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Research Article

PROTECTIVE EFFECT OF *RHINACANTHUS NASUTUS* ON BRAIN OXIDATIVE STRESS AND LIPID PEROXIDATION IN STREPTOZOTOCIN INDUCED DIABETIC MALE ALBINO RAT

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ABSTRACT

This research was to examine the protective effects of *Rhinacanthus nasutus* in streptozotocin (STZ)-induced diabetic rats through oral supplementation of 200 mg/kg body weight. Diabetes was induced in adult male albino rats weighing 200 g by intraperitoneal administration of STZ (40 mg/kg body weight). Glibenclamide (50 mg/kg body weight) was used as the standard drug. The diabetic rats exhibited higher levels of blood glucose and MDA content in their brain homogenates, along with decreased body weight, Superoxide dismutase, catalase, glutathione peroxidase activities, and glutathione levels in brain tissue. However, diabetic rats treated with oral supplements of *Rhinacanthus nasutus* extracts and glibenclamide showed reduced blood glucose levels and MDA, as well as increased Superoxide dismutase and catalase activities, GSH levels in the brain, and higher body weight. These results suggest that *Rhinacanthus nasutus* extract therapy has a protective effect against the progression of diabetes by reducing oxidative stress in the brain.

Keywords: Diabetes, *Rhinacanthus nasutus*, Oxidative Stress markers, Brain tissue.

INTRODUCTION

Diabetes occurs when the body's immune system attacks and destroys insulin-producing β cells in the pancreas. This autoimmune condition leads to high blood sugar levels, which can cause complications such as retinopathy, neuropathy, nephropathy, and cardiovascular issues, eventually leading to organ failure (Babu *et al*., 2009). Diabetic peripheral neuropathy (DPN) is one of the microvascular complications of diabetes, affecting about 50% of diabetic patients. Most patients are already developing DPN at the time of their primary diagnosis (Balaha *et al*., 2018). Sustained hyperglycemia in individuals with diabetes mellitus results in increased generation of free radicals through non-enzymatic protein glycation and glucose oxidation, leading to cellular dysfunction and oxidative harm to cell membranes (Valko *et al*., 2007). Reactive oxygen species (ROS) production is intimately linked with STZ-induced diabetes mellitus, contributing to oxidative damage (Cade *et al*., 2008). Prolonged and consistent high blood sugar levels in diabetics and animal models lead to elevated oxidative stress levels, compromising the effectiveness of the immune system's antioxidant defenses and promoting impaired GSH metabolism (McLennan *et al*., 1991). Malondialdehyde (MDA), a byproduct of lipid peroxidation, is implicated in the development of diabetes by disrupting the fluidity gradient across cell membranes, potentially hindering the function of enzymes within the membrane (Mancino *et al.,* 2011). Herbal remedies are gaining popularity for their natural origins, lower risk of side effects, and cost-effectiveness compared to synthetic

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medications (Pari *et al*., 2010). However, their efficacy may not always match that of conventional treatments like insulin and metformin. Medicinal plants often contain antioxidants, tannins, and flavonoids in substantial amounts. Current research suggests that the antioxidant properties of plant-based medicines may play a crucial role in their ability to lower blood sugar levels in individuals with diabetes. *Rhinacanthus nasutus*, also known as Snake Jasmine, is a flowering plant from the Acanthaceae family with significant therapeutic properties for its various medicinal uses (Kirtikar and Basu *et al*., 2005). Traditionally, the roots of R. nasutus have been employed in folk medicine to counteract snake venom effects (James and Tewin., 2011), while different plant parts have been utilized for treating ailments like diabetes, eczema, pulmonary tuberculosis, herpes, hypertension, hepatitis, and various skin conditions. In Thailand, R. nasutus has been historically used for addressing different types of cancers such as colon (Kupradinun *et al*., 2009), cervical, and kidney cancers (Rojanapo *et al*., 1990). A recent study examined the impact of *Rhinacanthus nasutus* extract treatment on brain oxidative stress and lipid peroxidation in streptozotocin-induced diabetic rats.

MATERIEL AND METHODS

Animals

In this study, we utilized 30 Wistar strain male albino rats, aged 3 months and weighing between 180 to200 g. The rats were fed a standard pellet diet and had access to water ad libitum. They were housed in clean, dry polypropylene cages in a well-ventilated animal facility with a 12-hour light-dark cycle. All experiments were conducted between 8 am to 10 am to minimize the influence of circadian rhythm on the results. The study was approved by the University Animal Ethical Committee, and all experiments were performed in compliance with laboratory care and use regulations.

Preparation of the extract

R. nasutus fresh leaves weighing 500g were dried in the shade and ground into a fine powder using a mechanical grinder from TTK Prestige in Chennai, India. The powdered plant material was then soaked in methanol and agitated in a bath shaker from Thermo Scientific in Mumbai, India for 48 hours. The resulting extract was filtered using Whatman no. 1 filter paper and evaporated under reduced pressure at 40°C using a rotary evaporator. The concentrated extract was then freeze-dried after being placed on aluminum foil. Prior to use, the remaining extract was dissolved in 1mL of sterile water.

Induction of diabetes

In groups II, III and V, rats were administered a single intraperitoneal injection of a streptozotocin solution at a dose of 1 ml/kg body weight with a concentration of 40 mg/ml. To counter the significant release of pancreatic insulin triggered by streptozotocin, rats were given oral 20% glucose (5–10 ml) 6 hours post-injection and continued every 48 hours to prevent hypoglycemia. Throughout the duration of the study, no mortality or adverse effects were observed at the dosage administered. Rats exhibiting symptoms of diabetes (elevated blood glucose levels of 200–300 mg/dL, glycosuria, and hyperglycemia) were selected for the experiment after one week.

Experimental design

Rats of the same age group (3 months) were divided into 5 groups, six rats in each group, and were treated as follows: Group I- Normal control (NC): Six rats were received the 0.9%Nacl / kg bodyweight via Orogastric tube for a period of 30 days. Group II - Diabetic control (DC): Six rats were used as diabetic control rats by giving the fasted animals intraperitoneal injections of STZ (40 mg/kg b.w.). Group III - Diabetic Control and *R. nasutus* Extract (DC+Rn.E): For 30 days, this group of rats received the same STZ and *Rhinacanthus nasutus* treatments as those in groups 2 and 4. Group IV (Gt): For 30 days, normal rats were given an ethanolic extract of *R. nasutus* (200 mg/kg body weight). 5. Group V (DC+Glb): Diabetic animals treated with 50mg/kg b.w. glibenclamide for 30days. Glibenclamide is a sulfonylurea antidiabetic agent, a class of drugs used to treat diabetes mellitus. This disease is a chronic metabolic complaint characterized by insulin deficiency, a hormone produced by the pancreas which controls the sugar in the blood. For that, in this study we are using glibenclamide as a standard drug for the comparison of efficacy with *Rhinacanthus nasutus* treated diabetic rats.

Tissue collection and Analytical procedures

The animals were euthanized using cervical dislocation, and their brain tissues were extracted at 40°C after the 30-day treatment period had concluded. The tissues underwent rapid storage at -80°C following immersion in liquid nitrogen for further biochemical analysis, and were then cleansed with ice-cold saline. The activity of superoxide dismutase (SOD) in tissue homogenates was assessed using the Misra and Fridovich method on a Hitachi U-2000 spectrophotometer. Absorbance was recorded at 480 nm over a 4-minute period. SOD activity was quantified as the enzyme quantity required to decrease epinephrine oxidation by 50%, equivalent to 1 unit (U) per milligram of protein. The catalase (CAT) activity was assessed at room temperature following the Aebi method, which involved measuring the sample's absorbance at 240 nm for 1 minute with a spectrophotometer. The glutathione peroxidase (GPx) activity was determined by the Flohe and Gunzler method, utilizing NADPH in the presence of cumene hydrogen peroxide, with absorbance readings taken at 340 nm. The concentration of reduced glutathione (GSH) in brain region homogenates was quantified following the procedure outlined by Akerboom and Sies. The enzyme activities were quantified per milligram of protein, and the tissue protein concentration was determined using the Lowry method with bovine serum albumin (BSA) as a standard. Blood glucose levels were measured using an Accu-Chek glucometer from Roche (Germany). The

changes in body weight were monitored for all experimental groups over a 30-day period.

Chemicals

The chemicals utilized in this study were of Analar Grade (AR) quality and were sourced from various reputable scientific companies including Fisher (Pittsburgh, PA, USA), Sigma (St. Louis, MO, USA), Ranbaxy (New Delhi, India), Merck (Mumbai, India), and Qualigens (Mumbai, India).

Statistical Analysis

Analysis of variance (ANOVA) and Duncan's multiple comparison tests among data were carried out using the SPSS (Version 13.5; SPSS Inc., Chicago, IL, USA) and M.S. Office, excel software for the significance of the main effects (factors), and treatments along with their interactions. Statistical significance was set at $p < 0.001$.

RESULTS AND DISCUSSION

In the current study, diabetic rats exhibited a significant rise in blood glucose levels and a drop in body weight. Nonetheless, administering dietary R. nasutus Extract to diabetic rats led to a reduction in blood glucose levels and an increase in body weights (Table 1). Diabetic rats exhibited a notable decrease in SOD, CAT, and GPX activities, as well as GSH content, along with elevated MDA levels ($p < 0.001$). In contrast, diabetic rats treated with Rhinacanthus nasutus extract demonstrated a significant reduction in MDA levels and a restoration of SOD, CAT, GPx activities, and GSH content to levels close to normal ($p < 0.001$), indicating a rejuvenation of the antioxidant enzyme system (Figure 1-5) According to the current investigation, STZ-induced hyperglycemia in diabetic rats was accompanied by oxidative brain damage. There is a need for safer and more effective medications because the pharmacological regimens now used to manage diabetes mellitus have some limitations. In this investigation, we used STZ-induced diabetic rats to investigate the idea that *Rhinacanthus nasutus* protects against hyperglycemia-induced oxidative stress in the brain. According to current theory, the high blood glucose levels associated with diabetes cause the modification of sugar moieties on proteins and lipids, which frequently results in oxidative stress and cell death (Yribeygi *et al.,* 2020). Many secondary plant metabolites, including flavonoids, terpenoids, and a variety of others, have hypoglycemic effects in diverse experimental animal models (Grover *et al.,* 2000). Numerous researchers have claimed that chemicals found in *Rhinacanthus nasutus***,** such as plant-extract-treated diabetic rats may be due to the antioxidants present in the leaves (Jiang *et al*., 2006). These antioxidants include phenolic groups, the presence of which we confirmed through phytochemical analysis. Further studies to identify the exact composition of the extract will be useful in the future. polyphenolic compounds, tannins, flavonoids, and triterpenoids, have pharmacological effects that can lower blood sugar levels (Rao and Naidu *et al*., 2010). We found that the body weight of diabetic rats had reduced. Diabetes has been linked to both dehydration and weight loss. This demonstrates the polyphagic state, weight loss caused by increased tissue protein breakdown protein waste as a result of the lack of access to carbohydrates as an energy source, dehydration, and catabolism of fats and proteins. *Rhinacanthus nasutus* was given orally for 30 days to STZ diabetic rats, which increased body weight. This might be because the hyperglycemic condition in diabetic rats was better controlled. In a recent investigation, it was found that diabetic rats showed a significant decrease in antioxidant enzyme activities and a notable increase in MDA levels. The onset of disorders like diabetes mellitus has been linked to oxidative damage induced by reactive oxygen species (ROS) (Sánchez-Alcáza *et al*., 2023). Oxidative stress arises from the disparity between reactive oxygen species (ROS) production and removal. The development of diabetic complications is largely attributed to heightened oxidative stress, stemming from either increased ROS production or diminished ROS-scavenging capabilities. Various research studies have revealed lowered levels of both non-enzymatic antioxidants and enzymatic antioxidant activities in streptozotocin-induced diabetic rats (Ananthan *et al*., 2004).

Prakasam *et al* (2003) have reported an elevated lipid peroxidation and lowered antioxidants in streptozotocin-induced diabetes mellitus. Enzymatic antioxidants like SOD, CAT, GPx, and GSH serve as the primary defense against ROS-induced oxidative stress, as highlighted by Nonaka, Manabe, and Tobe in (1991). Our findings support these conclusions, validating the importance of antioxidant mechanisms in protecting against oxidative damage. The antioxidative defence system enzymes, e.g. SOD and CAT, showed lower activities in brain tissue during diabetes and the results agree well with the earlier published data (Veera Nagendra Kumarsat *et al*., 2023). The reduced functioning of SOD and CAT enzymes may result from heightened generation of H_2O_2 and O_2- through the auto-oxidation of excess glucose and non-enzymatic glycation of proteins (Argano *et al*., 1997). Studies by Pigeolet *et al*. (1990) have shown that hydroxyl radicals and hydrogen peroxide can partially deactivate these enzyme activities. Additionally, the diminished activity of SOD and CAT in diabetic conditions may also stem from lower protein expression levels, as recently observed in the liver (Sindhu *et al*., 2004).

In diabetic brain tissues, the levels of the important antioxidant enzyme glutathione peroxidase (GPx) were found to be decreased, leading to reduced ability to remove harmful substances like H_2O_2 and lipid hydroperoxides. This aligns with previous findings by Friesen, *et al*., 2004), suggesting that the decrease in GPx activity is a compensatory response to the presence of H_2O_2**.** When diabetic animals were treated with *Rhinacanthus nasutus*, there was a significant restoration of antioxidant enzyme activities such as superoxide dismutase (SOD), catalase (CAT), and GPx ($p < 0.001$). This beneficial effect of *Rhinacanthus nasutus* could be attributed to its diverse

array of antioxidant compounds, including phenolic ketone derivatives, volatile oils, and flavonoids. These antioxidant components of *Rhinacanthus nasutus* may play a role in regulating antioxidant enzyme levels in diabetic rats, as suggested by studies conducted by Rao *et al*., (2005).

Table 1. Blood glucose levels and body weight changes in STZ-induced rats followed by *Rhinacanthus nasutus* and glibenclamide treatment.

Groups	Blood glucose (mg/dl)		Body weight (g)	
	0th Day	30th Day	0th Day	30th Day
Group I (NC)	81 ± 1.14	95± 1.91	187 ± 9.66	211 ± 12.54
Group III (DC)	259 ± 2.49*	261 ± 1309*	185 ± 2.73*	147 ± 6.05
Group IV (DC + Rn.E)	250 ± 2.11**	124 ± 4.28	183 ± 6.32	195 ± 4.19**
Group II (Gt)	82 ± 1.29	86± 1.83	195 ± 7.07	88 ± 6.09
Group V (DC + Gli)	252* ± 1.87**	93 ± 2.69**	188 ± 3.12	203 ± 2.31**

All the values are mean ± SD of six individual observations.

Values are significant compared to normal control (*p < 0.001) and diabetic control (** < 0.01).

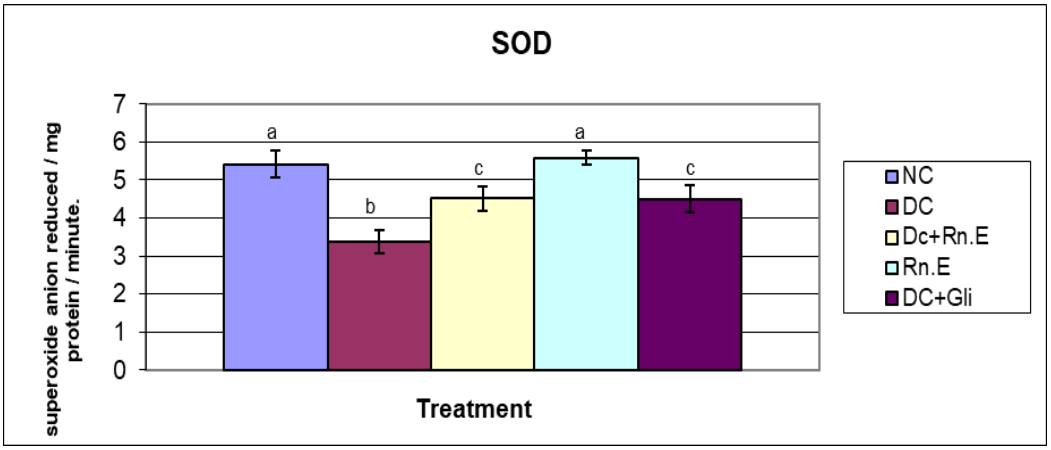

Figure 1. Changes in SOD activity in the brain of Normal Control (NC), Diabetic control (DC), Diabetic rats treated with *Rhinacanthus nasutus* extract (DC+Rn.E), *Rhinacanthus nasutus* extract (Rn.E), Diabetic rats treated with *Glibenclamide.* Each vertical bar represents the mean ± SD (n=6). Top of the vertical bars having the same letter do not differ significantly at p<0.001.

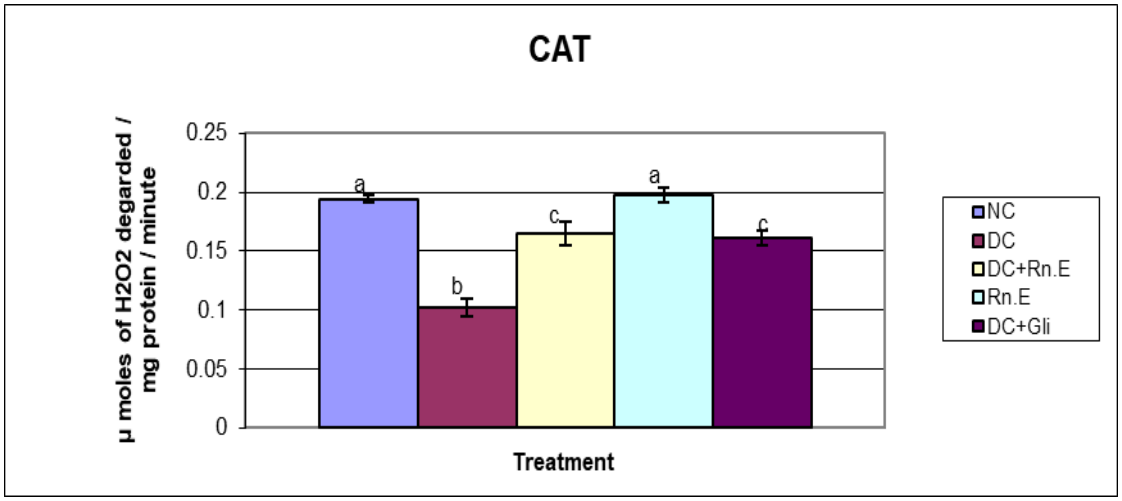

Figure 2. Changes in CAT activity in the brain of Normal Control (NC), Diabetic control (DC), Diabetic rats treated with *Rhinacanthus nasutus* extract (DC+Rn.E), *Rhinacanthus nasutus* extract (Rn.E), Diabetic rats treated with

Glibenclamide. Each vertical bar represents the mean ± SD (n=6). Top of the vertical bars having the same letter do not differ significantly at p<0.001.

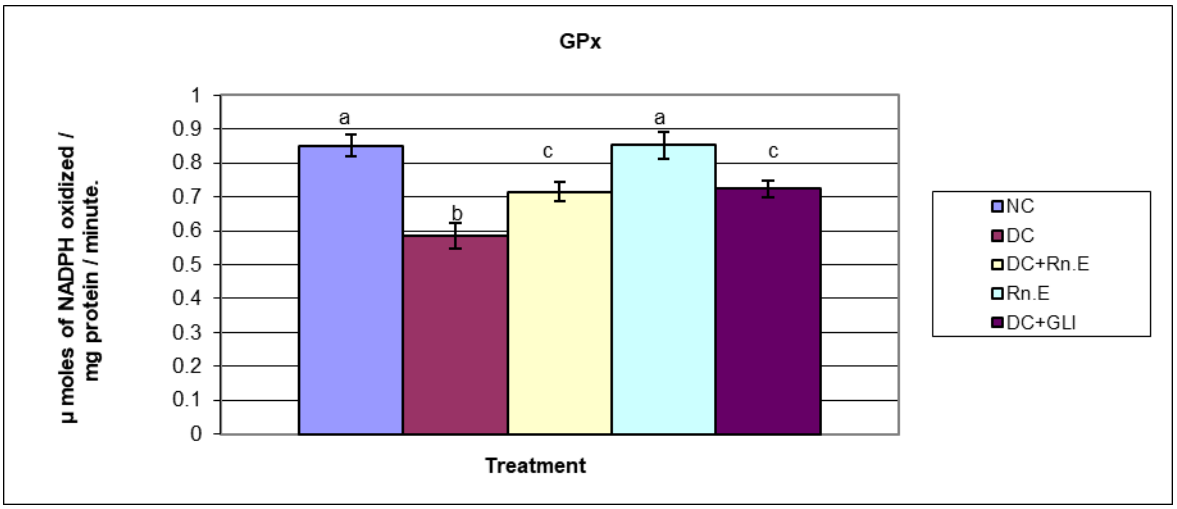

Figure 3. Changes in GPX activity in the brain of Normal Control (NC), Diabetic control (DC), Diabetic rats treated with *Rhinacanthus nasutus* extract (DC+Rn.E), *Rhinacanthus nasutus* extract (Rn.E), Diabetic rats treated with *Glibenclamide.* Each vertical bar represents the mean ± SD (n=6). Top of the vertical bars having the same letter do not differ significantly at p<0.001.

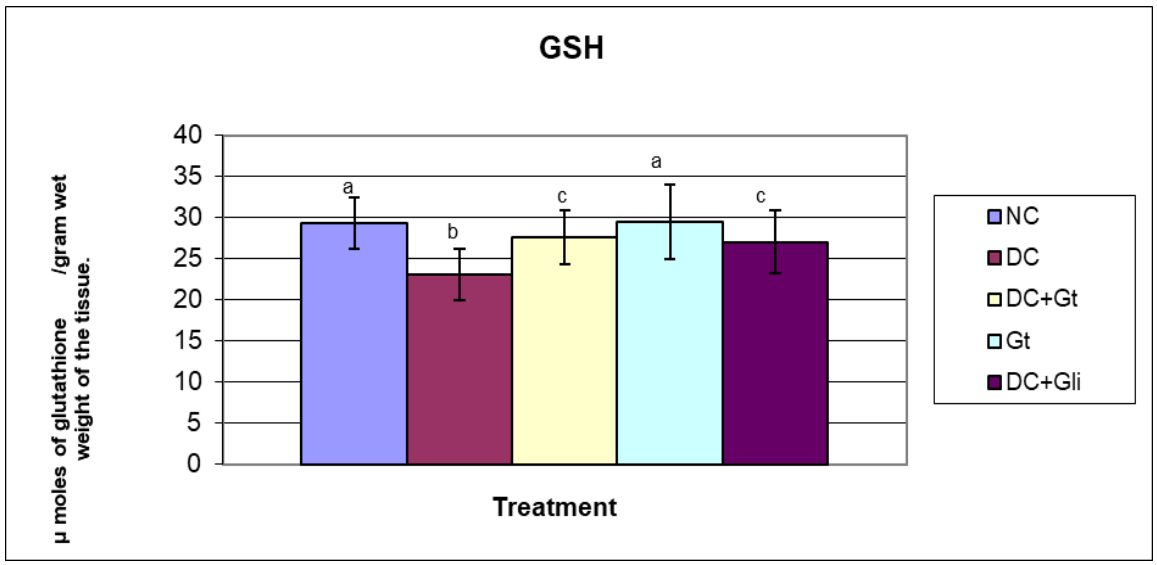

Figure 4. GSH changes in the brain Normal Control (NC), Diabetic control (DC), Diabetic rats treated with *Rhinacanthus nasutus* extract (DC+ Rn.E), Control rats treated with *Rhinacanthus nasutus* extract (Rn.E), Diabetic rats treated with Glibenclamide. Each vertical bar represents the mean ± SD (n=6). Top of the vertical bars having the same letter do not differ significantly at p<0.001.

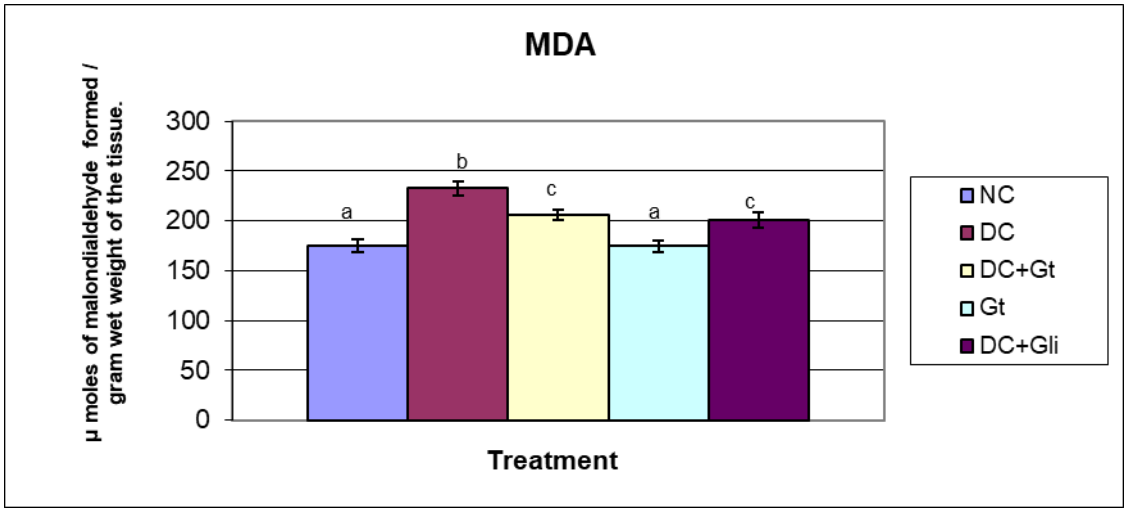

Figure 5. Status of MDA content in the brain of Normal Control (NC), Diabetic control (DC), Diabetic rats treated with *Rhinacanthus nasutus* extract (DC+Rn.E), Control rats treated with *Rhinacanthus nasutus* extract (Rn.E), Diabetic rats treated with Glibenclamide. Each vertical bar represents the mean ± SD (n=6). Top of the vertical bars having the same letter do not differ significantly at $p<0.001$.

Glutathione serves as a sensitive marker of oxidative stress and it plays an important role in maintaining the integrity of the cell system. GSH is involved in several reactions in the body and is one of the most prominent non-enzymatic antioxidants (Meister & Anderson, 1983). In the present study, GSH level was decreased in brain tissues of diabetic rats . Depletion of tissue GSH levels enhances cellular damage caused by oxidative stress. Significant depletion of GSH ($p < 0.001$) in diabetic rats suggests its increased utilisation against reactive oxygen species. (Tachi *et al*., 2001). However, *Rhinacanthus nasutus* treatment in diabetic rats reversed the GSH to normal levels, this shows that *Rhinacanthus nasutus* has an antioxidant property. The current study's findings that lipid peroxidation is more common in people with diabetes may be related to the disease's ineffective antioxidant system (Safinaz *et al.,* 2008). This could be because the brain has a disproportionately high quantity of fatty acids that are susceptible to oxidation (Waleed Javed Hashmi *et al*., 2018). Iron is a metal that, in its free state, is catalytically implicated in the generation of harmful oxygen free radical species, and it is known that particular regions of the brain are substantially enriched in iron (Nistico *et al.,* 1992). Reduced antioxidant scavenger systems in diabetes mellitus can lead to increased oxidative stress in the cell, which can lead to increased lipid peroxidation. The current research identifies *Rhinacanthus nasutus* treatment's ability to significantly reduce the lipid peroxidation of rats exposed to STZ. This hypothesis suggests that the antioxidant properties of flavonoids found in *Rhinacanthus nasutus extract*, which in turn operate as potent superoxide radical scavengers and singlet oxygen quenchers, may be responsible for the protective effects of *Rhinacanthus nasutus* extracts.

CONCLUSION

Our study suggests that Rhinacanthus nasutus demonstrates a neuroprotective effect against oxidative stress in diabetic rats, helping to partially restore balance between reactive oxygen species (ROS) generation and scavenging enzyme activity. Treatment with Rhinacanthus nasutus was shown to protect against brain damage caused by oxidative stress induced by STZ, showcasing potential hypoglycemic effects similar to insulin. Additionally, Rhinacanthus nasutus extract helped regulate antioxidant levels and improve lipid metabolism. This plant contains various pharmacological compounds with diverse known actions, making it a promising candidate for further research to fully understand how it enhances the antioxidant defense system in diabetes.

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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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