals subsequent to relinquishing them and promptly put away in super cold PBS (10 mmol/L, pH 7.4.). Super cold PBS (pH 7.4) was utilized to get ready 25% homogenate, at that point it was centrifuged at 4000rpm for 10min at 4°C for to wash out cell trash and supernatant was gathered and put away at -80°C till measurement of examines.

Carbohydrate metabolism

Hexokinase assay

Hexokinase was measured by the approach for Brandstrup et al. (13). Solution of glucose 1ml, MgCl (0.5ml), K_2HPO_4 (0.5 ml), KCl (0.4ml), NaF (0.1ml) in addition to pH 8.0 concentration of Tris-HCl. Incubation at 37°C was started to above 5ml mixture for 5min. The response was started by adding the 1 ml of homogenate solution. Immediately (zero and 30min), 1.0 ml of aliquot mixture was taken to a tube containing 1ml of 10% TCA. The formation of precipitate expelled by centrifugation by adding O-toluidine. The separated supernatant was mixed together 4ml of O-toluidine reagent. The green shading solution was perused at 620 nm. The measure of glucose phosphorylated was given by the distinction between the two qualities.

Activity of hexokinase (µmoles of carbohydrate phosphorylated / h/mg protein) =

$$\frac{\mu \text{ moles of glucose phosphorylated}}{\text{Vol. of aliquot used}} \times \frac{\text{Total volume of aliquot}}{\text{Incubation time}} \times \frac{60}{\text{mg. protein}}$$

G-6-P (Glucose 6-phosphatase) assay

G-6-P was measured by the technique for Hikaru and Toshitsugu, (14). Pipetted out 300µl citrate buffer, 500µl of metabolizing enzyme in addition to 200µl of enzyme source incubated for 1h at 37°C. 10% TCA (1ml) was used to add to stop the protein action. The phosphate substance of the supernatant was then assessed. After the reactions started by 1ml of supernatant, 1ml of $(NH_4)_6Mo_7O_{24}$ also 0.4ml of ANSA. The formation of blue colour was perused at 620 nm. A test tube without the protein filled in as control. The following deliberation used to estimate G-6-P.

G-6-P (µmoles of in organic phosphate liberated /min/mg. Protein) =

$$\frac{\mu\text{moles inorganic phosphate liberated}}{\text{Vol. of tissue homogenate}} \times \frac{1}{60} \times \frac{1}{\text{mg. protein}}$$

FBP-1, 6 (Fructose 1, 6-bisphosphatase) assay

FBP-1, 6 was measured by the strategy for Gancedo and Gancedo (15). The medium contained 1ml of Tris-HCl, substrate (0.4ml), 0.1 ml of $MgCl_2$, KCl (0.2ml), EDTA (0.1ml) along with tissue homogenate (0.2ml). The test tube was kept on water bath for 15 min at 37°C. The reaction was ended by the adding of 1 ml of 10% TCA. To 1.0ml of supernatant, 0.3ml of water in addition to 0.5ml of $(NH_4)_6Mo_7O_{24}$ were included. Subsequent to 10min, 0.2 ml of ANSA reagent also included. The test tubes were kept aside for 20min as well as formation of blue colour perused at 620nm. The following equation used to deliberate the FBP-1, 6.

FBP-1, 6 (µ moles of inorganic phosphorous/h/mg of protein) =

$$\frac{\mu\text{moles inorganic phosphorous liberate}}{\text{Vol. of supernatant}} \times \frac{\text{Total Volume}}{\text{Vol. of tissue homogenate}} \times \frac{1}{\text{incubation time}} \times \frac{60}{\text{mg. protein}}$$

G-6PDH (Glucose-6-phosphate dehydrogenase) assay

G-6PDH was assessed reliant on the Worthington and Freehold, (16) technique. The 3 ml of absolute response arrangement contained pH 7.8 tris HCL (0.055 M), 0.1ml of 0.06 M NAD, 0.1ml of 0.1M glucose 6-phosphate. The absolute test arrangement was hatched for 8min at 30°C to achieve temperature equilibration and a while later 0.1ml of weakened chemical source was incorporated and the extension esteems were recorded for 5 min at 340nm. The following equation was used to determine G6PDH.

$$\text{G6PDH (Units/mg)} = \frac{\Delta A340/\text{min}}{6.22 \text{ X mg enzyme/ml reaction mixture}}$$

Units/mg as µmoles of inorganic phosphate liberated/min/mg protein

Estimation of Carbohydrate Profile in Liver tissue

Total carbohydrates

The total carbohydrate content was estimated by the method of Carroll et al., (17). The liver tissues were homogenised in 10% Trichloro- acetic acid to prepare 1% (W/V) homogenate. The proteins precipitated were removed by centrifuging the homogenates for 15 minutes at 3000g. The clear supernatant was taken for the estimation of total carbohydrates. To 0.1 ml of the supernatant, 5 ml of anthrone reagent was added and kept in a boiling water bath for 15 minutes. Then the contents were cooled and read at 620 nm against the reagent blank. The total carbohydrate content was expressed as mg of glucose/gm wet weight of the tissue.

Glycogen

Glycogen content was determined as described by Ong and Khoo (18). Weighed amounts of liver tissues (0.3-0.5) were homogenized in 10 volumes of ice cold 30% KOH and boiled at 100°C for 30 min. glycogen was precipitated with ethanol pelleted, washed, and resolubizilized in distilled water. Glycogen content was determined by treatment with anthrone reagent and measured at 625 nm.

Glucose

Glucose levels were estimated by a commercially available glucose kit based on the glucose oxidase method (Sigma Diagnostics, St.Louis,MO)

Statistical analysis

The experimental results were expressed as mean ± SE (n=6). The results were analyzed by using one-way analysis of variance and the group means were compared by Tukey's HSD and DMRT (SPSS version 16. SPSS Inc. Chicago, IL, USA). A differentiation was measured to be statistically significant when the p-value is lower than $p < 0.05$ and $p<0.01$.

Results

Effect of long-term treatment of MeCV, MeCG and glibenclamide on fasting blood glucose levels (FBGL) of diabetic rats

The levels of blood glucose of normal control, diabetic control, glibenclamide, MeCV and MeCG treated rat are shown in Figure 1.a and Figure 1.b. Prominent levels of blood glucose levels were observed in diabetic control rats (402±11.41 mg/dL) on 28th day while lowest levels were observed in normal control (86.33±2.67 mg/dL). Glibenclamide (20 mg/kg b.w) showed the highest reduction in blood glucose levels (-239.56%) in diabetic rats, followed by MeCV (400 mg/kg b.w) with -108.48% and MeCG (400 mg/kg b.w) with -66.39%. These results indicate that MeCV is more effective than MeCG in lowering blood glucose levels in diabetic rats.

Impact of long-term treatment of MeCV, MeCG and glibenclamide on body weights of diabetic rats

The body weights of normal control, diabetic control, glibenclamide, MeCV and MeCG treated rats were shown in Figure 2.a and Figure 2.b. The lowest body weight was observed in diabetic control rats (108.33±4.01g) on 28th day while highest body weight was observed in normal control (236.66±6.14 g). Glibenclamide significantly increased body weight by 6.24%, while MeCV showed a slight increase of 0.92%. In contrast, MeCG led to a decrease of -9.57% in body weight. These results suggest that MeCV helps maintain body weight better than MeCG in diabetic rats.

Effect of glibenclamide, MeCV and MeCG on Carbohydrate Profiles and Oxidative Enzymes.

Carbohydrate Content in Liver Tissue

The total carbohydrate levels in the liver tissues of diabetic rats significantly restored after 28-days treatment of methanolic extract of MeCV and methanolic extract of MeCG. Diabetic rats showed a noticeable ($P < 0.01$) decrease in total carbohydrate levels. Administration of MeCV, MeCG, and glibenclamide reversed this reduction effectively. MeCV demonstrated superior efficacy among the two extracts. It is showing carbohydrate levels nearer to those observed in glibenclamide-treated rats. (Figure. 3).

Glucose Levels in Liver Tissue

The MeCV and MeCG also normalised hepatic glucose levels in diabetic rats after 28 days treatment. The diabetic condition resulted in a significant ($P < 0.01$) elevation of glucose levels in the hepatic tissue. The MeCV significantly reduced glucose levels compared to MeCG in liver tissue, it is nearer to glibenclamide values (Figure 4).

Glycogen Levels in Liver Tissue

Liver glycogen levels, which were significantly reduced ($P < 0.01$) in STZ-induced diabetic rats due to impaired insulin activity and glycogen synthesis, were significantly improved following treatment with MeCV and MeCG.

Both MeCV and glibenclamide restored glycogen levels to near-control values, with MeCV showing better efficacy compared to MeCG. These results highlight MeCV's superior ability to enhance glycogenesis, potentially by activating glycogen synthase and inhibiting glycogen phosphorylase (Figures 5).

Effect of glibenclamide, MeCV and MeCG on the actions of hepatic tissue carbohydrate metabolic enzymes.

Hexokinase

Hexokinase activity levels was shown in Table 1 and Figure 6. Normal control rats had the highest hexokinase activity (381.60±9.52 U/mg protein) whereas diabetic control rats had the lowest activity (179.28±8.16 U/mg protein). Treatment with 20 mg/kg b.w. of glibenclamide raised hexokinase activity by 80.72% compared to diabetic controls. MeCV increased activity by 55.82%, while MeCG showed a 22.89% increase. Hence, MeCV treated diabetic rats showed significant hexokinase activity compared to MeCG treated diabetic rats, it is nearer to glibenclamide treated diabetic rats' values.

G-6-P (Glucose 6- phosphatase)

MeCV (400 mg/kg b.w.) increased activity by 127.15%, while MeCG (400 mg/kg b.w.) showed an 89.48% increase. Treatment with 20 mg/kg b.w. of glibenclamide increased G-6-P activity by 143.96% compared to diabetic controls. Diabetic control rats had the lowest activity (160.50±2.83 U/mg protein), while normal control rats had the highest (436.71±0.97 U/mg protein). Therefore, MeCV exhibited significantly higher G-6-P activity in diabetic rats with compared to those treated with MeCG. This values closely approaching those of glibenclamide-treated rats (Table 1 and Figure 7).

FBP-1, 6 (Fructose1, 6-bisphosphatase)

The highest levels of FBP-1, 6 activities were observed in diabetic control rat (514.44± 11.21 U/mg protein) while lowest levels were observed in normal control (146.16± 2.72 U/mg protein). MeCV treatment with 400 mg/kg b.w. led to a 55.47% reduction, whereas 400 mg/kg b.w. of MeCG resulted in a 44.34% decrease than diabetic control rats (Table 1 and Figure 8). Treatment with 20 mg/kg b.w. of glibenclamide significantly reduced FBP-1,6 activity by 57.26% compared to diabetic control rats. Therefore, 400 mg/kg b.w. of MeCV showed significantly higher G-6-P activity compared to 400 mg/kg b.w. of MeCG. This values closely resembling those of glibenclamide-treated rats.

G-6PDH (Glucose-6-phosphate dehydrogenase)

The lowest levels of G-6PDH activity were observed in diabetic control rats (0.59±0.011 U/mg protein) while highest levels were observed in normal control (1.42±0.009 U/mg protein). In 20mg/k.g/b.w glibenclamide treated diabetic rat, G-6PDH activity levels were significantly increased by 107.09% compared to diabetic control. While 400mg/k.g/b.w of MeCV treated diabetic rat showed G-6PDH activity levels were significantly increased by 96.62%. In 400mg/k.g/b.w of MeCG treated diabetic rat, G-6PDH activity levels were significantly increased by 57.77% compared to diabetic control (Table 1 and Figure 9)

Discussion

Being one of the chronic metabolic disorder, DM affecting many millions of people worldwide by altering the carbohydrate, fat and protein metabolism. The present study explores potential antihyperglycaemic activity of methanolic extract of *Cleome viscosa L.* (MeCV) and *Cleome gynandra L.* (MeCG) by evaluating their effects on blood glucose levels and carbohydrate metabolism in hepatic tissue of STZ-induced diabetic rats. The excess generation of free radicals may increase oxidative stress which may lead to pancreatic β-cell damage and the progression of STZ-induced insulin-dependent diabetes mellitus (19). The endeavour has been made to decide the capacity of the both plant

concentrates to evaluate the activity over the acute diabetic condition.

Single dose (*i.p.*) treatment of rats with STZ (45 mg/kg b.w) significantly ($p< 0.05$) increased glucose in blood as shown in Figure 1a & 1b. Treatment with MeCV, MeCG and glibenclamide were found to reduce the elevated total blood glucose levels markedly in STZ-induced diabetic test animals. In this study, STZ-induced diabetic rats had high blood glucose levels during the whole treatment period and it was due to the STZ caused β-cells death and there by reduction in pancreatic β-cells. Thus, it causes insufficient release of insulin from β-cells and subsequently, the elevation of blood glucose level occurs (20). MeCV significantly decreased blood glucose levels more than MeCG. This effect may be attributed to increased insulin levels, enhanced insulin activity, and/or reduced hepatic gluconeogenesis. These suggest that MeCV has potential antihyperglycaemic activity while contrasted by *MeCG*.

In this study, the body weights of untreated diabetic control rats were declined considerably ($p<0.01$). But the rodent's increases the body weights were noticed in MeCV along with MeCG administered diabetic rats as contrasted by the control diabetic rats. It suggests that treatment of diabetic rats by MeCV and MeCG had restored the body weight reduction in diabetic rats. Our results were in accordance with the results of Gholami et al (21) and Erion et al (22) studies. It has been accounted to facilitate treatment of diabetic rats body weight loss as compared to normal controls and it could be due to the loss of adipose tissue and muscle mass, breakdown of tissue proteins in diabetic rats (23). MeCV more significantly increased body weight of diabetic rats than that of MeCG. It indicates that MeCV has the potential of protecting body weight by decreasing the loss of adipose tissue and muscle mass, breakdown of tissue proteins in diabetic rats.

From this investigation we comprehend that MeCV has successful blood glucose bringing down movement, no loss in body weights and can be valuable in the administration of diabetes. Further trials are expected to recognise the active antihyperglycaemic segments and to determine the system of activity.

The liver plays a crucial role in the regulation of blood glucose levels. Therefore, it is important to evaluate the effects of MeCV, MeCG, and glibenclamide on key hepatic enzymes involved in carbohydrate metabolism. The liver maintains blood glucose homeostasis primarily through its ability to store glucose as glycogen (glycogenesis) and to produce glucose via the gluconeogenic pathway, including the breakdown of glycogen into glucose (glycogenolysis) (24). For the period of diabetes, nearby is a declined in the mass of liver organ because of improved molecules like glycogen, proteins and lipids splitting process (25). Accordingly, the measurement of hexokinase, G-6-P, FBP-1, 6 and G-6PDH are considered as critical liver markers of diabetes mellitus.

The liver, a critical organ in glucose metabolism, plays a central role in maintaining glucose homeostasis through processes such as glycolysis, gluconeogenesis, glycogen synthesis, and glycogenolysis (24). Hyperglycaemia, a defining feature of diabetes, results from increased endogenous glucose production and reduced insulin-mediated glucose clearance (26). The dysregulation of key hepatic enzymes, including glucokinase, phosphofructokinase, and pyruvate kinase, further exacerbates this metabolic imbalance, leading to diminished peripheral glucose utilisation and elevated hepatic glucose production (27).

The significant reduction in hepatic carbohydrate content observed in STZ-induced diabetic rats is consistent with prior findings in diabetic models, where diminished carbohydrate levels were attributed to disrupted hepatic metabolism and pronounced depletion of glycogen (28). Treatment with MeCV significantly improved carbohydrate content, suggesting its potential to counteract the metabolic impairments seen in diabetes. This result parallels earlier studies where plant-based therapies such as bitter gourd (*Momordica charantia*) and turmeric (*Curcuma longa*) demonstrated similar efficacy in restoring hepatic carbohydrate levels (28). The observed effects position MeCV as a promising candidate for complementary diabetes therapy, with its ability to normalize hepatic carbohydrate metabolism.

Hyperglycaemia in diabetes stems from increased gluconeogenesis and glycogenolysis, driven by insulin resistance and reduced insulin secretion (29). Chronic hyperglycaemia exacerbates metabolic imbalances, as elevated hepatic glucose production is associated with increased expression of glucose-6-phosphatase and impaired insulin signalling (30). In this study, MeCV significantly reduced hepatic glucose levels, bringing them closer to normal values, which suggests its ability to modulate gluconeogenesis and glucose output. This effect is consistent with reports that plant-based extracts such as *Eugenia jambolana* enhance insulin secretion and glucose uptake (31, 32). MeCV's superior performance compared to MeCG may indicate a more pronounced insulinotropic effect, enhancing glucose metabolism in diabetic rats. it is attributed to increased gluconeogenesis and impaired insulin signalling. By these results suggested that MeCV may increase glucose uptake and utilisation more effectively in liver tissue, it is possibly by improving insulin sensitivity and modifying key enzymes involved in gluconeogenesis and glycolysis

Glycogen is the primary storage form of glucose, and its synthesis is critically dependent on insulin, which activates glycogen synthase and inhibits glycogen phosphorylase. In diabetes, reduced insulin levels and increased glycogenolysis lead to significant depletion of glycogen reserves in hepatic tissues (33, 34). This study observed a marked decrease in hepatic glycogen levels in diabetic rats, consistent with earlier findings in diabetic models (35, 36). Treatment with MeCV and MeCG significantly improved glycogen content, with MeCV demonstrating a stronger effect, likely due to enhanced glycogenesis and improved insulin sensitivity.

Previous studies have shown similar effects with *Trigonella foenum-graecum* and *Momordica charantia*, which restored hepatic glycogen levels through insulinotropic mechanisms and improved pancreatic β-cell function (37). The restoration of glycogen levels by MeCV highlights its potential to normalise hepatic glycogen stores, reflecting its ability to mitigate the metabolic disturbances caused by STZ-induced diabetes.

Hexokinase is an important enzyme in the glycolysis pathway that depends on insulin. It helps maintain normal blood sugar levels by converting glucose into glucose-6-phosphate (G-6-P). This is a key step in how the body uses sugar for energy. Insulin increases the activity of hexokinase in the liver, which boosts glycolysis and helps the body use more glucose to produce energy (38). However, in diabetes, hexokinase activity is reduced due to a lack of insulin. This leads to decreased glucose entry into cells, reduced glucose utilisation by tissues, and increased glucose production in the liver through gluconeogenesis (39). In the present study, hexokinase activity was found to be significantly reduced in the diabetic control group compared to the normal

control group, likely due to insulin deficiency associated with diabetes. Reduced hexokinase activity has also been reported in diabetic rats, leading to depletion of glycogen stores in the liver and muscle (40). Administration of MeCV, MeCG (at 400 mg/kg body weight), and glibenclamide (at 20 mg/kg body weight) to diabetic rats improved hepatic hexokinase activity toward normal levels. This effect may be attributed to the stimulation of insulin secretion from pancreatic β-cells. The present findings are supported by an earlier study by Sundaram et al. (41), who reported the modulatory effects of green tea extract on key hepatic enzymes involved in glucose metabolism in STZ and high-fat diet-induced diabetic rats (41).

G-6-P and FBP-1, 6 are the key catalysts in gluconeogenesis. G-6-P is a key catalyst engaged with the support of blood glucose homeostasis and it catalyzes the terminal pace in gluconeogenesis and glycogenolysis and FBP-1, 6 is a hepatic enzyme that changes over FBP-1, 6 to F-6-P (fructose *6*-phosphate) in the gluconeogenic pathway (42).

In the present study, the hepatic gluconeogenic enzyme glucose-6-phosphatase (G-6-Pase) was found to be significantly lower in the diabetic control group compared to the normal control. Previous studies have also reported reduced levels of this enzyme in STZ-induced diabetic male Wistar rats (43). The reduced levels of gluconeogenic enzymes may be due to insulin deficiency, as insulin normally acts as a suppressor of gluconeogenic enzyme activity under normal physiological conditions (44). In the present examination, the exercise of G-6-P was observed to be increased essentially during the liver of MeCV, MeCG along with glibenclamide treated diabetic animals. As indicated by Gupta et al., (45) this increased levels might be because of the modulation and regulation of the exercises of this gluconeogenic catalyst either through guideline of cAMP or inhibition of gluconeogenesis (45). Previously, several phytochemical compounds—such as pterostilbene (42), coumarin (46), and diosmin (47)—have been investigated in antidiabetic studies focusing on carbohydrate-metabolizing enzymes, and all have been reported to exert a stimulatory effect on glucose-6-phosphatase (G-6-Pase) activity. Another study consistent with the present investigation reported that Astragaloside IV—a cycloartane-type triterpene glycoside extracted from *Astragalus membranaceus* (Fisch.)—significantly reduced blood glucose levels and inhibited glucose-6-phosphatase (G-6-Pase) activity in diabetic rats. (48).

In this study, the activity of FBP-1, 6 of untreated diabetic rats was increased significantly. But the decreased FBP-1, 6 activity was seen in MeCV, MeCG and glibenclamide treated diabetic rats as compared to the diabetic control. This enzyme converts FBP-1, 6 to F-6-P in gluconeogenesis and the Calvin cycle. It has been shown that diabetes causes excessive production of glucose in the blood through gluconeogenesis pathway (49). Inhibition of FBP-1, 6 lowers blood glucose levels in T2DM patients. The decreased activity of FBP-1, 6 in MeCV treated diabetic rats suggests that this plant has higher antihyperglycaemic activity and reduced glucose levels than MeCG.

Glucose-6-phosphate dehydrogenase (G-6-PDH) is a key regulatory enzyme of the pentose phosphate pathway, which runs parallel to glycolysis and controls carbon flow through this cycle. Specifically, G-6-PDH catalyses the first and rate-limiting step of the pathway, leading to the production of pentose phosphates and the generation of NADPH. NADPH is essential for reductive biosynthesis and maintaining the cellular redox balance. Alterations in G-6-PDH activity can significantly influence oxidative stress and affect cellular homeostasis. (50). In our findings, G-6-PDH activity was reduced in diabetic animals, and this reduction was restored toward normal levels following treatment with MeCV and MeCG. In STZ-induced diabetic rats, hepatic G-6-PDH activity is significantly decreased, which impairs glucose utilisation and contributes to the development of hyperglycaemia (51). The MeCV- and MeCG-treated groups showed a significant increase in G-6-PDH activity compared to the diabetic control group. This enhancement in enzyme activity aligns with previous findings. For instance, administration of mangiferin to diabetic animals significantly increased G-6-PDH activity (52). Similarly, Kondeti et al. (38) reported that glucose-6-phosphate dehydrogenase activity was markedly reduced in STZ-induced diabetic animals.

Conclusion

The study demonstrates that the methanolic extract of *Cleome viscosa L.* (MeCV) exhibits significant antihyperglycemic activity in diabetic rats. This is evident from the substantial reduction in fasting blood glucose levels (-108%) compared to diabetic controls, surpassing the efficacy of *Cleome gynandra L.* (MeCG) (-66%) and closely approaching the effect of glibenclamide, a standard hypoglycemic drug. Additionally, both MeCV and MeCG effectively prevented diabetes-induced body weight loss, though no significant weight gain was observed, indicating their role in mitigating diabetes-associated cachexia.

MeCV exhibited superior efficacy in restoring carbohydrate metabolism, significantly improving total carbohydrate, glucose, and glycogen levels in liver tissue to values comparable to those achieved with glibenclamide treatment. This highlights its potential as a complementary therapeutic agent for diabetes management.

Furthermore, MeCV demonstrated potent regulatory effects on key metabolic enzymes involved in carbohydrate metabolism, bringing their activity levels close to normal and outperforming MeCG in this regard. This suggests its role in improving hepatic glucose metabolism, thereby enhancing overall glycemic control.

The hepatoprotective properties of MeCV were also evident, as it helped prevent diabetes-related liver damage, further supporting its traditional use in managing metabolic disorders. Given these findings, MeCV holds significant promise as a complementary antihyperglycaemic agent for diabetes mellitus and its associated complications. However, further studies are necessary to explore its precise mechanism of action and potential clinical applications.

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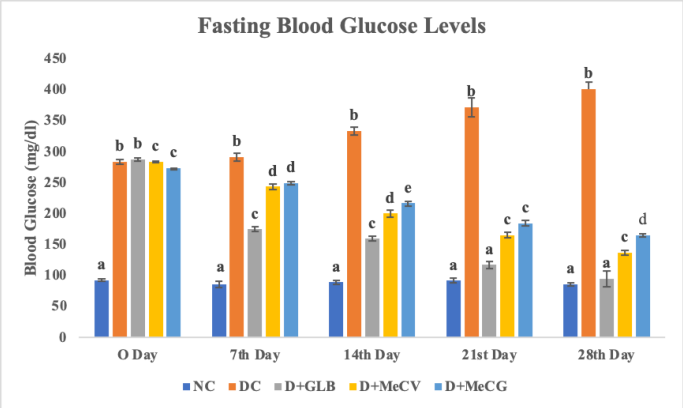
Table 1: The percentage of decreasing or increasing levels of hexokinase, G-6-P, FBP-1, 6 and G-6PDH activities in diabetic treated and untreated rats.

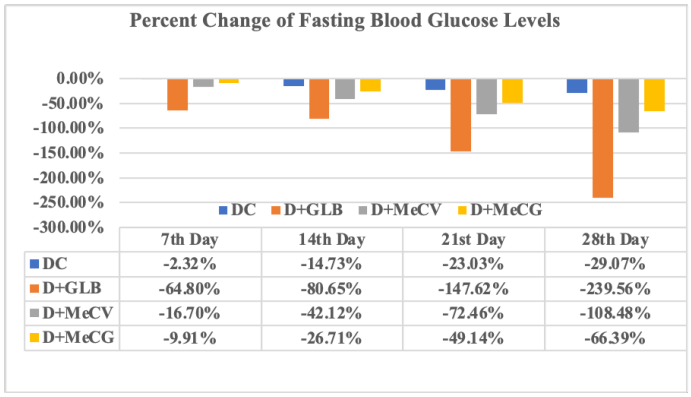
Groups	% Hexokinase activity	% G-6-P activity	% FBP-1,6 activity	% G-6PDH activity
Diabetic control (STZ-induced)	53.01▼	63.24▼	251.97▲	58.30▼
Diabetic + Glibenclamide-20mg/kg b.w treated	80.72▲	143.96▲	57.26▼	107.09▲
Diabetic+ MeCV-400mg/kg b.w treated	55.82▲	127.15▲	55.47▼	96.62▲
Diabetic+ MeCG-400mg/kg b.w treated	22.89▲	89.48▲	44.34▼	57.77▲

Figure 1a.: Fasting blood glucose levels of normal control rats, diabetic control rats, glibenclamide, MeCV and MeCG treated diabetic rats



Data were given as mean ± SE for six animals in each group. Values not sharing a common letter differ significantly at P<0.01 by DMRT.

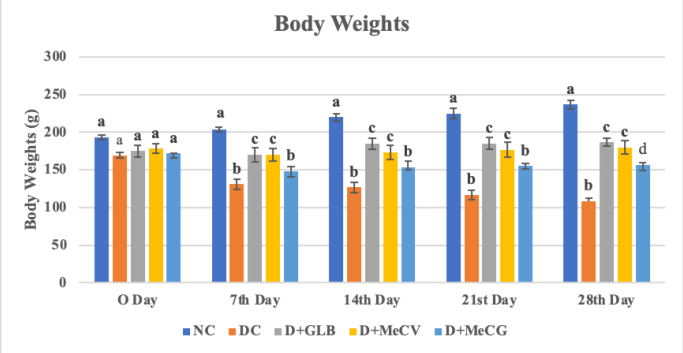
Figure 1b: Percent change of fasting blood Glucose levels of various groups



	7th Day	14th Day	21st Day	28th Day
DC	-2.32%	-14.73%	-23.03%	-29.07%
D+GLB	-64.80%	-80.65%	-147.62%	-239.56%
D+MeCV	-16.70%	-42.12%	-72.46%	-108.48%
D+MeCG	-9.91%	-26.71%	-49.14%	-66.39%

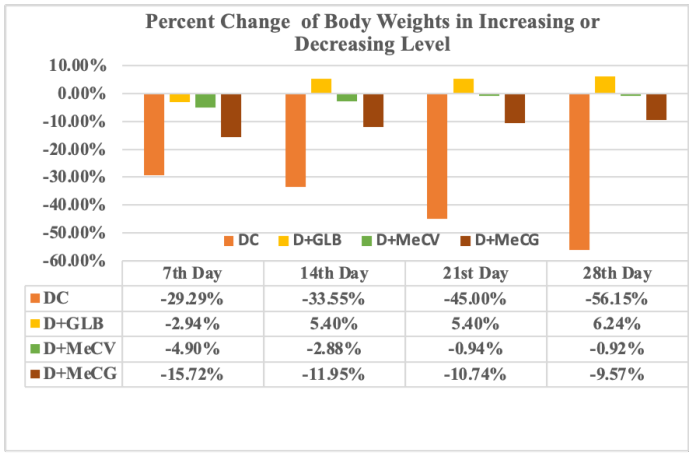
Percent change showed the relative blood glucose levels increased and decreased. The percent change values were calculated over zero-time values.

Figure 2a: Body weights of normal control rats, diabetic control rats, glibenclamide, MeCV and MeCG treated diabetic rats



Mean ± SE was given in data (n=6 in every group). The data not distribution a common alphabet significantly p<0.01 differ by DMRT

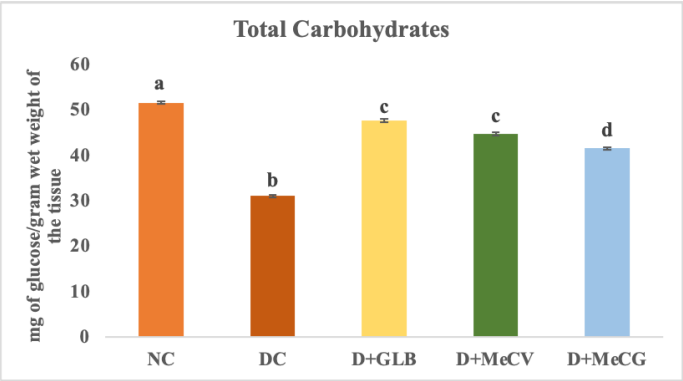
Figure 2b: Percent change of body weights of various groups



	7th Day	14th Day	21st Day	28th Day
DC	-29.29%	-33.55%	-45.00%	-56.15%
D+GLB	-2.94%	5.40%	5.40%	6.24%
D+MeCV	-4.90%	-2.88%	-0.94%	-0.92%
D+MeCG	-15.72%	-11.95%	-10.74%	-9.57%

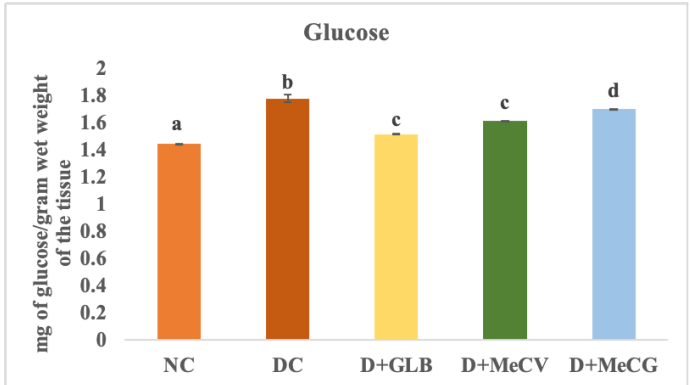
Percent change showed the relative weight increased and decreased. The percent change values were calculated over zero-time values.

Figure 3: Hepatic total carbohydrate content of normal control rats, diabetic control rats, glibenclamide, MeCV and MeCG treated diabetic rats



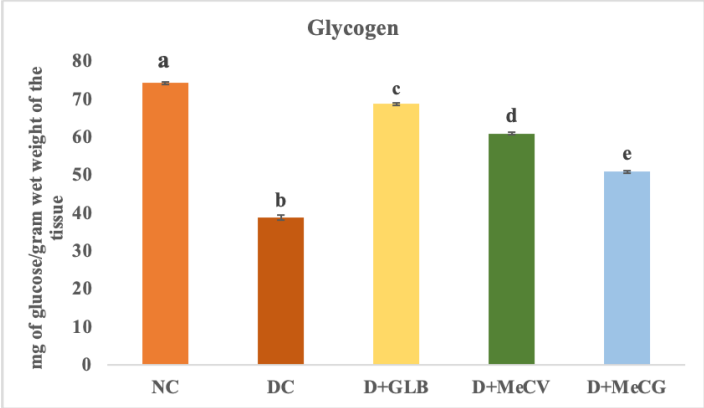
Mean ± SE was given in data (n=6 in every group). The data not distribution a common alphabet significantly p<0.01 differ by DMRT

Figure 4: Hepatic glucose levels of normal control rats, diabetic control rats, glibenclamide, MeCV and MeCG treated diabetic rats



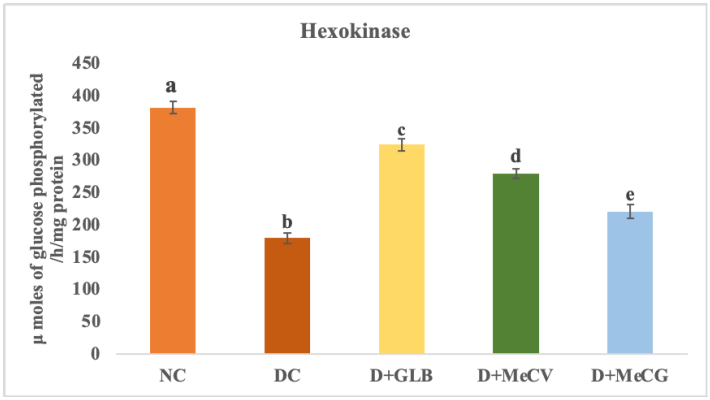
Mean ± SE was given in data (n=6 in every group). The data not distribution a common alphabet significantly p<0.01 differ by DMRT

Figure 5: Hepatic glycogen levels of normal control rats, diabetic control rats, glibenclamide, MeCV and MeCG treated diabetic rats



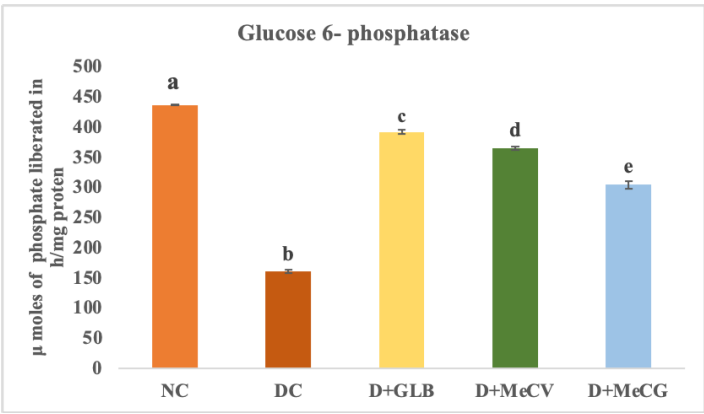
Mean ± SE was given in data (n=6 in every group). The data not distribution a common alphabet significantly p<0.01 differ by DMRT

Figure 6: Hexokinase activity of normal control rats, diabetic control rats, glibenclamide, MeCV and MeCG treated diabetic rats



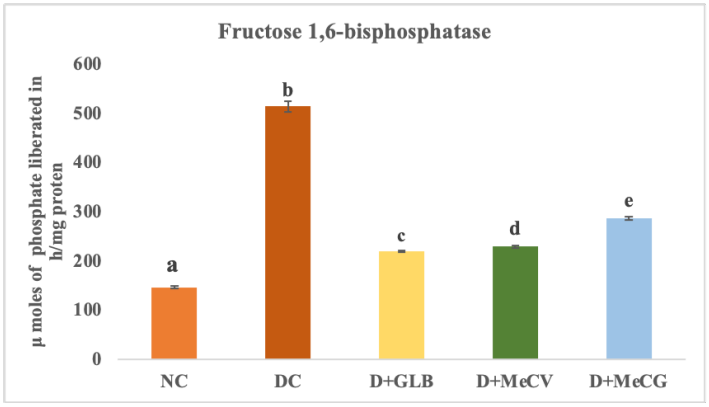
Mean ± SE was given in data (n=6 in every group). The data not distribution a common alphabet significantly p<0.01 differ by DMRT

Figure 7: Glucose 6- phosphatase activity of normal control rats, diabetic control rats, glibenclamide, MeCV and MeCG treated diabetic rats



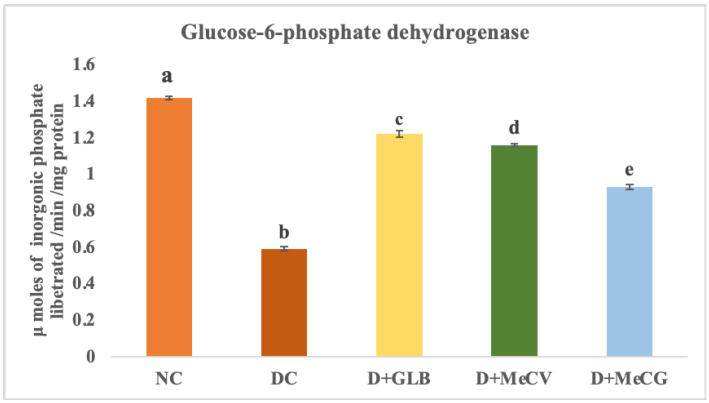
Mean ± SE was given in data (n=6 in every group). The data not distribution a common alphabet significantly p<0.01 differ by DMRT

Figure 8: Fructose 1,6-bisphosphatase activity of normal control rats, diabetic control rats, glibenclamide, MeCV and MeCG treated diabetic rats



Mean ± SE was given in data (n=6 in every group). The data not distribution a common alphabet significantly p<0.01 differ by DMRT

Figure 9: Glucose-6-phosphate dehydrogenase activity of normal control rats, diabetic control rats, glibenclamide, MeCV and MeCG treated diabetic rats



Mean ± SE was given in data (n=6 in every group). The data not distribution a common alphabet significantly p<0.01 differ by DMRT

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