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RESEARCH ARTICLE

Antioxidant and Hepatoprotective Effects of *NewBouldia laevis* Extract and Its Homeopathic Formulations in Streptozotocin-Induced Diabetic Rats

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ABSTRACT

Chronic hyperglycemia and elevated oxidative stress are characteristics of diabetes mellitus. It is a metabolic condition that frequently causes tissue damage, especially to the liver. This study investigates the antioxidant and hepatoprotective effects of *Newbouldia laevis* extract and its homeopathic formulations in streptozotocin (STZ)-induced diabetic rats. Diabetes was induced using a single intraperitoneal injection of STZ (50 mg/kg body weight). Fifty-five male albino rats were randomly assigned into eleven groups of five. Group 1 served as the normal control, and Group 2 as the diabetic control. Group 3 received glibenclamide (standard drug), while Groups 4–6 were treated with 200, 400, and 600 mg/kg of crude ethanol extract of *N. laevis*, respectively. Groups 7–11 received homeopathic dilutions [1X (4.5×10^{-3}mg) , 2X (4.5×10^{-4}mg), 3X (4.5×10^{-5}mg), 6X (4.5×10^{-8}mg) , and 30C (4.5×10^{-62}mg)] administered orally every eight hours for 21 days. Total Antioxidant Capacity (TAC) was assessed using standard biochemical methods, while liver tissues were examined histologically using hematoxylin and eosin staining. Results showed that *N. laevis* extract significantly increased TAC levels in diabetic rats, with 400–600 mg/kg doses producing effects comparable to the standard drug. Notably, the 1X to 3X homeopathic potencies also maintained higher TAC levels, while 6X and 30C showed limited antioxidant activity. Histopathological analysis revealed that 1X to 3X potencies had significant hepatoprotection, with the 3X group exhibiting nearly normal liver and kidney architecture. These findings highlight the potential of *N. laevis*, particularly in its lower homeopathic potencies, as a complementary or alternative therapy for oxidative stress-related hepatic complications in diabetes management.

Key words: Antioxidant activity, Homeopathic formulations, Hepatoprotection, *Newbouldia laevis*, Streptozotocin-induced diabetes.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, resistance to insulin action, or a combination of both (American Diabetes Association, 2023; Goyal *et al*., 2023). Chronic hyperglycemia, the hallmark of diabetes, is associated with long-term damage and dysfunction of various tissues and organs (Giacco & Brownlee, 2010). One of the key pathogenic mechanisms involved in diabetic complications is oxidative stress, which arises from an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense systems (Rains & Jain, 2011). In the diabetic state, prolonged hyperglycemia promotes glucose auto-oxidation, protein glycation, and activation of the polyol pathway, all of which lead to excessive ROS generation and the deterioration of antioxidant defenses (Baynes & Thorpe, 1999; Maritim *et al*., 2003). These processes often result in oxidative stress and tissue damage (Baynes & Thorpe, 1999).

The liver, being central to glucose metabolism and detoxification, is particularly vulnerable to oxidative stress in diabetes. Mitochondria in hepatocytes are a major source of ROS, which contribute to the

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development of necro-inflammation (Wang *et al*., 2013). Hepatic injury in diabetes is commonly characterized by inflammation, steatosis and hepatocellular necrosis, all of which may promote the progression of non-alcoholic fatty liver disease (NAFLD) and other hepatic complications (Tilg & Moschen, 2010; Akshintala *et al*., 203).

The assessment of oxidative stress biomarkers such as Total Antioxidant Capacity (TAC) offers a composite measure of the body's overall antioxidant status. These antioxidants are crucial for scavenging ROS across various cellular compartments, especially in response to stress (Prior *et al*., 2005; Ghiselli *et al*., 2000; Jena *et al*., 2023). Evaluating the capabilities of both known and unidentified antioxidants, along with their synergistic interactions, helps to clarify the delicate balance between oxidants and antioxidants *in vivo* (Ghiselli *et al*., 2000).

This study investigates the antioxidant and hepatoprotective effects of *Newbouldia laevis* extract and its homeopathic formulations in diabetic rats. These interventions provide a comprehensive approach to evaluating antioxidant therapies for managing diabetes-related complications. *N. laevis*, a flowering plant native to tropical West Africa—including countries such as Sierra Leone, Ghana, Nigeria, and Ivory Coast—is widely used in traditional African medicine to treat various ailments (Eluu *et al*., 2023b). Its therapeutic potential is attributed to its rich content of bioactive compounds (Eluu *et al*., 2023a).

MATERIALS AND METHODS

Animals

The study involved fifty-five adults male Wistar rats (80–120 g) obtained from the Department of Zoology and Environmental Biology, University of Nigeria, Nsukka. All procedures complied with IACUC guidelines for laboratory animal care (ICMR, 2001).

Plant material

N. laevis leaves were collected from Agulu, Anambra State, and authenticated by Dr. C.F. Iroka, a taxonomist from the Department of Botany, Nnamdi Azikiwe University, Awka, Nigeria.

Methods

Plant extraction

To prepare the extract, *N. laevis* leaves were washed, shade-dried for seven days, and ground into coarse powder. The powder was then cold-macerated in ethanol (1:1) for 48 h. The resulting filtrate was concentrated at 40 °C using a rotary evaporator and stored under refrigeration until use.

Preparation of potentized homeopathic remedies

Preparation of the homeopathic mother tincture

The *N. laevis* extract homeopathic mother tincture was prepared by dissolving one part by weight of the *N. laevis* extract (4mg) in 9 parts by weight (36ml) of Absolute Ethanol (99.5% w/w) (Rawat, 2016).

Preparation of dilute ethanol

To prepare 87% ethanol, one part of distilled water is added to seven parts of absolute ethanol.

To prepare dilute ethanol, 7 parts of the 87% ethanol is added to three parts of distilled water.

Preparation of the homeopathic X potencies

The 1X potency was prepared by mixing one part of the homeopathic mother tincture with nine parts of dilute ethanol and succussing the mixture a hundred times on the palmor the backof a thick book. Subsequent potencies (2X to 6X) were made by serially diluting one part of the previous potency with nine parts of dilute ethanol. This process of serial dilution and succussion continued progressively up to the 6X potency.

Preparation of the homeopathic C potencies

The 1C potency was prepared by diluting one part of the homeopathic mother tincture with 99 parts of dilute ethanol, followed by 100 succussions. Each subsequent potency (2C to 30C) was prepared by serially diluting one part of the previous potency with 99 parts of dilute ethanol and succussing the mixture. This process was repeated up to the 30C potency, with dilutions beyond 12C likely containing little to no molecules of the original substance due to exceeding Avogadro's limit.

Induction of diabetes

Diabetes was induced in rats using a single intraperitoneal injection of streptozotocin (50 mg/kg body weight) dissolved in cold citrate buffer (pH 4.5). After 48 h, blood glucose levels were measured, and rats with glucose levels above 240 mg/dL were considered diabetic and included in the study. These diabetic rats were then randomly assigned into 11 groups, with five rats per group.

Experimental design

Fifty-five male albino rats were divided into eleven groups of five. Group 1 served as the normal control, while Group 2 was the diabetic control. Group 3 received glibenclamide as a standard treatment. Groups 4 to 6 were treated with 200, 400, and 600 mg/kg of the crude ethanol extract, respectively. Groups 7 to 11 received homeopathic dilutions of the extract at potencies 1X, 2X, 3X, 6X, and 30C, administered as three oral drops every eight hours and the study lasted 21 days.

Total antioxidant capacity (TAC) assessment

TAC is the cumulative ability of various compounds within a plant extract to neutralize free radicals and prevent oxidative damage. The method described by Sellappan *et al*. was used in the for the Total

Antioxidant Capacity (TAC) assessment (Sellappan *et al*., 2002).

Histopathological analysis

At the conclusion of the 21-day treatment period, the rats in the experimental groups were euthanized and their liver and kidneys were carefully excised for histo-pathological examination. The tissue sections were stained with hematoxylin and eosin (H&E), following the standard procedure described by Drury and Wallington (1981).

Statistical analysis

Data obtained was analyzed using One Way Analysis of Variance (ANOVA) and expressed as mean ± SEM. The significance between means was determined at $p < 0.05$ using the LSD post hoc test.

RESULTS AND DISCUSSION

Effect of *N. laevis* extract and formulations on TAC levels in diabetic rats over time

The Total Antioxidant Capacity (TAC) is a crucial biomarker for assessing oxidative stress and the body's ability to counteract free radicals. In this study, the TAC levels of diabetic rats varied significantly among treatment groups, providing insights into the antioxidant effects of *N. laevis* and its formulations (Fig 1). After induction, the induced and untreated groups had significantly higher ($p < 0.05$) TAC levels compared to the other groups. This initial increase in TAC may be attributed to a compensatory response by the body's endogenous antioxidant system to counteract oxidative stress induced by hyperglycemia (Matough *et al*., 2012). However, this response is often unsustainable, leading to subsequent reductions in TAC, as oxidative stress overwhelms the body's defense mechanisms.

On Day 11, the induced and untreated group had significantly lower ($p < 0.05$) TAC levels compared to all other groups, except those treated with 6X and 30C, which were not significantly ($p > 0.05$) different from the induced and untreated group. There were no significant differences ($p > 0.05$) in the TAC levels of the standard drug, 200mg/kg of *N. laevis*, 400mg/kg of *N. laevis*, 600mg/kg of *N. laevis*, 1X, 2X, 3X, and 6X when compared to each other. Meanwhile, the group treated with 30C had significantly lower ($p < 0.05$) TAC levels compared to 400mg/kg of *N. laevis* and 600mg/kg of *N. laevis*. This indicates that higher doses of the extract may provide better antioxidant protection.

After treatment, the induced and untreated groups had significantly higher ($p<0.05$) TAC levels compared to other groups, except for the group treated with 30C. It was also observed that the group treated with 600mg/kg of *N. laevis* had significantly higher ($p < 0.05$) TAC levels than all the other groups, except the uninduced and untreated group, which showed no significant difference ($P>0.05$) compared to the group treated with 600mg/kg of *N. laevis*. There were no significant differences ($P>0.05$) in TAC levels among the groups treated with the standard drug, 400mg/kg of *N. laevis*, 1X, and 3X when compared with each other. The comparable efficacy of *N. laevis* to the standard drug suggests that plant-based therapies may serve as complementary or alternative treatments in diabetes management. This aligns with previous research findings indicating that medicinal plants with high polyphenolic and flavonoid content exert significant antioxidant activity, thereby mitigating diabetes-induced oxidative stress (Salehi *et al*., 2019). Additionally, there were no significant differences ($P>0.05$) in the TAC levels of the group treated with 200mg/kg of *N. laevis* compared to 2X and the standard drug group, while the group treated with400mg/kg of

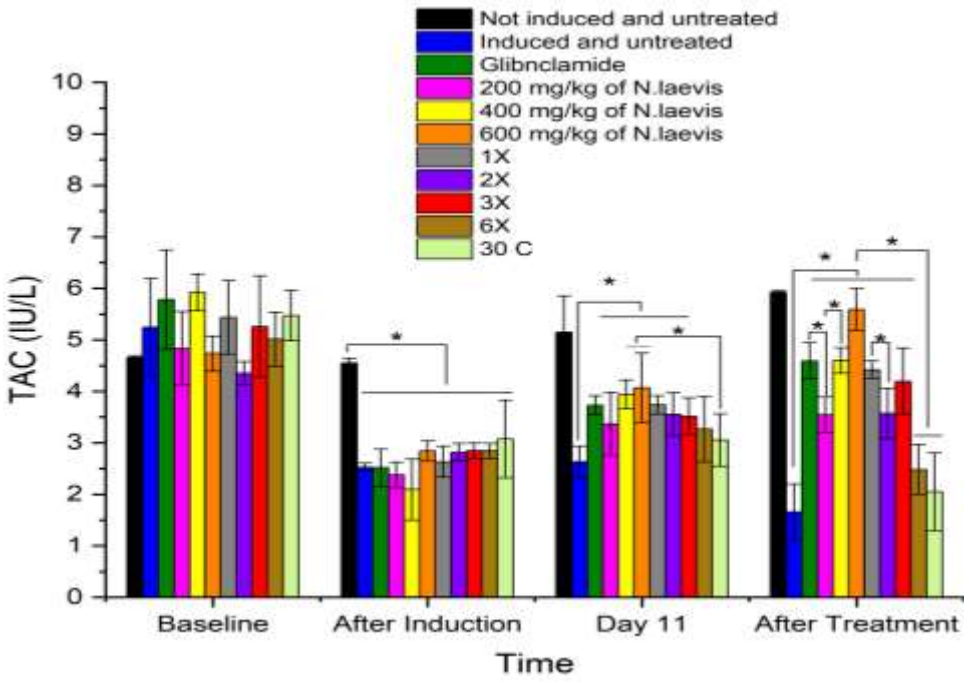

Fig. 1: Effect of *N. laevis* extract on TAC levels in induced and treated groups over time. Asterisk (*) shows that the mean difference between groups is significant at $P<0.05$.

N. laevis had significantly higher ($p < 0.05$) TAC levels compared to the group treated with 200 mg/kg of *N. laevis* and 2X. However, there were no significant differences ($p > 0.05$) in the TAC levels of 3X compared to those of 200mg/kg of *N. laevis* and 2X. The observed trends in TAC levels emphasize the role of *N. laevis* as a potential antioxidant therapy in diabetes management (Osigwe *et al*., 2017). Oxidative stress plays a critical role in diabetic complications, contributing to endothelial dysfunction, lipid peroxidation, and cellular damage (Maritim *et al*., 2003). The ability of *N. laevis* to maintain or improve TAC levels suggests its therapeutic potential in reducing oxidative stress- related complications. It was also observed that 6X had significantly lower ($p < 0.05$) TAC levels compared to all other groups except 30C, while 30C had significantly lower ($p < 0.05$) TAC levels compared to all other groups except the induced and untreated group and 6X.

Effect of *N. laevis* extract and formulations on histopathology of the liver

The hepatocytes, or liver cells, are responsible for the organ's numerous functions. The histopathological assessment of the liver following twenty-one days of treatment with *N. laevis* extract and homeopathic formulations demonstrated varying degrees of hepatic protection (Fig. 2a-2k).

The histological evaluation of liver tissues in Fig. 2a to 2k reveals the hepatoprotective potential of *N. laevis* in comparison with both untreated and standard drug-treated groups. In Fig. 2a, representing the uninduced and untreated control group, liver tissue displayed well-preserved architecture, characterized by a distinct central vein (V), polygonal hepatocytes with centrally located nuclei, and clearly radiating hepatic sinusoids. This structure served as a baseline reference for assessing hepatic integrity. In contrast, Fig. 2b (induced but untreated group) shows disrupted hepatic architecture, with signs of hepatocellular disorganization and mild multifocal necrosis, accompanied by leukocyte infiltration. These features are indicative of hepatocellular injury, consistent with diabetes-induced oxidative stress and the accumulation of reactive oxygen species (ROS) (Oguntibeju, 2019; 2010; Nahdi *et al*. 2018).

Fig. 2c, representing the standard drug-treated group, shows near-complete restoration of normal hepatic histology. The central vein, hepatocytes, and portal triads are all clearly identifiable and well-organized, suggesting that the standard treatment effectively mitigated liver damage. This group serves as a positive therapeutic control, demonstrating that hepatocellular injury can be reversed with appropriate pharmacological intervention. Liver sections in Fig. 2d to 2f depict the effects of *N. laevis* at doses of 200 mg/kg, 400 mg/kg, and 600 mg/kg, respectively. At 200 mg/kg, there was mild structural improvement, with partial realignment of hepatocytes. The 400 mg/kg dose leads to more pronounced architectural recovery, including clearer hepatic sinusoids and reduced inflammation. At 600 mg/kg, liver histology appears nearly normal, with distinct hepatocyte borders and visible portal triads, indicating a strong hepato-protective effect at higher dosages. Fig. 2g through 2k demonstrate the impact of repeated *N. laevis* treatments (1X to 3X). The 1X treatment group (Fig. 2g) shows moderate improvement in hepatic structure. With increasing treatment frequency 2X (Fig. 2h) and 3X (Fig. 2i) liver shows marked architectural restoration. In the 3x treated groups (Fig. 2i), liver histology closely resembles that of the control, with well-organized hepatocytes and intact portal triads. However, the 6X and 30C groups exhibit mild to moderate vacuolar degeneration in the periportal areas, which may signal early-stage hepatocyte injury resulting from oxidative stress or metabolic strain (Ibrahim *et al*., 2017).

Collectively, these results suggest that *N. laevis* confers both dose-dependent and frequency-dependent protection and regeneration of liver tissue. Groups treated with 200–600 mg/kg and 1X–3X doses showed normal hepatic histo-morphology, further confirming the extract's therapeutic potential. The observed hepato-protective effects are likely linked to the plant's antioxidant and anti-inflammatory properties, supported by earlier studies (Habu & Ibeh, 2008; Usma *et al*., 2008). The presence of bioactive compounds such as flavonoids and phenolics, known for neutralizing free radicals and reducing oxidative stress (Singh *et al*., 2022), may underlie these beneficial effects. Clinically, the findings underscore *N. laevis* as a promising candidate for the management of hepatic injuries, especially in conditions associated with oxidative damage such as diabetes. Its comparable efficacy to standard drugs, especially at higher doses and multiple treatment regimens makes it a potential alternative or complementary therapy where conventional treatments are inaccessible or unsuitable.

Effect of *N. laevis* extract and formulations on histopathology of the kidney in diabetic rats twenty-one days post treatments

The kidneys plays a vital role in excreting metabolic waste, regulating fluid and electrolyte balance, promoting bone integrity, and interacting with the cardiovascular system to maintain hemodynamic stability (Dalal *et al*., 2023). They maintain homeostasis by removing toxins, reabsorbing essential nutrients, and producing hormones like erythropoietin for red blood cell production. Diabetic nephropathy is one of the most prevalent issues that arise from diabetes (Donnelly *et al*., 2000). The histopathological assessment of renal tissues following twenty-one days of treatment with *N. laevis* extract and formulations (Fig. 3a-3k) revealed varying levels of renal protection.

The uninduced and untreated group showed a normal renal histo-architecture with well-preserved glomeruli (G) and renal tubules (Fig. 3a), confirming the

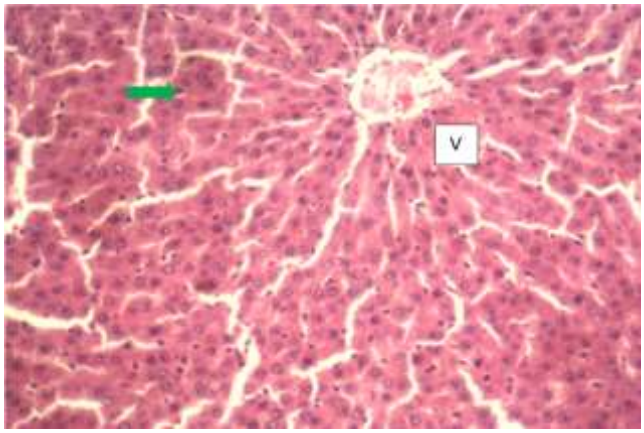

Fig. 2a: Histological section of the liver of uninduced and untreated group stained with hematoxylin and eosin. The label "V" indicates the central vein. Hepatocytes is the green arrow to surrounding pink polygonal cells with central nuclei. Hepatic Sinusoids are the white spaces radiating from the central vein between rows of hepatocytes.

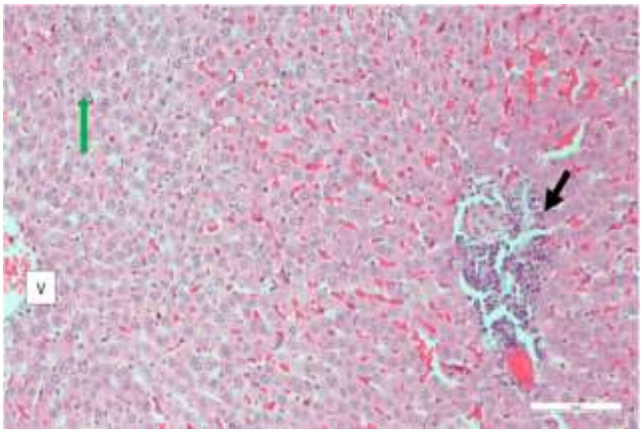

Fig. 2b: Histological section of the liver of induced and untreated group stained with hematoxylin and eosin. The label 'V' indicates the central vein. Hepatocytes is the green arrow to surrounding pink polygonal cells with central nuclei. The black arrow indicates the portal triad.

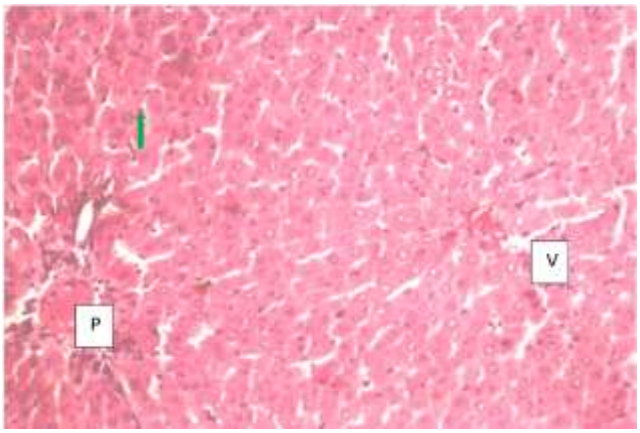

Fig. 2c: Histological section of the liver of standard drug treated group stained with hematoxylin and eosin. The label 'V' indicates the central vein. Hepatocytes is the green arrow to surrounding pink polygonal cells with central nuclei while 'P' represent the portal triad.

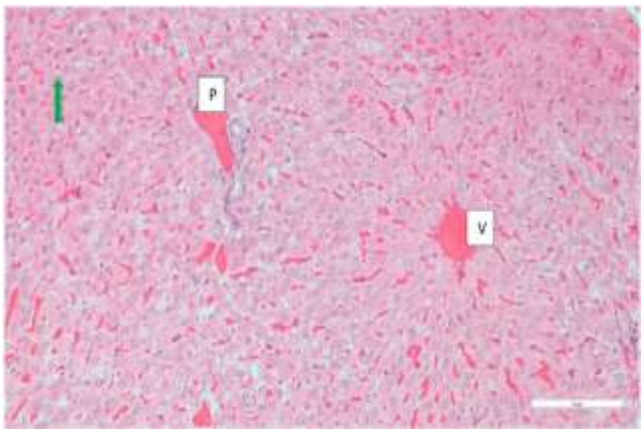

Fig. 2d: Histological section of the liver of 200mg/kg of N. laevis treated group stained with hematoxylin and eosin. The label 'V' indicates the central vein. Hepatocytes is the green arrow to surrounding pink polygonal cells with central nuclei while represent 'P' the portal triad.

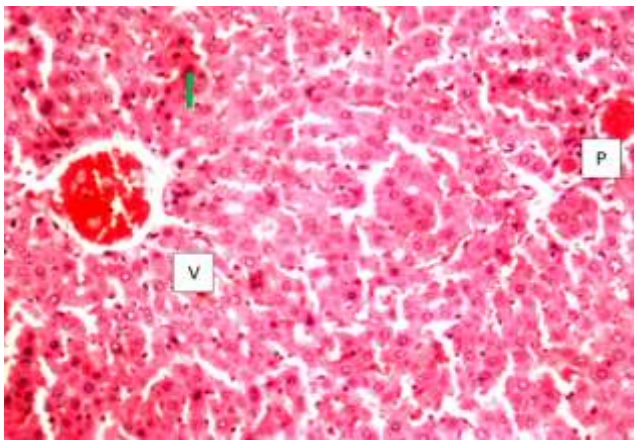

Fig. 2e: Histological section of the liver of 400mg/kg of N. laevis treated group stained with hematoxylin and eosin. The label 'V' indicates the central vein. Hepatocytes is the green arrow to surrounding pink polygonal cells with central nuclei while 'P' represent the portal triad.

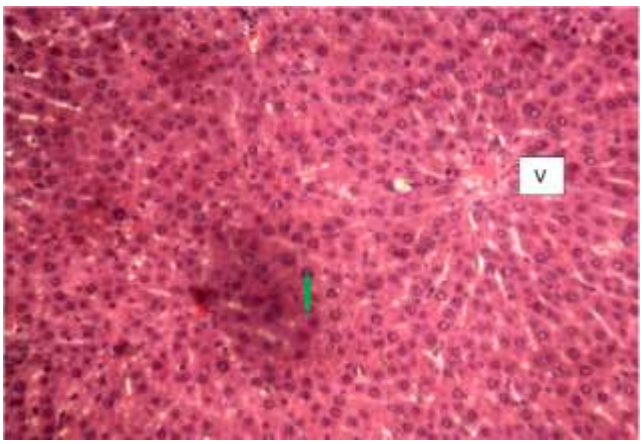

Fig. 2f: Histological section of the liver of 600mg/kg of N. laevis treated group stained with hematoxylin and eosin. The label 'V' indicates the central vein. Hepatocytes is the green arrow to surrounding pink polygonal cells with central nuclei while 'P' represent the portal triad.

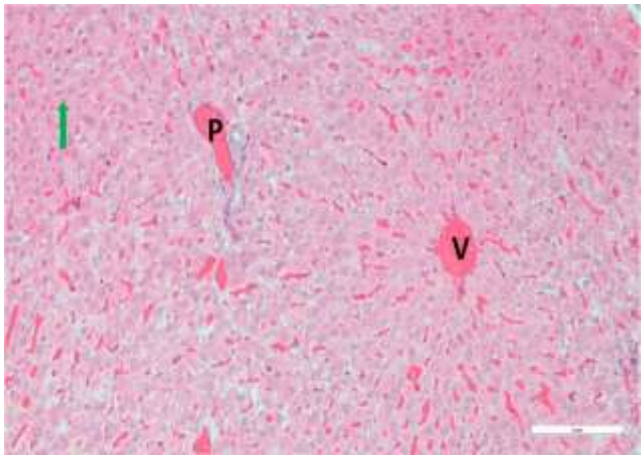

Fig. 2g: Histological section of the liver of 1X treated group stained with hematoxylin and eosin. The label 'V' indicates the central vein. Hepatocytes is the green arrow to surrounding pink polygonal cells with central nuclei while 'P' represent the portal triad.

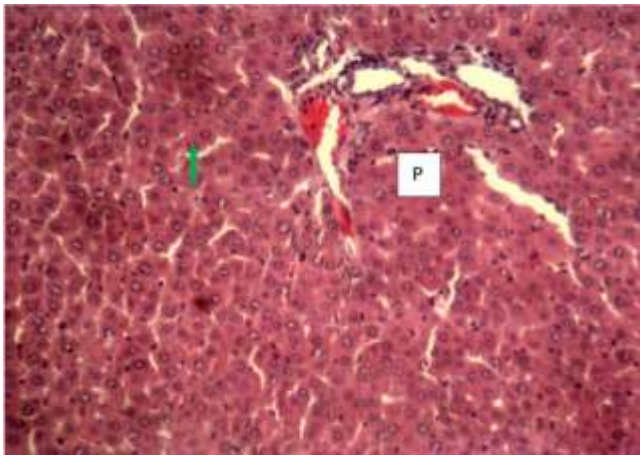

Fig. 2h: Histological section of the liver of 2X treated group stained with hematoxylin and eosin. Hepatocytes is the green arrow to surrounding pink polygonal cells with central nuclei while 'P' represent the portal triad.

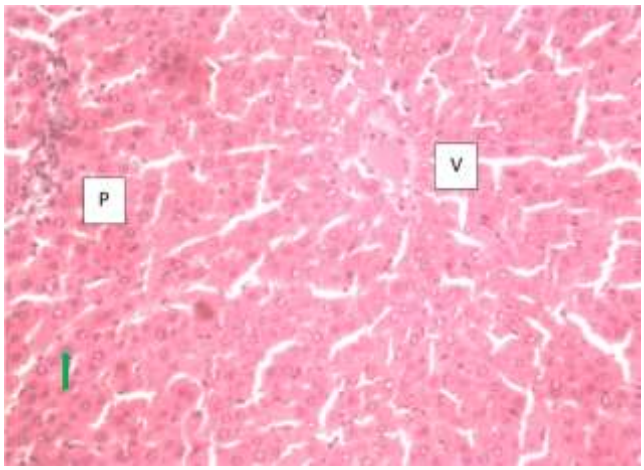

Fig. 2i: Histological section of the liver of 3X treated group stained with hematoxylin and eosin. The label 'V' indicates the central vein. Hepatocytes is the green arrow to surrounding pink poly-gonal cells with central nuclei while 'P' represent the portal triad.

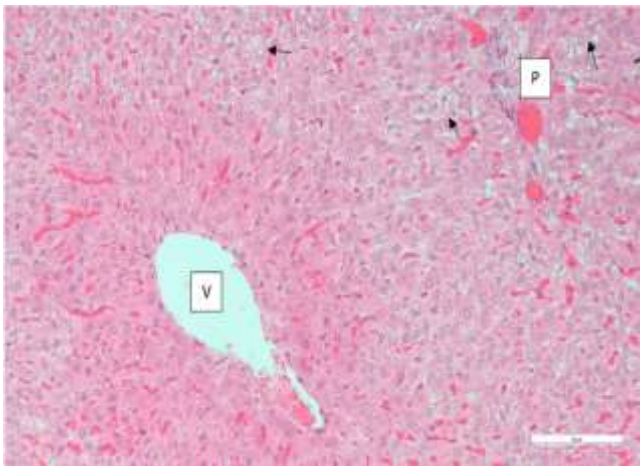

Fig. 2j: Histological section of the liver of 6X treated group stained with hematoxylin and eosin. The label 'V' indicates the central vein. Hepatocytes is the arrow to surrounding pink polygonal cells with central nuclei while 'P' represent the portal triad.

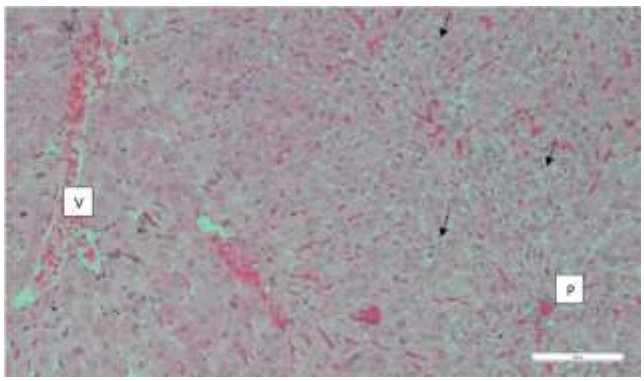

Fig. 2k: Histological section of the liver of 6X treated group stained with hematoxylin and eosin. The label 'V' indicates the central vein. Hepatocytes is the arrow to surrounding pink polygonal cells with central nuclei while 'P' represent the portal triad.

absence of renal stress or injury. In contrast, the diabetic-induced but untreated group displayed severe, widespread tubular vacuolar degeneration and necrosis (Fig. 3b), indicating significant renal damage. The destruction of tubular epithelial cells and glomerular damage observed in the induced and un-treated group results from hyperglycemia-induced kidney injury, which can lead to progressive renal dysfunction.

The standard drug-treated group exhibited normal renal histo-architecture (3c), reinforcing its efficacy in preserving kidney function. Similarly, *N. laevis* at 400 mg/kg and 600 mg/kg doses, 2X and 3X restored normal renal histo-architecture (Fig. 3e-f;3h-i), indicating its potential in mitigating diabetes-related nephrotoxicity. These results suggest that *N. laevis* possesses nephro-protective properties, potentially due to its antioxidant and anti-inflammatory constituents (Habu and Ibeh, 2008), which counteract oxidative stress and tubular necrosis. Also, the 1X group exhibited evidence of renal tubular regeneration with interstitial inflammatory activity (Fig. 3g). This suggests an adaptive healing

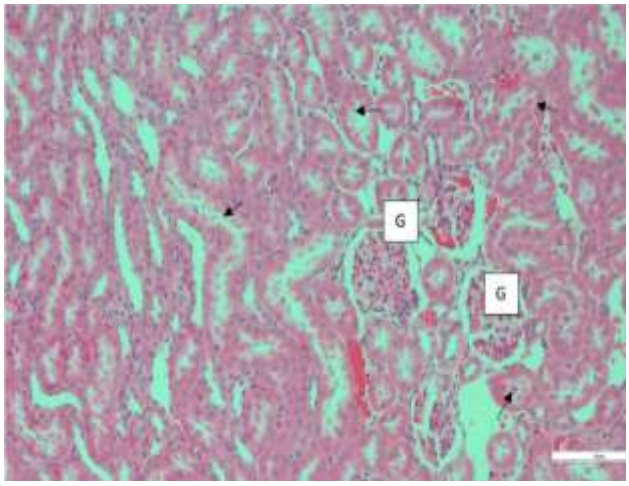

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Fig. 3a: Histological section of kidney tissue of uninduced and untreated group, showing the normal renal histo-architecture. The 'G' stands for glomeruli while the arrow points to renal tubules.

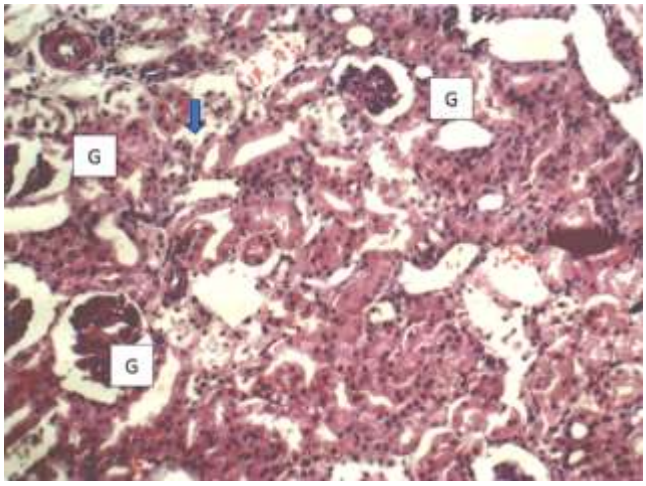

Fig. 3b: Histological section of kidney tissue of induced but untreated groupshowing severe widespread areas of tubular vacuolar degeneration and necrosis (arrow). The 'G' stands for glomeruli.

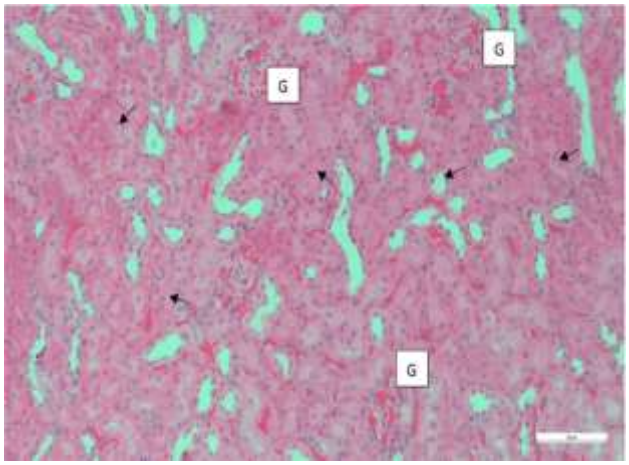

Fig. 3c: Histological section of kidney tissue of standard drug treated groupshowing normal renal histo-architecture. The 'G' stands for glomerulus while the arrow represents the renal tubules.

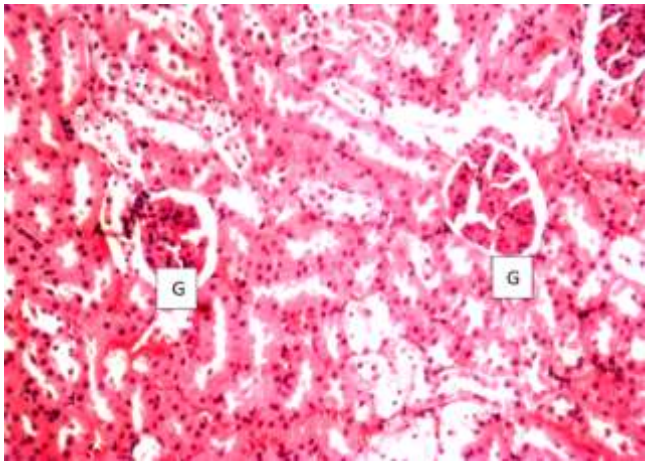

Fig. 3d: Histological section of kidney tissue of 200mg/kg of N. laevis showing mild multifocal areas of tubular vacuolar degeneration and necrosis (arrow) and glomeruli represented by G.

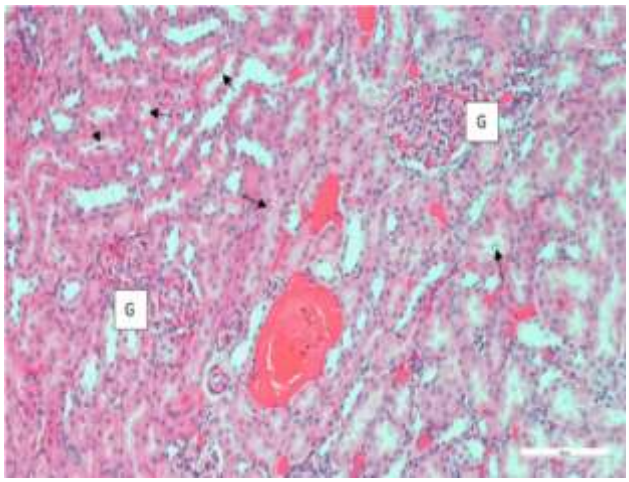

Fig. 3e: Histological section of kidney tissue of 400mg/kg of N. laevis treated group, showing the normal renal histo-architecture. The 'G' shows glomerulus while the renal tubules is indicated by arrow.

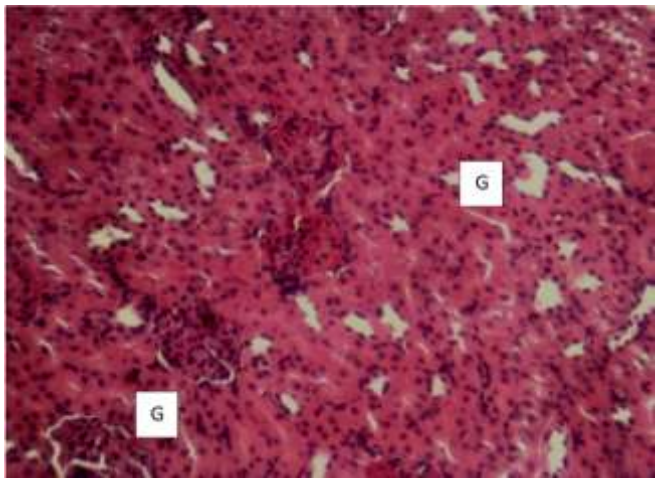

Fig. 3f: Histological section of kidney tissue of 600mg/kg of N. laevis treated group, showing normal renal histomorphology. The 'G' stands for glomeruli while the arrow shows renal tubules arrow.

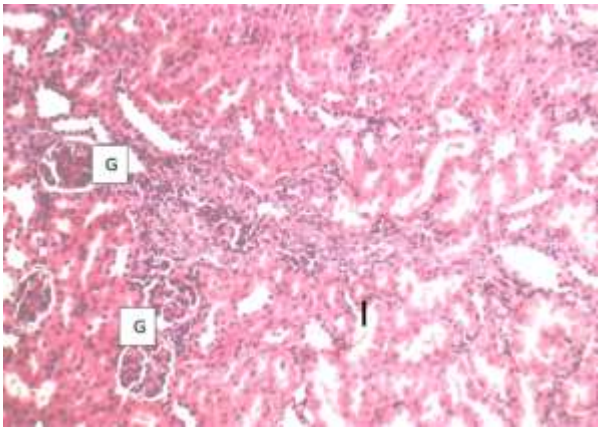

Fig. 3g: Histological section of kidney tissue of 1X treated group, showing areas of renal tubular regeneration as indicated with arrow while glomeruli are given by 'G'.

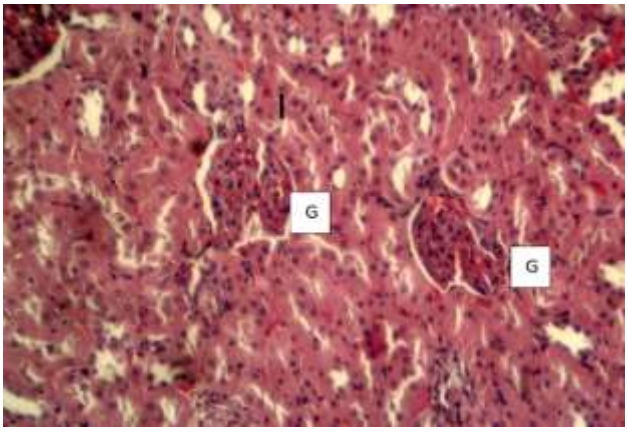

Fig. 3h: Histological section of kidney tissue of2X treated group, showing the normal renal histomorphology where 'G' stands for glomeruli; arrow shows renal tubules.

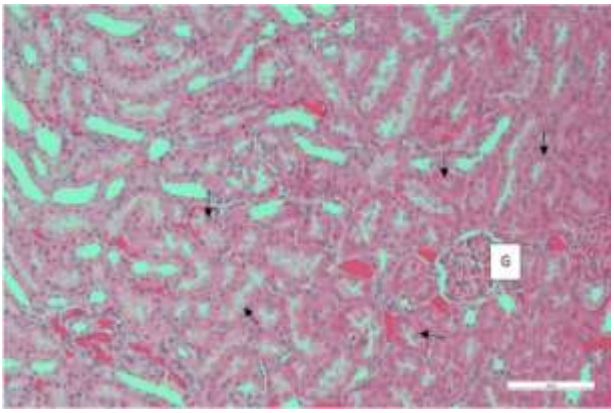

Fig. 3i: Histological section of kidney tissue of of 3X treated group, showing the normal renal histo-architecture where 'G' stands for glomeruli; arrow shows renal tubules

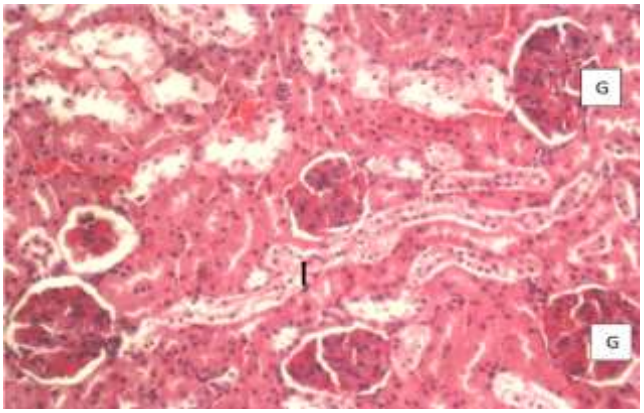

Fig. 3j: Histological section of kidney tissue of of 6X treated group, showing severe widespread areas of tubular vacuolar degeneration and necrosis (arrow) as well as glomeruli (G)

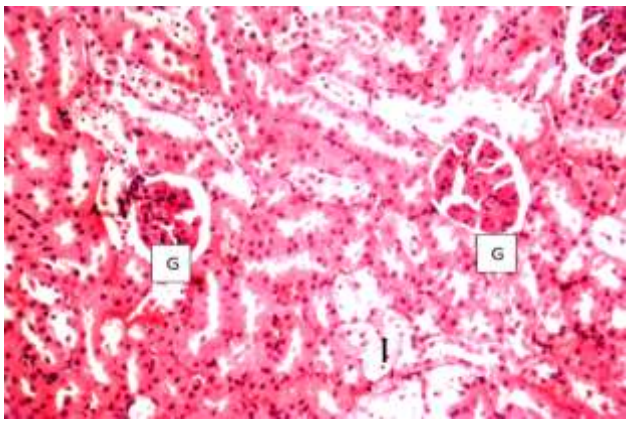

Fig. 3k: Histological section of kidney tissue of 30C treated group showing mild multifocal areas of tubular vacuolar degeneration and necrosis as indicated with arrow and the glomeruli is represented by letter 'G'.

response, possibly due to a delayed but ongoing regenerative process following initial injury.

In the 200 mg/kg and 30C treatment groups, the presence of mild multifocal tubular vacuolar degeneration and necrosis suggests a partial protective effect. While most treatment groups showed preserved renal morphology, the 6X group exhibited severe, widespread tubular vacuolar degeneration and necrosis, indicating dose-dependent toxicity.

Conclusion

These findings highlight the potential of *N. laevis*, particularly in its lower homeopathic potencies, as a complementary or alternative therapy for oxidative stress-related hepatic complications in diabetes management.

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