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Original Article

The Effectiveness of Enteral Administration of Binahong Leaf Extract (Anredera cordifolia (Tenore) Steenis) on Blood Glucose Levels, MDA, and NGF in Wistar Rats with Diabetic Neuropathy Model

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ABSTRACT

Background: Chronic hyperglycemia causes oxidative stress in the peripheral nervous system, which leads to the development of diabetic neuropathy. Free radicals initiate lipid peroxidation of membranes and produce malondialdehyde (MDA). Reduced Nerve Growth Factor (NGF) in diabetes indicates significant neuronal abnormalities. Binahong (Anredera cordifolia (Ten.) Steenis) belongs to the Basellaceae family and possesses therapeutic effects, making it a promising herbal remedy for the development of treatments for diabetic neuropathy. **Objective:** To determine the effectiveness of binahong leaf extract (Anredera cordifolia (Tenore) Steenis) in lowering blood sugar and MDA levels and increasing NGF in Wistar rats with diabetic neuropathy. **Methods:** This study was an experimental study using rats with a randomized control trial with a post-test control only design. The study population consisted of 36 Wistar rats divided into 6 groups randomly, which were then induced with diabetic neuropathy via streptozotocin injection at 65 mg/kg. Complete data collection was conducted, followed by blood glucose levels, MDA, and NGF measurements, and data analysis. **Results:** There were significant differences ($p<0.05$) in blood glucose levels, MDA, and NGF between the normal group, the 50 mg/kg binahong leaf extract group, the 100 mg/kg radish extract group, and the 200 mg/kg group compared to the negative control group. This indicates that binahong leaf extract, starting at a dose of 50 mg/kg, can reduce blood glucose levels and MDA while increasing NGF. **Conclusion:** Binahong leaf extract (Anredera cordifolia (Tenore) Steenis) is effective in lowering blood glucose levels and MDA levels while increasing NGF in a rat model of diabetic neuropathy.
Keywords: Anredera Cordifolia, Blood Glucose Levels, Diabetic Neuropathy, Malondialdehyde, Nerve Growth Factor, Wistar Rats

INTRODUCTION

The global epidemic of prediabetes and diabetes has led to a corresponding rise in diabetes-related complications, among which neuropathy is the most prevalent. Diabetic neuropathy, characterized by the loss of sensory function beginning in the distal lower extremities, is often accompanied by significant pain and morbidity. Over time, at least 50% of individuals with diabetes develop diabetic neuropathy. Among diabetes complications, a group of clinical syndromes caused by damage to the peripheral and autonomic nervous systems is the most common. Referred to collectively as various forms of neuropathy, these syndromes arise from diffuse and focal nervous system damage and affect half of all diabetes patients, with distal symmetric polyneuropathy being the most frequent manifestation[1].

Diabetic neuropathy is a heterogeneous condition involving both myelinated fibres (responsible for proprioception, touch/pressure perception, and motor function) and small, unmyelinated fibres (mediating temperature, pain, and autonomic functions). The primary pathology is peripheral nerve fibre loss, driven by multiple mechanisms, including: (1) chronic hyperglycaemia-induced metabolic disturbances (e.g., sorbitol pathway activation, advanced glycation end-product accumulation); (2) vascular dysfunction impairing nerve nutrient supply; (3) altered neurotrophic/growth factor availability; (4) autoimmune-mediated nerve damage; and (5) oxidative stress leading to neuronal dysfunction[2].

The exact cause of diabetic neuropathy (DN) is unclear, but both ischemic and metabolic factors are key. Chronic hyperglycaemia leads to blood flow reduction by increasing vascular resistance and depleting myoinositol, while also activating the polyol pathway. This causes sorbitol and fructose accumulation, oxidative stress, and non-enzymatic glycation of nerve proteins. Insulin resistance further increases aldose reductase activity, depleting NADPH/NAD+, reducing glutathione, and promoting AGEs and PKC pathway activation. These processes impair axonal transport, Schwann cell function, and nerve conduction. Despite promising animal results, aldose reductase inhibitors have limited human efficacy due to toxicity. Vascular changes and oxidative damage result in endoneural hypoxia, worsening neuropathy severity[3].

Oxidative stress occurs when cells or tissues fail to detoxify free radicals produced during metabolic activity. Diabetes is characterized by chronic hyperglycemia, which leads to dysregulation of cellular metabolism[4,5]. Chronic hyperglycemia increases the production of free radicals. Reactive Oxygen Species (ROS) are a group of free radicals, reactive molecules, and ions derived from oxygen.

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These free radicals initiate lipid peroxidation of cell membranes and produce malondialdehyde (MDA). One way to control excessive oxidative stress is by consuming antioxidants from food sources (exogenous antioxidants)[6].

In early diabetic neuropathy (DN), initial attempts at axonal regeneration, remyelination, and synaptogenesis - likely mediated by growth factors - ultimately fail to restore function and are accompanied by increased apoptosis. This failure is evidenced by findings that diabetic neuronal abnormalities can be replicated through depletion of growth factors, their receptors, or binding proteins. Studies report decreased levels of critical growth factors (including significantly reduced Nerve Growth Factor [NGF]) and neurotransmitters (substance P, CGRP) in both diabetic models and humans, contributing to small fibre dysfunction[2]. While current DN treatment focuses on glycaemic control, adjunct pharmacologic agents (ROS inhibitors, aldose reductase inhibitors, PKC inhibitors, SNRIs, anticonvulsants, NMDAR antagonists) face limitations including side effects, high costs, and poor compliance, driving global interest in herbal medicines[7]. Medicinal plants like Anredera cordifolia (binahong), containing bioactive flavonoids and saponins, demonstrate antimicrobial, anti-inflammatory, and wound-healing properties, showing promise for DN treatment[7,8,9], similar to how vinca alkaloids from Catharanthus roseus revolutionized cancer therapy[10]. This has spurred pharmaceutical R&D into safer, efficacious herbal alternatives[11].

Therefore, our aims is to demonstrate the effects of 28-day enteral administration of binahong leaf extract (Anredera cordifolia (Tenore) Steenis) in Wistar rat models of diabetic neuropathy.

METHODS

This experimental study employed a randomized controlled trial (RCT) design with a post-test-only control group, comparing diabetic neuropathy-induced Wistar rats treated with *Anredera cordifolia* leaf extract against controls. Animal housing and diabetic neuropathy induction were conducted at the Pharmacology Laboratory, Universitas Sumatera Utara, while ELISA assays and data analysis were performed at the Integrated Laboratory of the Faculty of Medicine, Universitas Sumatera Utara. The study duration was approximately six months.

Male *Rattus norvegicus* Wistar rats (n = 36) aged 8–11 weeks (150–200 g) were selected based on inclusion criteria (healthy, active) and exclusion criteria (aggressive behaviour). Dropout criteria included immediate post-induction mortality or death during the study. Sample size was calculated using Federer's formula for experimental designs (minimal error degree of freedom = 15):

$$(n-1)\,(t-1) \geq 15$$

where; t= treatment groups (6) and n = samples per group. Solving $5(n-1) \geq 15$ yielded $n \geq 4$; thus, each group comprised 6 rats (4 minimum + 2 reserves).

Thirty-six male Wistar rats were acclimatized for one week under standardized laboratory conditions (temperature 23°C, 12-hour light/dark cycle) with ad libitum access to standard food and water. After initial body weight measurement, the animals were randomly assigned into six groups (n = 6 per group) and housed in cages measuring 50×50×20 cm with three rats per cage. The groups were as follows: Group K– (normal control) received a standard diet without any treatment; Group K+ (diabetic control) received 10% glucose solution following streptozotocin (STZ) induction; Group P1 received glibenclamide at a dose of 0.65 mg/kg body weight (BW); and Groups P2, P3, and P4 were treated with binahong (*Anredera cordifolia*) leaf extract at doses of 50, 100, and 200 mg/kg BW, respectively.

To induce diabetic neuropathy, all groups except the normal control received a single intraperitoneal injection of STZ at 65 mg/kg BW after a 6-hour fasting period. Following induction, the rats were given 10% glucose solution for 24 hours to prevent hypoglycemia, which was then replaced with regular water. Diabetes was confirmed on the third day post-induction (Day-3) by measuring fasting blood glucose levels, with a threshold of ≥250 mg/dL considered diabetic (Morrow, 2004; Furman, 2015). On day 28 post-STZ induction (Day-28) and fasting blood glucose levels were measured. After 28 days of treatment (T1), blood samples were collected via intracardiac puncture under ketamine anaesthesia (80–100 mg/kg BW). Serum samples were analysed for malondialdehyde (MDA) and nerve growth factor (NGF) levels using ELISA and blood glucose levels were also reassessed.

Fresh *Anredera cordifolia* (Tenore) Steenis leaves (2 kg) were washed, shade-dried for 5 days, and ground into powder. Methanolic extraction was performed via maceration for 72 hours, followed by rotary evaporation[12,13]. Based on prior dose-response studies[13], three oral doses (50, 100, 200 mg/kg BW/day) were administered for 28 days, with 50 mg/kg demonstrating optimal antihyperglycemic effects without dose-dependent escalation.

Thermal nociception was evaluated using a 49°C hot-plate test (Morrow, 2004). Latency periods (9-10 sec baseline) for paw withdrawal, licking, or jumping were recorded (<15 sec cutoff to prevent tissue damage). Diabetic neuropathy progression was confirmed by thermal hyperalgesia at 4 weeks post-STZ induction[14].

Blood glucose levels were measured via tail-vein sampling using a glucometer at three critical timepoints: Day-3 (72 hours post-STZ induction, with diabetes confirmed at >250 mg/dL), Day-28 (neuropathy onset), and T1 (post-treatment after 16-hour fasting) (Morrow, 2004). Oxidative stress was assessed by quantifying serum malondialdehyde (MDA) levels through TBARS-ELISA, involving incubation of 40µL samples with 10µL anti-MDA antibody followed by streptavidin-HRP binding and colorimetric detection at 450 nm. Nerve growth factor (NGF) was measured using sandwich ELISA with biotinylated antibody binding and HRP-substrate reaction (450 nm detection). Statistical analysis included normality testing with Shapiro-Wilk (α=0.05), with data presented as mean ±SD for normally distributed parameters or median [min-max] for non-normal distributions. Group comparisons employed ANOVA for normal data or Kruskal-Wallis tests for non-parametric data, with appropriate post-hoc analyses. All experimental procedures complied with ARRIVE guidelines and received approval from the Institutional Ethics Committee.

RESULTS

The study evaluated the antidiabetic potential of binahong leaf extract in STZ-induced diabetic rats fed a high-sugar diet. Blood glucose levels were measured across six groups: normal control (101.6 ± 12.36 mg/dL), negative control (STZ-induced, untreated; 278 ± 21.93 mg/dL), positive control (STZ-induced with standard treatment; 116 ± 6.93 mg/dL), and three treatment groups receiving binahong extract at 50 mg/kg (213.8 ± 16.18 mg/dL), 100 mg/kg (194.2 ± 20.07 mg/dL), and 200 mg/kg (146.8 ± 9.09 mg/dL). One-way ANOVA revealed highly significant differences among all groups (p<0.001). Post-hoc Tukey's test was subsequently performed to determine specific intergroup differences in blood glucose levels (Table 1).

Table 1. Blood Glucose Levels

Group	Glucose level (mg/dL)	P-value
Normal	101.6 ± 12.36	P<0.001
Negative	278 ± 21.93	
Positive	116 ± 6.93	
50 mg/kg	213.8 ± 16.18	
100 mg/kg	194.2 ± 20.07	
200 mg/kg	146.8 ± 9.09	

Post-hoc analysis (Tukey's test) revealed significant differences ($p<0.05$) in blood glucose levels between the negative control group and all other groups (normal control, positive control, and binahong extract groups at 50, 100, and 200 mg/kg), demonstrating the antidiabetic effect of binahong leaf extract starting from the lowest tested dose of 50 mg/kg. However, no significant difference was observed between the 50 mg/kg and 100 mg/kg treatment groups ($p=0.367$), suggesting comparable efficacy at these doses. Notably, the standard treatment group (0.65 mg/kg of reference drug) exhibited superior antidiabetic effects compared to all binahong extract treatment groups, as shown in Table 2.

The normal control group showed MDA levels of 2.6 ± 0.21 nmol/mg, while the negative control (STZ-induced, untreated) exhibited significantly elevated levels (6.16 ± 0.92 nmol/mg). Treatment groups demonstrated dose-dependent reductions: 4.48 ± 0.41 nmol/mg (50 mg/kg), 3.74 ± 0.4 nmol/mg (100 mg/kg), and 2.78 ± 0.26 nmol/mg (200 mg/kg). The positive control (standard treatment) showed 2.98 ± 0.13 nmol/mg. One-way ANOVA revealed significant differences among groups ($p<0.001$), with post-hoc Tukey test confirming the extract's antioxidant effects (Table 3).

The normal control maintained 604.6 ± 48.22 pg/mL NGF, which decreased to 255.8 ± 15.58 pg/mL in the negative control. Binahong extract treatment showed dose-responsive increases: 305.4 ± 13.65 pg/mL (50 mg/kg), 385.4 ± 29.16 pg/mL (100 mg/kg), and 495.8 ± 72.99 pg/mL (200 mg/kg), approaching the positive control value (459 ± 31.7 pg/mL). Statistical analysis confirmed significant intergroup differences ($p<0.001$), with Tukey's test demonstrating the extract's neuroprotective potential (Table 3).

Post-hoc analysis on MDA Levels demonstrated significant differences ($p<0.05$) in oxidative stress markers between the negative control and all treatment groups (normal control, positive control, and binahong extract at 50-200 mg/kg), confirming the antioxidant capacity of binahong extract from the lowest tested dose. The 100 mg/kg ($p=0.141$) and 200 mg/kg ($p=0.983$) doses showed statistically equivalent antioxidant effects to 0.65 mg/kg glibenclamide (positive control), with the 200 mg/kg dose exhibiting the most potent clinical effects through complete normalization of oxidative markers and superior dose-response outcomes. These findings position the 200 mg/kg binahong extract as a potentially effective natural alternative to conventional antioxidant therapy in diabetes management, demonstrating comparable efficacy to standard pharmaceutical treatment (Table 4).

The analysis of NGF levels (Table 5) revealed significant differences ($p<0.05$) between the negative control and the normal control, positive control (0.65 mg/kg glibenclamide), and binahong extract groups at 100-200 mg/kg, demonstrating the extract's neuroprotective effects at doses ≥100 mg/kg. Notably, both the 100 mg/kg ($p=0.081$) and 200 mg/kg ($p=0.709$) doses showed comparable NGF-enhancing effects to standard glibenclamide treatment, indicating equivalent efficacy. Clinical evaluation identified the 200 mg/kg dose as particularly

Table 2. Post-hoc Tukey's test of Blood Glucose Levels

Group	Normal	Negative	Positive	50 mg/kg	100 mg/kg	200 mg/kg
Normal		P<0.001*	0.682	P<0.001*	P<0.001*	0.001*
Negative			P<0.001*	P<0.001*	P<0.001*	P<0.001*
Positive				P<0.001*	P<0.001*	0.044*
50 mg/kg					0.367	P<0.001*
100 mg/kg						0.001*
200 mg/kg						

Table 3. MDA and NGF Levels

Group	MDA Levels (nmol/mg)	NGF Levels (pg/mL)	P-value
Normal	2.6 ± 0.21	604.6 ± 48.22	
Negative	6.16 ±.92	255.8 ±.15.58	
Positive	2.98 ± 0.13	459 ± 31.7	P<0.001
50 mg/kg	4.48 ± 0.41	305.4 ± 13.65	
100 mg/kg	3.74 ± 0.4	385.4 ± 29.16	
200 mg/kg	2.78 ± 0.26	495.8 ± 72.99	

Table 4. Post hoc MDA Level test

Group	Normal	Negative	Positive	50 mg/kg	100 mg/kg	200 mg/kg
Normal		P<0.001*	0.882	P<0.001*	0.014*	0.998
Negative			P<0.001*	P<0.001*	P<0.001*	P<0.001*
Positive				P<0.001*	0.141	0.983
50 mg/kg					0.160	P<0.001*
100 mg/kg						0.035
200 mg/kg						

Table 5. Post hoc NGF Level test

Group	Normal	Negative	Positive	50 mg/kg	100 mg/kg	200 mg/kg
Normal		P<0.001*	P<0.001*	P<0.001*	P<0.001*	P<0.001*
Negative			P<0.001*	0.411	P<0.001*	P<0.001*
Positive				P<0.001*	0.081	0.709
50 mg/kg					0.048*	P<0.001*
100 mg/kg						0.003*
200 mg/kg						

effective, producing the most robust NGF elevation among all treatment groups, which suggests its potential as a therapeutic alternative for diabetic neuropathy. These results parallel the extract's dose-dependent antioxidant effects observed in MDA reduction, further supporting its dual mechanism of action in diabetes management.

DISCUSSION

Anredera cordifolia, commonly known as binahong, has demonstrated promising antidiabetic activity in various preclinical studies, particularly through its ability to reduce blood glucose levels in diabetic animal models. Both ethanol extracts and leaf infusions of binahong have been shown to significantly decrease hyperglycemia in alloxan-induced diabetic rats. Notably, ethanol extract at a dose of 35 mg/kg body weight (BW) reduced blood glucose levels by 40.6%, while the infusion at a dose of 140 mg/kg BW led to a 30.5% reduction, suggesting a dose-dependent response and differing efficacy based on the preparation method[15]. These hypoglycemic effects are believed to be primarily attributed to the plant's phytochemical constituents, namely flavonoids and saponins. Flavonoids exhibit antioxidant activity by neutralizing free radicals associated with diabetes pathogenesis and stimulating regeneration of pancreatic β-cells, which are essential for insulin production. In parallel, saponins have been reported to enhance β-cell proliferation, thereby increasing insulin levels and improving glycaemic control[16-19].

In vitro analyses further support the antidiabetic mechanisms of binahong. Leaf extracts have demonstrated inhibitory effects on α-glucosidase and α-amylase enzymes, which are involved in carbohydrate digestion and glucose absorption, thus reducing postprandial hyperglycaemia. Additionally, binahong extract has shown modulation of dipeptidyl peptidase IV (DPP-IV), an enzyme that plays a critical role in glucose homeostasis and insulin secretion[20-22].

In vivo findings using streptozotocin (STZ)-induced diabetic rat models further substantiate binahong's therapeutic potential. Administration of binahong infusion at a concentration of 151.2 mg per 180 mL water significantly reduced blood glucose levels, promoted pancreatic β-cell regeneration, and suppressed tumor necrosis factor-alpha (TNF-α) expression, suggesting anti-inflammatory properties that support β-cell repair. Moreover, oral administration of binahong leaf extract emulsion at a dose of 400 mg/kg BW in hyperglycemic rats resulted in a significant glucose-lowering effect, with reductions up to 305.75 mg/dL, indicating potential roles as an insulin secretagogue or insulin-mimetic agent[21,22,23]. Collectively, these findings highlight the multifaceted antidiabetic actions of *Anredera cordifolia*, including β-cell protection, enzyme inhibition, and insulin-like activity, making it a promising adjunct therapy for type 2 diabetes mellitus.

Anredera cordifolia (binahong) has been shown to effectively reduce levels of malondialdehyde (MDA), a key biomarker of oxidative stress, in various preclinical studies. MDA is produced as a result of lipid peroxidation of polyunsaturated fatty acids when exposed to oxidative agents. Studies have demonstrated that binahong extract can significantly reduce MDA levels in glucose-induced cataract goat lens models and in rats with unilateral ureteral obstruction (UUO)-induced kidney injury, attributed to its high antioxidant content[25]. The antioxidant properties of binahong contribute to the suppression of oxidative stress by restoring the oxidant–antioxidant balance in the body. Specifically, the extract inhibits MDA production and enhances endogenous antioxidant systems such as superoxide dismutase (SOD) and catalase, thereby supporting its therapeutic role in preventing cataracts and kidney damage[26-28].

The therapeutic potential of binahong is largely mediated by its phytochemical constituents—mainly flavonoids, saponins, alkaloids, and triterpenes. Flavonoids, well known for their antioxidant capacity, function as radical scavengers and inhibit lipid peroxidation. They promote vasodilation, contribute to wound healing, and prevent cataract formation by maintaining lens clarity[27-33]. Additionally, saponins and ascorbic acid in binahong stimulate collagen synthesis via activation of proline hydroxylase, enhancing wound closure and tissue repair while reducing inflammation. The anti-inflammatory action of binahong is associated with its ability to inhibit cyclooxygenase (COX) enzymes and suppress the production of prostaglandins and proinflammatory cytokines, thereby lowering oxidative stress and MDA levels[28,32]. In wound models, MDA reduction is closely linked to these anti-inflammatory and antioxidant effects, which collectively promote vascularization, epithelialization, and infection prevention[29,31].

Furthermore, binahong exhibits antihyperlipidemic and cardioprotective properties that indirectly contribute to the reduction of MDA. Studies have shown that binahong extract lowers total cholesterol, LDL, and triglyceride levels while increasing HDL, by mechanisms such as inhibition of lipase secretion and suppression of cholesterol reabsorption[27,29,30].

Flavonoids within the plant also inhibit fatty acid synthesis, thereby attenuating oxidative stress induced by dyslipidemia. In glucose-induced cataract models, binahong was able to maintain lens transparency and significantly reduce MDA levels, reinforcing its anti-cataract potential through ROS suppression[29,31]. The antihypertensive effects of binahong—mediated by oleanolic acid and flavonoids—contribute to vascular relaxation, decreased peripheral resistance, and improved metabolic regulation, further reducing oxidative stress and MDA production. Collectively, these findings underscore the multifaceted antioxidant, anti-inflammatory, and metabolic-regulating properties of binahong, positioning it as a promising therapeutic agent for managing oxidative stress-related conditions[27-33].

The leaf extract of *Anredera cordifolia* (binahong) has been extensively studied for its potential in various health-related applications, particularly in wound healing and tissue regeneration. Preliminary studies suggest that binahong extract can upregulate growth factors such as Platelet-Derived Growth Factor (PDGF) and Transforming Growth Factor-β (TGF-β), which play pivotal roles in wound repair and tissue remodelling[34]. Its bioactive constituents, notably flavonoids and saponins, contribute to its anti-inflammatory effects and stimulation of collagen synthesis. Flavonoids function as natural antibiotics with anti-inflammatory, anti-allergic, and antiviral properties. They inhibit inflammatory processes by blocking arachidonic acid release and lysosomal enzyme secretion, thereby shortening the inflammatory phase through neutralization of reactive oxygen species (ROS) and enhancement of endogenous antioxidant activity[35-37]. Meanwhile, saponins stimulate collagen production, essential for tissue repair, and possess cleansing and antiseptic properties that help prevent pathogenic microbial growth. These combined biological activities position binahong as a natural agent capable of modulating inflammation and promoting tissue regeneration[37-40].

Cell types such as macrophages are involved in secreting growth factors that activate fibroblasts during the tissue repair process. It is hypothesized that the saponin and flavonoid content in binahong may serve as precursors of inflammatory mediators, attracting leukocytes to wound areas and thereby stimulating tissue regeneration[37-40].

Additionally, growth factors such as Epidermal Growth Factor (EGF) and Fibroblast Growth Factor (FGF) have been referenced in the context of tissue recovery, indicating a potential role in binahong's therapeutic effect, although direct evidence remains limited in currently published literature. Binahong extract has also been shown to promote granulation tissue formation, a crucial phase in wound healing, and to reduce the distance between wound edges, suggesting accelerated wound closure. Furthermore, its antibacterial properties help prevent

infection—a major barrier to effective healing[37-40]. This study addresses a notable knowledge gap identified in literature reviews, by highlighting the potential of binahong leaf extract as an adjuvant therapy to prevent further nerve damage and stimulate nerve regeneration, as previously noted by Decroli et al. (2019), who emphasized the importance of malondialdehyde (MDA) and nerve growth factor (NGF) in diabetic neuropathy, with NGF showing a stronger correlation to neuropathy scores compared to MDA[35-37].

CONCLUSION

Anredera cordifolia leaf extract demonstrated significant efficacy in mitigating diabetic neuropathy in rat models. The extract effectively reduced blood glucose and malondialdehyde (MDA) levels while concurrently elevating nerve growth factor (NGF) expression. An antidiabetic effect was observed starting at a dose of 50 mg/kg body weight (BW), though the glibenclamide group (0.65 mg/kg BW) exhibited superior glycemic control. Antioxidant activity, indicated by reduced oxidative stress, was evident at 50 mg/kg BW, with the 200 mg/kg BW dose providing the most potent clinical antioxidant effect among all treatment groups. Furthermore, the extract enhanced NGF at doses ≥100 mg/kg BW, with both the 100 mg/kg and 200 mg/kg BW groups showing non-significant differences compared to the positive control (glibenclamide 0.65 mg/kg BW), suggesting comparable antioxidant efficacy to the standard treatment at these doses.

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