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Original Article

Hypoglycemic, Hypolipidemic and Antioxidant Effects of Chloroform Seed Extracts of Three Cleome Species and their Synergistic Combination in Streptozotocin-Induced Diabetic Rats

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ABSTRACT

Background: Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycaemia, dyslipidaemia, oxidative stress, and progressive tissue damage. This study evaluated the antidiabetic, hypolipidaemic, and antioxidant effects of chloroform seed extracts of *Cleome rutidosperma, C. gynandra, C. viscosa*, and their combined extract in Streptozotocin (STZ)-induced diabetic rats. **Materials and Methods:** Diabetes was induced in Wistar rats by a single intraperitoneal injection of STZ (50 mg/kg). Diabetic rats received glibenclamide (5 mg/kg), individual *Cleome* extracts, or the combined extract (70 mg/kg) orally for 28 days (*n*=6/group). Fasting blood glucose, body weight, serum lipid profile, liver enzymes (ALT, AST, ALP), hepatic antioxidant enzymes (SOD, CAT, GPx), and pancreatic histopathology were evaluated. **Results:** All treatments significantly improved diabetic parameters compared with the diabetic control. The combined extract produced the greatest reduction in fasting blood glucose (139.71 ± 6.10 mg/dL on day 28), improved body weight, reduced serum cholesterol and triglycerides, normalized ALT, AST, and ALP activities, enhanced hepatic antioxidant enzyme levels, and markedly restored pancreatic islet architecture. **Conclusion:** The combined chloroform seed extract of *C. rutidosperma, C. gynandra*, and *C. viscosa* exhibited significant antidiabetic, hypolipidaemic, hepatoprotective, and antioxidant activities in STZ-induced diabetic rats. These findings support its potential as a promising plant-derived antidiabetic candidate and warrant further phytochemical and mechanistic investigations.

Keywords: Antioxidant, *Cleome gynandra*, *Cleome rutidosperma*, *Cleome viscosa*, Diabetes mellitus, Hypoglycaemic activity, Streptozotocin.

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycaemia resulting from impaired insulin secretion, insulin action, or both. Progressive oxidative stress contributes to β-cell dysfunction and the development of vascular complications including nephropathy, retinopathy, neuropathy, and cardiovascular disease (Osadebe *et al*., 2014; Modak *et al*., 2007; Wild *et al*., 2004; Atkinson *et al*., 2014). Although conventional therapies, including insulin, sulfonylureas such as glibenclamide, and biguanides, effectively reduce blood glucose levels (Ceriello and Motz, 2004; Govindappa, 2015), their long-term use is frequently associated with adverse effects and limited efficacy in preventing diabetic complications. Consequently, there is growing interest in identifying safer and more effective plant-derived antidiabetic agents.

The genus *Cleome* (Cleomaceae) comprises approximately 200 species of annual and perennial herbs distributed throughout Africa and Asia. Among them, *Cleome rutidosperma, Cleome gynandra*, and *Cleome viscosa* have been widely used in traditional medicine for the treatment of fever, helminthic infections, diarrhoea, mental disorders, and infantile convulsions (Chweya and Mnzava, 1997; Mule *et al*., 2008; Parimala *et al*., 2003; Parimala *et al*., 2002; Williams *et al*., 2003). These species are also consumed as edible vegetables or seeds in several regions, reflecting their nutritional and ethnopharmacological importance (Upadhyay, 2015; Van den Heever and Venter, 2007). Our previous phytochemical investigation demonstrated that the chloroform seed extracts of these three *Cleome* species contain diverse bioactive constituents with antibacterial activity

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(Kanimathi *et al.*, 2019) suggesting their potential for broader pharmacological applications. However, despite their traditional medicinal use and reported phytochemical composition, the antidiabetic, hypolipidaemic, antioxidant, and pancreatic protective effects of their chloroform seed extracts, individually and in combination, have not been systematically investigated.

Therefore, this study aimed to evaluate the hypoglycaemic, hypolipidaemic, antioxidant, and pancreatic protective effects of Chloroform Seed Extracts of *C. rutidosperma* (CRCE), *C. gynandra* (CGCE), *C. viscosa* (CVCE), and their combination (CRGVCE) in streptozotocin-induced diabetic rats.

MATERIALS AND METHODS

Preparation of plant extract

Cleome rutidosperma DC., *Cleome gynandra* L., and *Cleome viscosa* L. (Cleomaceae) were collected from Chennai, Tamil Nadu, India, and authenticated by Prof. P. Jayaraman, Plant Anatomy Research Centre. Voucher specimens (Nos. 4037, 4038, and 4036, respectively) were deposited in the departmental herbarium. Seeds were shade-dried, powdered, extracted with chloroform and the solvent was evaporated at room temperature to obtain the crude extracts.

Animals

Healthy Wistar albino rats of either sex (220-400 g) were obtained from Biogen Animal House (Bangalore, India). Animals were housed under standard laboratory conditions with free access to food and water and acclimatized for two weeks before the study. All experimental procedures were approved by the Institutional Animal Ethics Committee (Approval No. LV/03/CLBM/2019).

Acute toxicity and induction of diabetes

Acute oral toxicity was evaluated according to OECD Guideline 423. Diabetes was induced by a single intraperitoneal injection of streptozotocin (50 mg/kg; Sisco Pharmaceuticals Ltd., Mumbai) dissolved in 0.1 M sodium citrate buffer (pH 4.5). Rats were fasted overnight before injection and provided with 5% glucose solution overnight to prevent hypoglycaemic shock. Animals with fasting blood glucose levels >200 mg/dL after 48 hr were considered diabetic and included in the study (Jain *et al.*, 2017).

Experimental design

Forty-two rats were randomly divided into seven groups (n=6): normal control, diabetic control, glibenclamide (5 mg/kg), CRCE (70 mg/kg), CGCE (70 mg/kg), CVCE (70 mg/kg), and the combined extract (CRGVCE, 70 mg/kg). Treatments were administered orally once daily for 28 days (Hussein and Gobba, 2013; Al-Faris *et al.*, 2010).

Biochemical and histological analyses

Fasting blood glucose was measured on days 0, 7, 14, and 28 using the Glucose Oxidase-Peroxidase (GOD-POD) method, while body weight was recorded throughout the study. At the end of the experiment, blood samples were collected under mild ether anaesthesia, and serum was separated for estimation of Total Cholesterol (TC), Triglycerides (TGL), Alanine Aminotransferase (ALT), aspartate Aminotransferase (AST), and Alkaline Phosphatase (ALP) using commercial assay kits. Liver tissues were excised to determine Superoxide Dismutase (SOD), Catalase (CAT), and Glutathione Peroxidase (GPx) activities. Pancreatic tissues were collected, washed with ice-cold saline, and processed for histopathological examination.

Statistical analysis

Data are presented as mean ± SD (n=6). Statistical analyses were performed using GraphPad Prism version 5. Differences among groups were analysed by one-way ANOVA followed by Bonferroni's multiple comparison test, with p<0.05 considered statistically significant.

RESULTS

Acute toxicity

No signs of toxicity or mortality were observed in rats administered the chloroform extracts at 70 mg/kg throughout the study period. Therefore, this dose was selected for the evaluation of antidiabetic activity.

Effect on fasting blood glucose

Streptozotocin (50 mg/kg) successfully induced diabetes, with fasting blood glucose levels exceeding 300 mg/dL in diabetic rats. Oral administration of CRCE, CGCE, CVCE, CRGVCE, and glibenclamide significantly reduced blood glucose levels compared with the diabetic control group over the 28-day treatment period (Figure 1). The combined extract (CRGVCE) showed the greatest antihyperglycaemic effect, reducing blood glucose to 139.71 ± 6.10 mg/dL on day 28. Among the individual extracts, the glucose-lowering efficacy was ranked as CVCE > CGCE > CRCE.

Effect on body weight

Diabetic control rats exhibited progressive body weight loss throughout the study, whereas normal control rats showed a gradual increase in body weight (Table 1). Treatment with glibenclamide and all *Cleome* extracts attenuated diabetes-induced weight loss. The combined extract (CRGVCE) showed the greatest improvement in body weight by day 28, followed by CVCE and CGCE, while CRCE produced the least improvement.

Effect on serum lipid profile

Diabetic rats showed elevated serum TC and TGL levels compared with normal controls. Treatment with CRCE, CGCE, CVCE, and CRGVCE significantly reduced both TC and TGL levels (Figure 2). The combined extract showed the greatest hypolipidaemic effect, followed by CVCE, CGCE, and CRCE.

Effect on liver function markers

Serum ALT, AST, and ALP activities were significantly elevated in the diabetic control group, indicating hepatic injury (Figure 2). Administration of all *Cleome* extracts significantly reduced these enzyme levels compared with diabetic controls. The greatest reduction was observed in the CRGVCE-treated group, with enzyme activities approaching those of the glibenclamide-treated group.

Effect on hepatic antioxidant enzymes

Streptozotocin-induced diabetes significantly decreased hepatic SOD, CAT, and GPx activities (Figure 3). Treatment with CRCE, CGCE, CVCE, and CRGVCE restored antioxidant enzyme activities, with the combined extract producing the greatest increase, particularly in CAT activity.

Comparative therapeutic efficacy

The percentage improvement in blood glucose, body weight, lipid profile, liver enzyme activities, and antioxidant enzyme levels is summarised in Table 2. Overall, the combined extract (CRGVCE) demonstrated the highest therapeutic efficacy across all evaluated parameters. While the individual extracts also improved diabetic biomarkers, CRCE showed comparatively lower effects on body weight and ALT activity, whereas CVCE exhibited the strongest activity among the individual extracts.

Histopathological findings

Histological examination of pancreatic tissue revealed normal islet architecture in the normal control group, whereas diabetic control rats showed shrunken islets, degenerative changes, and necrosis (Figure 4). Treatment with glibenclamide and all *Cleome* extracts improved pancreatic morphology to varying degrees. The CRGVCE-treated group exhibited the greatest restoration of islet architecture, closely resembling the normal and glibenclamide-treated groups.

DISCUSSION

The present study demonstrated that chloroform seed extracts of *Cleome rutidosperma, Cleome gynandra*, and *Cleome viscosa* possess significant antidiabetic activity in Streptozotocin (STZ)-induced diabetic rats. Among the treatment groups, the Combined Extract (CRGVCE) consistently produced the greatest improvement in glycaemic control, body weight, and lipid profile, indicating that combining the three *Cleome* species enhanced the overall therapeutic response compared with the individual extracts.

STZ-induced diabetes is a well-established experimental model that mimics pancreatic β-cell damage, resulting in persistent hyperglycaemia and metabolic disturbances. In the present study, treatment with all three extracts significantly reduced fasting blood glucose levels throughout the 28-day treatment period, with the combined extract producing the greatest antihyperglycaemic effect. Similar glucose-lowering activity has previously been reported for methanolic extracts of *C. viscosa*, supporting the antidiabetic potential of this genus (Devi and Ramesh, 2015). Although the precise mechanism was not investigated, the observed reduction in blood glucose suggests that the extracts may improve glycaemic control through preservation of residual pancreatic β-cell function, enhanced insulin action, or increased peripheral glucose utilization.

Loss of body weight is a characteristic feature of uncontrolled diabetes and results from impaired glucose utilization, increased protein catabolism, and enhanced fat mobilization. Consistent with previous reports, STZ-treated rats exhibited progressive weight loss, whereas treatment with the *Cleome* extracts attenuated this decline. The improvement was most pronounced in the CRGVCE-treated group, suggesting better metabolic regulation following treatment. Restoration of body weight is considered an indirect indicator of improved glycaemic control and reduced tissue protein breakdown, further supporting the therapeutic efficacy of the combined extract.

Diabetic dyslipidaemia, characterized by elevated serum cholesterol and triglyceride concentrations, is a major contributor to cardiovascular complications in diabetes. Administration of the *Cleome* extracts significantly improved both lipid parameters, with CRGVCE producing the greatest reduction. Improvement of lipid metabolism may result from enhanced insulin activity, reduced hepatic cholesterol synthesis, or improved lipid utilization. Comparable hypolipidaemic effects have been reported for several medicinal plants, including *Cleome arabica*, in experimental diabetes (Taderera *et al.*, 2016; Chi and Koh, 1982; Boublata *et al.*, 2020). The superior lipid-lowering activity of the combined extract suggests that multiple phytochemicals may act through complementary mechanisms to restore lipid homeostasis, thereby reducing one of the major metabolic complications associated with diabetes.

The liver plays a central role in glucose and lipid metabolism, and hepatic dysfunction is a common consequence of diabetes mellitus. Elevated serum ALT, AST, and ALP activities observed in diabetic rats are indicative of hepatocellular injury and altered membrane permeability resulting from hyperglycaemia-induced oxidative stress. Treatment with the *Cleome* extracts significantly restored these biochemical markers toward normal values, with CRGVCE producing the greatest hepatoprotective effect.

Table 1: Effect of test drugs on body weight in Streptozotocin induced diabetic rats.

Group No.	Treatment	Body weight (g) on post induction days			
		Initial	7th day	14th day	28th day
I	Normal control	250.15±3.42	254.19±4.21	255.4±5.18	257.35±4.15
II	Diabetic Control	262.19±3.72	240.20± 6.64	235.42±4.10**	204.35±5.13**
III	Diabetic rats + Glibenclamide	261.32±2.16	264.41 ± 4.17	269.8±3.34*	282.10 ± 1.26**
IV	Diabetic rats + **CRCE** 70mg/kg	306.40±5.32	294.62 ± 4.23	298.10 ± 6.16*	296.11± 3.69**
V	Diabetic rats + **CGCE** 70mg/kg	320.12±3.11	310.11±2.82	314.71±5.21*	316.31±3.02**
VI	Diabetic rats+ **CVCE**70mg/kg	281.10±2.80	269.09±6.07	278.02±3.05	283.02±1.20
VII	Diabetic rats+ **CRGVCE** 70mg/kg	325.06±3.04	310.08±2.06	321.11±1.21	328.16±2.17

**Data are expressed as Mean ± SD (n=6). Statistical analysis was performed using one-way ANOVA followed by Bonferroni's multiple comparison test. *p<0.05, **p<0.01, ***p<0.001 compared with the diabetic control group.

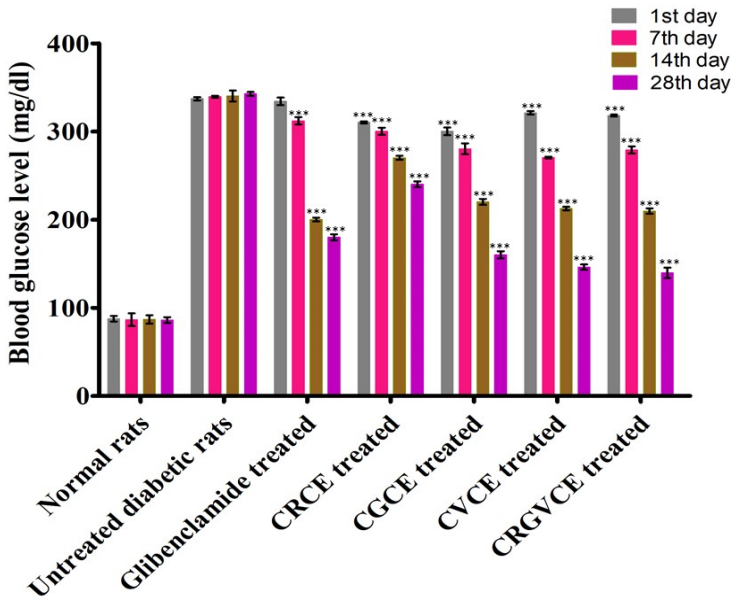

Figure 1: Effect of CRCE, CGCE, CVCE, CRGVCE (70 mg/kg), and glibenclamide (5 mg/kg) on fasting blood glucose levels in Streptozotocin (STZ)-induced diabetic rats. Blood glucose was measured on days 1, 7, 14, and 28 of treatment. Data are expressed as Mean ± SD (n=6). Statistical analysis was performed using one-way ANOVA followed by Bonferroni's multiple comparison test. **p<0.05, **p<0.01, ***p<0.001 compared with the diabetic control group.*

Restoration of liver enzyme activities suggests improved hepatic integrity and metabolic function, which may contribute to better regulation of glucose and lipid homeostasis. Similar hepatoprotective effects have been reported for *Cleome gynandra* and other medicinal plants in experimental diabetic models, supporting the therapeutic potential of phytochemical-rich plant extracts in mitigating diabetes-associated liver injury (Sravanthi *et al.*, 2016; Ravichandra *et al.*, 2014; Parasuraman *et al.*, 2019).

Oxidative stress is a major factor in the pathogenesis and progression of diabetes, arising from excessive production of reactive oxygen species and depletion of endogenous antioxidant defences. Consistent with this mechanism, STZ administration markedly reduced hepatic SOD, CAT, and GPx activities, whereas treatment with the *Cleome* extracts significantly restored these antioxidant enzymes. The combined extract produced the greatest enhancement of antioxidant status, particularly catalase activity, indicating improved protection against oxidative damage. These findings suggest that the extracts may alleviate oxidative stress by strengthening endogenous antioxidant defence systems, thereby reducing cellular injury associated with chronic hyperglycaemia. Comparable antioxidant effects have been reported for *Moringa oleifera* leaf extracts, which similarly restored antioxidant enzyme activities in STZ-induced diabetic rats (Bamagous *et al.*, 2018; Sulastri *et al.*, 2018).

Histopathological examination further supported the biochemical findings. Diabetic control rats exhibited characteristic pancreatic

damage, including shrunken islets and degenerative changes consistent with STZ-induced β-cell injury. In contrast, treatment with the *Cleome* extracts preserved pancreatic architecture, with the CRGVCE-treated group demonstrating the greatest restoration of islet morphology, closely resembling that observed in the glibenclamide-treated animals. Although the present study did not directly quantify β-cell regeneration or insulin secretion, the improvement in pancreatic morphology, together with the reduction in blood glucose and oxidative stress, suggests that the extracts may protect residual β-cells from oxidative injury and preserve pancreatic function. Similar histopathological improvements have been reported following treatment with several medicinal plant extracts possessing β-cell protective properties (Ghazanfar *et al.*, 2014; Yadav *et al.*, 2014). The superior efficacy of the combined extract compared with the individual extracts suggests that multiple phytoconstituents may exert complementary pharmacological actions on different pathways involved in diabetes. While the exact mechanisms remain to be elucidated, the observed improvements may be associated with enhanced peripheral glucose utilization,

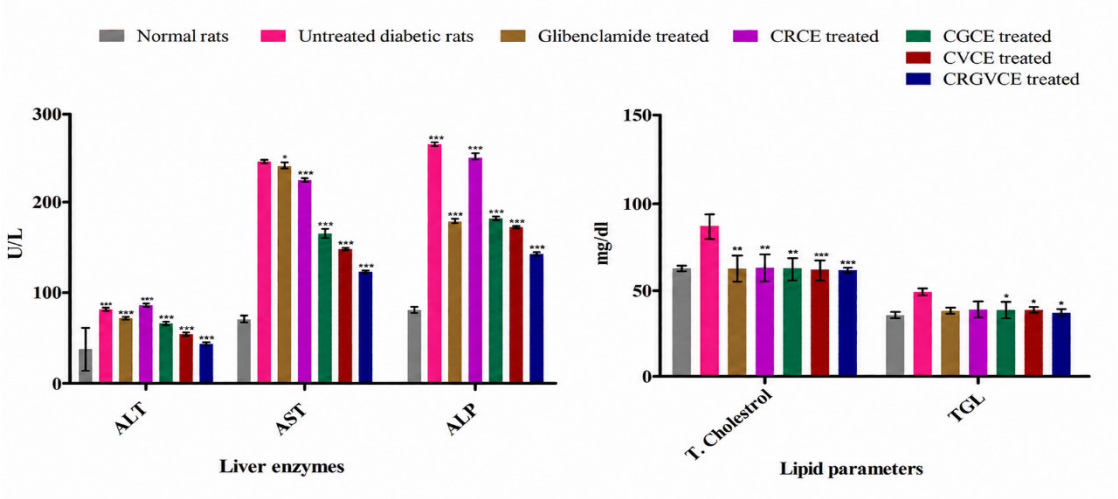

Figure 2: Effect of CRCE, CGCE, CVCE, CRGVCE (70 mg/kg), and glibenclamide (5 mg/kg) on serum lipid profile (total cholesterol and triglycerides) and liver enzyme activities (ALT, AST, and ALP) in Streptozotocin (STZ)-induced diabetic rats. Data are expressed as Mean ± SD (*n*=6). Statistical analysis was performed using one-way ANOVA followed by Bonferroni's multiple comparison test. **p<0.05, **p<0.01, ***p<0.001 compared with the diabetic control group.*

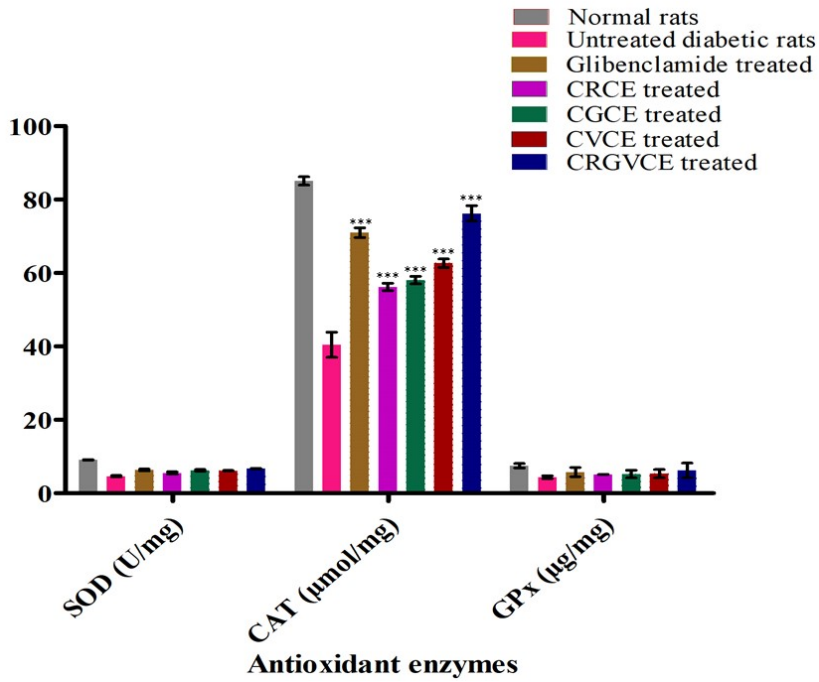

Figure 3: Effect of CRCE, CGCE, CVCE, CRGVCE (70 mg/kg), and glibenclamide (5 mg/kg) on hepatic antioxidant enzyme activities in Streptozotocin (STZ)-induced diabetic rats. Superoxide Dismutase (SOD), Catalase (CAT), and Glutathione Peroxidase (GPx) activities were determined in liver homogenates. Data are expressed as Mean ± SD (*n*=6). Statistical analysis was performed using one-way ANOVA followed by Bonferroni's multiple comparison test. **p<0.05, **p<0.01, ***p<0.001 compared with the diabetic control group.*

Table 2: Percentage improvement in blood glucose, body weight, lipid profile, liver enzyme activities and antioxidant parameters after 28 days of treatment.

	Blood glucose level	Body weight	Lipid parameters		Liver enzymes			Antioxidant activity		
			T. Cholesterol	TGL	ALT	AST	ALP	SOD	CAT	GPx
Diabetic rats + Glibenclamide	46.1	7.37	27.62	18.92	14.45	1.18	32.86	22.15	43.63	14.93
Diabetic rats + CRCE	22.52	-3.48	26.86	22.14	-3.79	7.47	7.13	22.45	30.91	25.78
Diabetic rats+ CGCE	46.6	-1.20	29.55	20.97	19.54	31.99	31.08	35.75	30.70	19.39
Diabetic rats+ CVCE	54.45	0.68	26.99	21.58	34.991	38.93	31.77	27	34.12	22.61
Diabetic rats+ CRGVCE	56.07	0.94	28.21	28.30	44.28	49.86	47.29	36.16	44.20	31.45

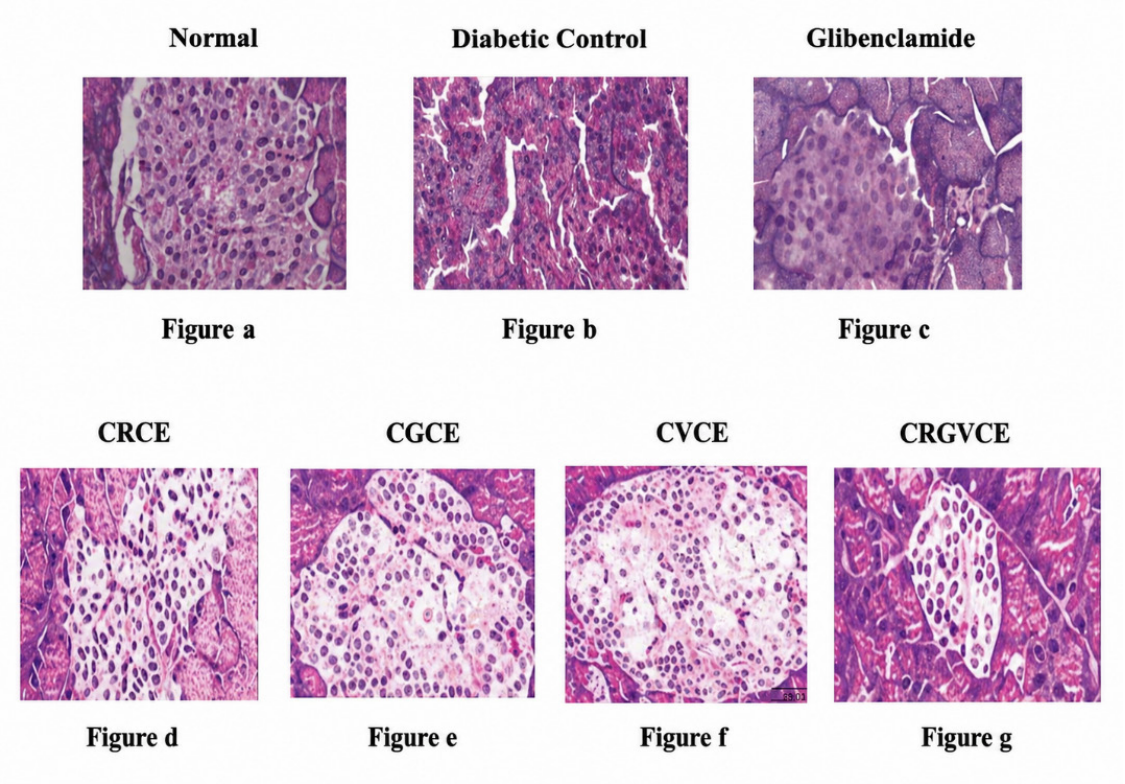

Figure 4: Representative photomicrographs of Hematoxylin and Eosin (H&E)-stained pancreatic sections from Streptozotocin (STZ)-induced diabetic rats. (A) Normal control; (B) diabetic control; (C) glibenclamide-treated; (D) CRCE-treated; (E) CGCE-treated; (F) CVCE-treated; and (G) CRGVCE-treated groups. The Combined Extract (CRGVCE) showed marked restoration of pancreatic islet architecture compared with the untreated diabetic group.

preservation of pancreatic β-cell function, improved insulin sensitivity, suppression of hepatic gluconeogenesis, or inhibition of endogenous glucose production, mechanisms that have been proposed for other plant-derived antidiabetic agents (Kumar *et al.*, 2011). A major strength of the present study is the comprehensive evaluation of antidiabetic efficacy using biochemical, antioxidant, and histopathological parameters, allowing assessment of both metabolic control and tissue protection. Furthermore, the comparison of three individual *Cleome* species with their combined extract provides valuable insight into their relative therapeutic potential. However, several limitations should be acknowledged. The study did not quantify circulating insulin levels, identify the active phytoconstituents responsible for the observed effects, or investigate the molecular mechanisms underlying the pharmacological activity. In addition, formal synergy analysis was not performed; therefore, the enhanced activity of the combined extract should be interpreted as an improved therapeutic response rather than confirmed pharmacological synergy.

The findings demonstrate that the combined chloroform seed extract of *C. rutidosperma, C. gynandra*, and *C. viscosa* effectively improved hyperglycaemia, dyslipidaemia, oxidative stress, hepatic dysfunction, and pancreatic damage in STZ-induced diabetic rats. These results support the potential of *Cleome*

species as promising sources of plant-derived antidiabetic agents. Nevertheless, further studies involving phytochemical isolation, mechanistic investigations, pharmacokinetic evaluation, and long-term safety assessment are required before clinical application can be considered. Although this study was conducted in an experimental animal model, the observed improvements in glycaemic control, lipid metabolism, antioxidant status, and pancreatic histology suggest that the combined *Cleome* extract may have potential as an adjunctive plant-based therapy for diabetes mellitus. However, its clinical applicability requires further validation through pharmacokinetic studies, toxicity evaluation, and well-designed clinical trials.

CONCLUSION

The combined chloroform seed extract of *C. rutidosperma, C. gynandra*, and *C. viscosa* significantly improved hyperglycaemia, dyslipidaemia, oxidative stress, liver function, and pancreatic histology in STZ-induced diabetic rats. These findings support the therapeutic potential of this polyherbal formulation as a promising source of novel plant - derived antidiabetic agents. Further mechanistic and phytochemical studies are required before clinical translation.

ABBREVIATIONS

STZ: Streptozotocin; **CRCE:** *Cleome rutidosperma* Chloroform Extract; **CGCE:** *Cleome gynandra* Chloroform Extract; **CVCE:** *Cleome viscosa* Chloroform Extract; **CRGVCE:** *Cleome rutidosperma gynandra viscosa* Chloroform extract; **TC:** Total Cholesterol; **TGL:** Triglycerides; **ALT:** Alanine Transaminase; **AST:** Aspartate Transaminase; **ALP:** Alkaline Phosphatase; **SOD:** Superoxide Dismutase; **CAT:** Catalase; **GPx:** Glutathione Peroxidase; **i.p:** Intraperitoneal.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AI DECLARATION

The authors used ChatGPT (OpenAI) solely for language editing and improvement of manuscript readability. All scientific content, data interpretation, and conclusions were independently reviewed and verified by the authors, who take full responsibility for the manuscript.

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