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Research Article

MODULATORY EFFECT OF *RHINACANTHUS NASUTUS* ON CARDIAC OXIDATIVE ENZYMES ACTIVITY IN STZ INDUCED DIABETIC RAT

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ABSTRACT

This study aimed to investigate the effects of *Rhinacanthus nasutus* administration on altered blood glucose levels, Oxidative Enzymes enzymes activity in streptozotocin-induced diabetes rats. The study divided Wistar strain rats into five groups: normal control, *Rhinacanthus nasutus* treated, diabetic control, diabetic plus *Rhinacanthus nasutus* treated, and diabetic plus glibenclamide treated groups. The diabetic group had significantly elevated blood glucose levels, which were significantly lowered by *Rhinacanthus nasutus* administration. The cytosolic enzyme G6PDH activity was significantly ($P<0.001$) decreased along with a significant increase in the LDH activity in diabetic rats heart tissue. The activities of SDH, MDH, GDH in the heart tissue of diabetic rats were significantly decreased, but the daily oral treatment of *Rhinacanthus nasutus* to diabetic rats for thirty days reversed the above changes in a significant ($P<0.001$) manner. The study demonstrated that an extract of *Rhinacanthus nasutus* could lower blood glucose levels, improve enzyme activities and body weight in diabetic rats. This suggests that *Rhinacanthus nasutus* extracts could be used as a cardio-protective supplement to reverse diabetic-induced complications.

Keywords: Diabetes, *Rhinacanthus nasutus*, Blood glucose, LDH, SDH, MDH, GDH.

INTRODUCTION

It is well known that long-term high levels of blood sugar, also known as chronic hyperglycaemia, can result in serious damage, reduced functioning, and potential organ failure. This is especially concerning for essential organs like the kidneys, nerves, heart, eyes, and blood vessels (Olokoba *et al*., 2012, Yun *et al*., 2021 A recent report about the prevalence of DM across the globe estimates that ~463 million people are currently affected by Diabetes Mellites. This report also proposes the figure may rise up to 578 million by 2030 and 700 million by 2045, respectively (Saeedi *et al*., 2019). Diabetes Mellites usually develops due to deficiency or lack of insulin secretion or may be also due to the diminished ability of the cells to utilize the insulin (Acharjee *et al* 2013). Maintaining proper blood glucose levels is essential for metabolic balance. Glucose metabolism relies on various enzymes such as hexokinase, G-6-P, FBP-1,6, and G-6PDH. Diabetes disrupts the function of these enzymes, causing unpredictable fluctuations in glucose levels.

Mitochondria play a crucial role in diabetes research by regulating energy balance. Enzymes associated with NAD/NADP are important for maintaining a balanced redox state within mitochondria, providing the necessary power to produce ATP through oxidative phosphorylation (Lowell and Shulman *et al*., 2005). However, excessive production of free radicals by mitochondria can damage β-cells, which are particularly vulnerable to these harmful molecules. Studies have shown a decrease in oxygen consumption and respiratory ratio in diabetic rats, along with reduced pyruvate dehydrogenase activity and increased NAD+/NADH ratio. It is believed that

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streptozotocin induces diabetes by inhibiting citric acid cycle enzymes (Albertoni Borghese *et al*., 2013).

Medicinal plants play an important role in both preventive and curative medicinal preparations for human beings. Herbal medicines are the only affordable source of healthcare, especially for the poorest patients. Plant-derived phytochemicals have beneficial effect against diabetes, microorganism, inflammation, cardiovascular diseases, blood disorders, cerebral disorders, immune system, oxidative stress, reproductive disorder, and cancer chemotherapy (Roychoudhury *et al*., 2021). Currently, scientists are evaluating the use of different herbal extracts for treating various diseases including DM Sharma, *et al*., (2020). The plants contain different types of free radical scavenging compounds such as flavonoids, polyphenols, triterpenes, vitamins which are well-off in antioxidant activity. The preliminary studies on in vitro antioxidant studies of *Rhinacanthus nasutus* (Linn) (R. nasutus) have been studied and showed significant activity (Maruthappan *et al*., 2010). There are no systemic studies of *Rhinacanthus nasutus* on cardiac tissue oxidative enzymes activity. *Rhinacanthus nasutus* have diverse pharmacological effects, including diabetes, hypertension, eczema, pulmonary tuberculosis, herpes, hepatitis, and various skin diseases, and the active components of this plant have been widely investigated (Gotoh *et al*., 2010). R. nasutus has been found to possess antimicrobial properties that can control a variety of infecting organisms, anti-diabetic and hypolipidemic activities (Rao *et al*., 2011).

MATERIAL AND METHODS

Animal care and maintenance

Male albino Wistar rats weighing between 180 to 200 grams were utilized in this research. They were kept in clean polypropylene cages, with six rats in each cage, in a sterile environment. The room temperature was maintained at 27±2° C, and the rats were subjected to a 12-hour light and 12-hour dark cycle. The rats were cared for following the guidelines of the National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, India, and the Institutional Animal Ethical Committee at S.V. University, Tirupati, Andhra Pradesh approved the protocols. Throughout the study, the rats were provided with a standard rat pellet diet from Lipton India Ltd., Mumbai, India, and had unlimited access to water.

Chemicals

The materials utilized in this study were of exceptional quality (analytical grade) and were sourced from well-known suppliers such as Fischer (Pittsburgh, PA, USA), Sigma (St. Louis, MO, USA), Ranbaxy (New Delhi, India), Merck (Mumbai, India), and Qualigens (Mumbai, India).

Induction of diabetes

Induction of diabetes was conducted in healthy male Wistar albino rats aged approximately 3 months and weighing between 200-250 g. This was achieved by administering a single intraperitoneal injection of freshly prepared streptozotocin (STZ) at a dose of 40 mg/kg body weight. The STZ was dissolved in ice-cold 0.1 M citrate buffer with a pH of 4.5**.** Prior to the injection, the rats underwent an overnight fast lasting 12-15 hours, following the protocol set by Rakieten *et al*. Eight hours post-STZ administration, the rats were provided with a 15% glucose solution for the next 24 hours to prevent hypoglycemia. This precaution was necessary as STZ has the potential to induce fatal hypoglycemia by damaging the beta cells within the pancreas, leading to excessive insulin release. To evaluate the onset of diabetes, fasting blood glucose levels were measured 48 hours post-STZ injection. The blood glucose levels in the STZ-administered rats were noticeably elevated compared to normal levels. Following a week, once the diabetic state was stabilized, rats exhibiting severe hyperglycemia (blood glucose level ≥ 250 mg/dl) were chosen for further examination. Blood samples were obtained from the tail vein for subsequent testing and analysis.

Preparation *Rhinacanthus nasutus* extract

The study commenced with the procurement of fresh *Rhinacanthus nasutus* rhizomes from the local market. These rhizomes underwent air drying, following which two kilograms of the dried material was finely powdered and subjected to cold percolation with 95% ethanol for a duration of 24 hours. The resulting extract was collected, and additional 95% ethanol was added to the *Rhinacanthus nasutus* powder. This extraction process was repeated thrice. The combined extracts were filtered, and the filtrate was condensed to dryness using a rotary evaporator under reduced pressure. The resultant ethanolic extract, appearing as a dark-brown, gelatinous substance, was air-dried and weighed. This extract, without any further refinement, was utilized for the experiments. A dosage corresponding to 200 mg of extract per kg body weight was determined and suspended in a 2% tween-80 (v/v) solution for the experiments, following the protocol delineated by Bhandari *et al*. (2005).

The rats were divided into 5 groups, six rats in each group and treated as follows:

I). Normal Control (NC): This group of rats received vehicle solution (2% of tween 80).

II): Diabetic control (DC): Streptozotocin is given intraperitonially for the induction of diabetes to this group (STZ 50 mg/kg body weight).

III). Diabetic on *Rhinacanthus nasutus* treatment, (DC+Rn.E): Diabetic rats received *Rhinacanthus nasutu s*ethanolic extract as described in group II for a period of 30 days

IV) *Rhinacanthus nasutus* treatment (Rn E): This group of rats received *Rhinacanthus nasutus* ethanolic extract via orogastric tube for a period of thirty days at the dose of 200 mg/kg body weight.

V): Diabetic on Glibenclamide treatment (DC + Gli): Diabetic rats treated with glibenclamide 600 µg/kg body weight in aqueous solution orally for a period of 30 days.

After receiving a 30-day treatment, the animals were humanely euthanized by cervical dislocation. The heart tissue was then harvested at a temperature of 4°C, washed with ice-cold saline solution, and promptly immersed in liquid nitrogen before being stored in a deep freezer at -80°C for future biochemical analysis. Various enzyme activities in both the cytosol and mitochondria were assessed through specific assays. The activity of glucose-6-phosphate dehydrogenase (G6PD) was measured using the method developed by Lohr and Waller in 1974. The activity of lactate dehydrogenase (LDH) was monitored with a method adapted from Prameelamma and Swami in 1975, initially described by Nachlas *et al*. Mitochondrial enzyme activities, including succinate dehydrogenase (SDH) and malate dehydrogenase (MDH), were assayed using a modified version of the technique by Nachlas *et al*. in **1960.** Furthermore, the activity of glutamate dehydrogenase (GDH) was determined following the procedure established by Lee and Lardy in 1965**.** All enzymatic assays were conducted using the heart's crude homogenate. Blood samples were taken from the rats before euthanasia for the estimation of blood glucose levels. The rats' body weights were recorded before and after the treatment, as well as immediately post-sacrifice.

Statistical Analysis

The data was analyzed using SPSS (Version 13.5; SPSS Inc., Chicago, IL, USA) and Microsoft Office Excel software to determine the significance of the main effects and their interactions. A one-way analysis of variance (ANOVA) was conducted, followed by Dunnett's multiple comparison test to identify significant differences, with significance set at $P < 0.001$.

RESULTS AND DISCUSSION

In diabetic rats injected with streptozotocin (STZ), blood glucose levels were found to be nearly three times higher than in normal control rats, even after 30 days. However, treatment with *Rhinacanthus nasutus* for the same period significantly reduced the elevated blood glucose levels in diabetic rats ($p<0.001$). Comparatively, the effects of *Rhinacanthus nasutus* extract were similar to those of the standard antidiabetic drug glibenclamide, which also led to a significant decrease in blood glucose levels ($p<0.001$), akin to levels seen in normal control rats (refer to Table 1). Additionally, diabetic rats showed a notable decrease in body weight compared to normal control rats after 30 days ($p<0.001$). Yet, administration of *Rhinacanthus nasutus* to the diabetic rats resulted in a significant increase in their body weights (refer to Table 1 and 2). In diabetic rats, the cytosolic enzyme G6PDH showed a significant decrease ($p<0.001$), while LDH activity was significantly increased. Treatment with glibenclamide, a common medication for diabetes, had similar effects to the daily oral administration of *Rhinacanthus nasutus* to diabetic rats over 30 days. This effectively reversed the changes in G6PDH and LDH activities in a statistically significant manner ($p<0.001$). In contrast, the activity of both enzymes remained unchanged in control rats treated solely with *Rhinacanthus nasutus*. In diabetic control rats, the activities of mitochondrial enzymes (SDH, MDH, GDH) were notably reduced ($p<0.001$) compared to normal control rats. However, no significant changes were seen in these enzyme activities in control rats treated solely with *Rhinacanthus nasutus*. Conversely, diabetic rats receiving oral *Rhinacanthus nasutus* showed a marked increase in enzyme activities compared to untreated diabetic control rats. The enzyme activities in *Rhinacanthus nasutus*-treated diabetic rats were comparable to the enhancement observed with glibenclamide administration.

Diabetes mellitus is a disorder in which the body tissues failed to utilize the glucose which leads to increased utilization of proteins responsible for reduction in body weight (Kumar *et al*., 2021. There is compelling evidence indicating a connection between diabetes and tissue damage caused by oxidative stress. Studies have shown this in the livers, skeletal muscles, and cardiac tissues of diabetic rodents induced by streptozotocin (Aragno *et al*., 2008). Diabetic rats have been observed to exhibit reduced oxygen utilization and respiratory efficiency in their mitochondria (Puckett *et al*., 1979). Additionally, research by Sener *et al*. revealed decreased activities of citric acid cycle enzymes (Sener *et al*., 1990). Recent metabolomic studies on type 1 diabetes models have also highlighted the downregulation of crucial tricarboxylic acid (TCA) cycle and mitochondrial proteins, as well as enzyme activities (Chowdary *et al*., 2010).

In a recent study, diabetic rats showed elevated blood glucose levels, likely due to the effects of streptozotocin-induced diabetes, which leads to the destruction of beta cells in the pancreas. This results in decreased insulin secretion and various complications such as heart, cardiovascular, nerve, kidney, and bladder issues due to oxidative stress. However, after 30 days of supplementing with an ethanolic extract of *Rhinacanthus nasutus*, diabetic rats experienced a significant decrease in fasting blood glucose levels compared to the control group. This indicates the potential anti-diabetic properties of *Rhinacanthus nasutus*, supported by its phenols, polyphenolic compounds, and flavonoids which are known for their hypoglycemic effects. The study also found that diabetic rats had decreased body weight, suggesting a loss of structural proteins associated with diabetes. Overall, the findings suggest that *Rhinacanthus nasutus* treatment has promising anti-hyperglycaemic effects similar to glibenclamide, a standard hypoglycemic drug, validating its traditional use in treating diabetes.

In the present study, the observed decrease in the activities of mitochondrial enzymes in the kidney of the diabetic rats were significantly enhanced upon Rn E treatment. In insulin dependent diabetes mellitus (IDDM) various agents like interleukin-1 beta, interferon gamma, tumor necrosis factor alpha, alloxan and streptozotocin - could operate by forming free radicals that could attack the

mitochondrial genome (Gerbitz., 1992). The increased production of free radicals in mitochondria may damage *β*-cells, which is known to be very sensitive to free radicals (Panneerselvam and Swaminathan Govindaswamy *et al*., 2002). Also, a decrease in oxygen consumption and respiratory ratio were observed in the mitochondria of diabetic rats (Obrosova *et al*., 1999). A similar decrease in the activities of citric acid cycle enzymes was also observed by Sener *et al.,* (Sima *et al*., 2003).

Table1. Effect of *Rhinacanthus nasutus* and glibenclamide on blood glucose level in diabetic rats.

Groups	Blood Glucose (mg/dl)	
	0^{th} day	30^{th} day
Normal control	80±1.29	91±2.4
Diabetic control	259±2.	265±13.4*
Diabetic *and Rhinacanthus nasutus*	121±1.18	89±1.85*
Rhinacanthus nasutus	82±3.88	86±5.44*
Diabetic and Glibanclamide	125±1.61	93±3.78*

All the values are mean, ± SD of six individual observations, *significant at p<0.001

Table 2. Effect of *Rhinacanthus nasutus* and glibenclamide on body weight change in diabetic rats.

Groups	Body weight(grams)	
	0^{th} day	30day
Normal control	191±8.21	215±13.25
Diabetic control	195±6.94	189±7.12
Diabetic *and Rhinacanthus nasutus*	183±2.65*	148±4.99
Rhinacanthus nasutus	181±5.31	190±4.21
Diabetic and Glibanclamide	186±2.98*	151±1.02

Table 3. Effect of *Rhinacanthus nasutus* and glibenclamide on heart SDH, MDH, GDH enzymes activities in the control and experimental groups.

Parameter	SDH (Ψ)	MDH (Ψ)	GDH (Ψ)
Normal control	3.86±0.11*	4.81±0.15**	4.37±0.11**
Diabtic control	5.19±0.15*	4.59±0.14**	4.59±0.16**
Diabtic *and Rhinacanthus nasutus*	4.88±0.06*	6.90±0.13**	6.43±0.13**
Rhinacanthus nasutus	3.98±0.07*	4.89±0.33**	4.43±0.09**
Diabetic and Glibanclamide	4.98±0.05*	6.85±0.061**	6.25±0.05**

Ψ (μ moles of formazan formed/mg protein/h).

Value represents mean ± SD for 6 rats per group.

∗P < 0.01 as compared to normal, nondiabetic rats' group

**P < 0.01 as compared to nontreated diabetic rats

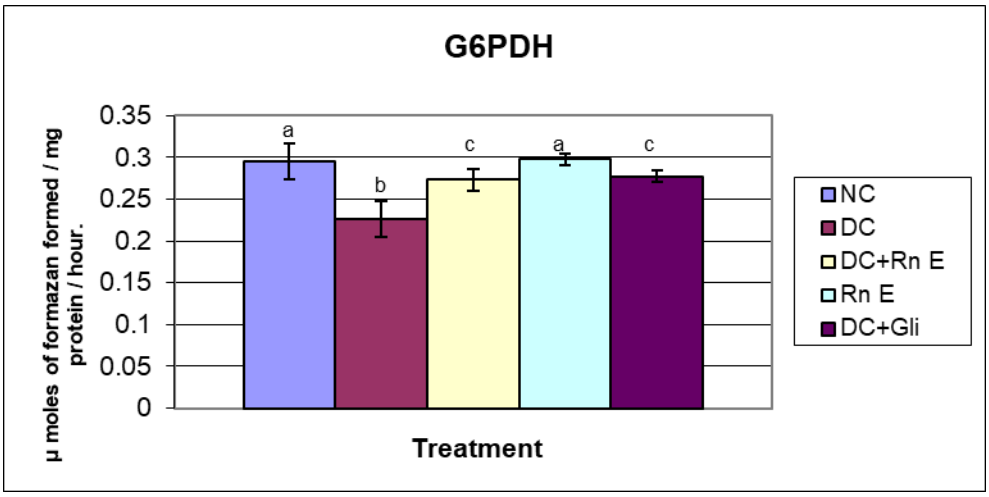

Figure 1. Effect of *Rhinacanthus nasutus* and glibenclamide on cardiac G6PD enzyme activity in the control and experimental groups.

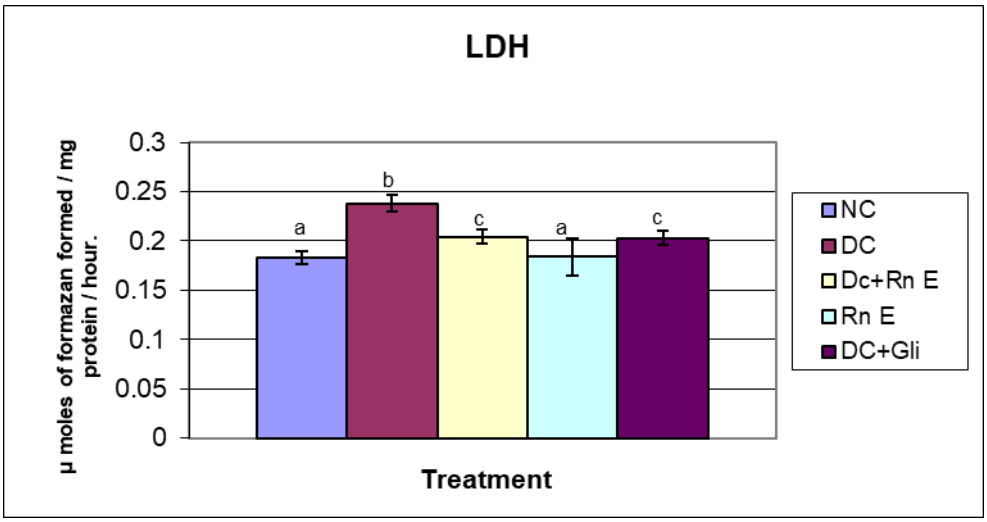

Figure 2. Effect of *Rhinacanthus nasutus* and glibenclamide on cardiac LDH enzyme activity in the control and experimental groups.

In our research, we have noted a decline in the levels of the enzyme glucose-6-phosphate dehydrogenase (G6PDH) in the cardiac tissue of diabetic rats. These findings are consistent with previous studies indicating reduced G6PDH activity in diabetic tissues (Ramudu *et al*., 2011). This decrease in G6PDH activity suggests a lower conversion rate of glucose-6-phosphate to 6-phosphogluconate, resulting in diminished NADPH production and HMP shunt function. The diminished G6PDH activity may be an adaptive mechanism to limit the availability of NADPH for aldose reductase, as highlighted in prior research (Rao *et al et al*., 2013). Interestingly, our study revealed an elevation in G6PDH activity following the administration of *Rhinacanthus nasutus* to diabetic rats. This finding suggests that *Rhinacanthus nasutus* may offer potential benefits in mitigating diabetes-related complications. *Rhinacanthus nasutus*is known to various phytochemicals such as phenols, flavonoids, terpenoids, and other active compounds that contribute to its medicinal properties. Its dried extract contains mono-terpenes and sesquiterpenes. Lactate dehydrogenase in anaerobic glycolysis, catalyses the conversion of pyruvate to lactate which subsequently is converted to glucose in gluconeogenesis flux and the reaction occurs in both cytosolic and mitochondrial compartments. LDH activity is found to be altered by insulin, glucose, NADH, as well as increases in mitochondrial membrane potential, cytosolic free ATP and cytosolic free Ca2+ (Ainscow *et al*., 2000). The decreased level of activity of LDH in tissues could be important to ensure that a high proportion of both pyruvate and NADH, supplied by glycolysis, is subsequently oxidized by mitochondria. This excessive pyruvate is converted to

lactate for which LDH is needed and therefore the activity of LDH may be increased due to less insulin availability in diabetes (Awaji *et al*., 1990). The decreased availability of insulin in diabetes may contribute to the increased LDH activity. Lactate dehydrogenase activity is found to be altered by insulin, glucose, NADH, as well as increases in mitochondrial membrane potential, cytosolic free ATP and cytosolic free Ca^{2+} (Zhao and Wang., 2012). Interestingly, supplementation with *Rhinacanthus nasutus* in diabetic rats led to a reduction in LDH activity. This inhibition of LDH activity by *Rhinacanthus nasutus* was comparable to the effects of the anti-diabetic drug glibenclamide. *Rhinacanthus nasutus* compounds may be responsible for inhibiting LDH activity and contributing to the decrease in LDH activity observed in *Rhinacanthus nasutus*-treated diabetic rats. Overall, these findings suggest that *Rhinacanthus nasutus* supplementation may have potential benefits in reducing LDH activity and potentially managing diabetes.

In a recent study, a significant reduction ($p<0.001$) was noted in the activities of the mitochondrial enzymes succinate dehydrogenase (SDH) and malate dehydrogenase (MDH) in the hearts of rats with streptozotocin (STZ)-induced diabetes. The decrease in specific activity of MDH as a consequence of diabetes suggests decreased utilization of malate. The decrease in the activity levels of dehydrogenases is in consistent with the decreased conformation (Cederbaum and Rubin., 1974). These enzymes play a crucial role in ATP production, generating 36 moles of ATPs for each mole of glucose consumed (Panneerselvam *et al*., 2002). SDH and MDH are key players in the Krebs cycle, with SDH exhibiting the highest activity among the enzymes in the cycle. The decrease in SDH activity indicates a decline in oxidative metabolism within the mitochondria, particularly in the conversion of succinate to fumarate. Conversely, MDH contributes to the citric acid cycle by producing oxaloacetate for combining with acetyl-CoA to form citrate, as well as generating malate to support the cytosolic gluconeogenic pathway. The diminished levels of MDH enzyme in diabetic rats suggest a reduced utilization of malate. Previous research has also highlighted decreased SDH and MDH enzyme levels in diabetic rats (Panneerselvam and Swaminathan Govindaswamy., 2002). However, an intriguing discovery in this study was the restoration of reduced SDH and MDH activities in diabetic rats treated *with Rhinacanthus nasutus.* The elevated SDH and MDH activities in *Rhinacanthus nasutus* treated diabetic rats imply a more efficient utilization of energy-yielding intermediates by the tricarboxylic acid (TCA) cycle (Sima., 2003). The enhancement in mitochondrial marker enzymes noted in *Rhinacanthus nasutus* treated diabetic rats mirrored the effects seen with glibenclamide treatment.

In our current investigation, a decline in GDH activity was detected in heart tissue. This decrease in GDH activity is attributed to inhibition by high levels of ammonia, which acts as a product-inhibitor leading to a reduction in the enzyme's catalytic efficiency (Reddy and Rao.1991.) Additionally, our study revealed an uptick in LDH levels, consistent with lactate playing a role in the inhibition of GDH activity. The diminished GDH activities observed in the hearts of rats with enzyme dysfunction were linked to the activation of lipid peroxidation (Telushkin *et al*., 2005), indicating notable disruptions in energy metabolism. This disruption contributes to the impairment of glutamate utilization, leading to the advancement of glutamate-induced toxicity. Conversely, the rise in GDH activity noted in our study could be attributed to decreased oxidative stress due to *Rhinacanthus nasutus* and an increase in mitochondrial enzymes. Previous research has demonstrated that *Rhinacanthus nasutus* enhances GDH activity in diabetic rats. Various studies have reported that medicinal plants can inhibit GDH activity in diabetic rats, such as the normalization of mitochondrial enzymes in diabetic rats treated with Centella asiatica (Somara Sasikala *et al*., 2015).

CONCLUSION

The study indicates that the ethanolic extract from *Rhinacanthus nasutus* rhizome shows potential efficacy comparable to the anti-diabetic drug glibenclamide in mitigating diabetic-induced disruptions in cardiac cytosolic and mitochondrial enzymes. Improved enzyme activities were observed in diabetic rats treated with *Rhinacanthus nasutus*, suggesting its potential use as a nutraceutical supplement to counteract diabetic-related adverse effects and protect heart tissue from damage. However, additional pharmacological and biochemical research is necessary to identify the active ingredient, its mechanism of action, and fully understand the plant's bioactive and ameliorative properties.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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