Original Article

Riboceine Regimen Circumvents Reserpine-Induced Hepatotoxicity via the Modulation of Key Liver Function Markers in Adult Male Wistar Rats

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ABSTRACT

Reserpine, an antipsychotic and antihypertensive medication, has been associated with liver damage and dysfunction. The present study examined the potential hepatoprotective effect of a riboceine regimen against reserpine-induced hepatotoxicity in adult male Wistar rats. A total of twenty-five adult male Wistar rats were randomly assigned to five groups: The following combinations were administered: control, Reserpine, Reserpine + Citalopram, Reserpine + Riboceine, and Reserpine + Citalopram + Riboceine. Liver function markers, including alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP), were analysed in serum samples in order to assess liver health. Furthermore, a histopathological examination of the liver tissue was conducted to visualise any morphological changes. Serum levels of ALT and AST increased significantly in rats administered reserpine in isolation in comparison with the control group, indicating hepatocellular damage. Conversely, the Riboceine + Reserpine group demonstrated a substantial decrease in ALT and AST levels in comparison to the Reserpine group, thereby indicating a protective effect of riboceine against reserpine-induced hepatotoxicity. No significant difference was observed in the serum level of ALP across the experimental groups. Histopathological examination confirmed the attenuated liver injury in the Riboceine + Reserpine group, with a reduction in necrotic areas and inflammation compared to the Reserpine group. The findings indicate that a riboceine regimen effectively circumvents reserpine-induced hepatotoxicity in adult male Wistar rats. The modulation of key liver function markers, in conjunction with histopathological evidence, substantiates the hepatoprotective role of riboceine in mitigating liver damage induced by reserpine. This study offers a number of promising insights into the potential therapeutic use of riboceine as a hepatoprotective agent. It could therefore be beneficial for patients undergoing treatment with reserpine or similar medications.

Keywords: Reserpine, Riboceine, Hepatotoxicity, Oxidative Stress, Citalopram.

1. Introduction

Depression is among the most prevalent mental health disorders (1) and affects a considerable proportion of the population at some point in their lives (2). The presentation of depression can vary widely, encompassing a range of symptoms from fatigue to suicidal thoughts. The aetiology of the condition may be rooted in a number of factors, including genetic predispositions, psychological distress, and substance abuse (3). At the molecular level, depression has been shown to disrupt synaptic plasticity in the brain, resulting in atrophic changes in the cortical and hippocampal regions (2). Research studies have indicated that a significant decrease in monoamine neurotransmitters can be a contributing factor to the onset of depression. Reserpine, an antihypertensive medication, has been employed as a model to support the monoamine depletion hypothesis. In the aftermath of documented cases of depression in a number of individuals who had been administered reserpine, scientific analysis revealed a substantial decline in the synthesis of monoamine neurotransmitters (4). Rauwolfiia serpentine, a climbing shrub native to India, is the source of an alkaloid that is derived from the plant. The clinical application of reserpine has been demonstrated to be efficacious in the management of hypertension, insanity, insomnia and schizophrenia (5). Nevertheless, the utilization of reserpine as a pharmaceutical agent is constrained due to its propensity to induce hepatic and other organ damage through the process of excess free radical production and oxidative stress (6). Reserpine has been shown to act via irreversible blockade of VMAT-2 (vesicular monoamine transporter-2), thereby inhibiting the alpha-adrenergic neurotransmission pathway (5). The blockage of catecholamine pumps has been demonstrated to prevent the uptake of dopamine, norepinephrine, and serotonin into presynaptic storage vesicles. Oxidative stress is the consequence of an imbalance between antioxidants and prooxidants within the body. Antioxidants, while generally protective, can, on occasion, act as prooxidants under specific conditions. In the context of aerobic environments, these bacteria generate superoxide radicals, which dismutase to form H2O2. This, in turn, reacts with reduced metal ions and superoxide, leading to the generation of toxic reactive oxygen species (ROS) (7). The induction of oxidative stress is the consequence of radical species production and an imbalance in antioxidant defence systems. This imbalance has been demonstrated to result in damage to cellular biomolecules, including lipids, proteins, and DNA (8). Reactive oxygen species (ROS) interact readily with all cellular macromolecules due to their reactivity. Muriel and Gordillo (9) have demonstrated that ROS can cleave phosphodiester bonds that hold bases in RNA and DNA together, thereby disrupting the chain structure of these molecules. Excessive ROS production has been demonstrated to directly interact with cellular biomolecules, including DNA, lipids, and proteins (10). This interaction can result in modifications that may ultimately lead to cell death. Liver diseases are a significant global health concern. The liver is the body's primary detoxification organ and plays a crucial role in maintaining metabolic balance. The liver is responsible for the metabolism of various compounds, with the resultant production of reactive oxygen radicals (11). Oxidative stress has been demonstrated to disrupt redox balance, thereby impacting liver function and influencing inflammatory pathways, thus contributing to the development of various liver diseases. It has been implicated in a number of pathological conditions, including acute liver injury, the pathogenesis of prevalent infectious or metabolic chronic liver diseases, and the progression of liver diseases to liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), as discussed by Allameh et al (12). Riboceine, a patented molecule, has been demonstrated to effectively deliver cysteine molecules into cells, thereby enabling them to produce optimal amounts of glutamate (13). The substance under scrutiny contains ribose and cysteine, which are naturally present in the human body. Riboceine has been demonstrated to facilitate the synthesis of glutathione by cells, in accordance with the following chemical equation:D-ribose-L-cysteine (14).

2. Materials and Methods

2.1 Major Apparatus and Equipment

The following items are required for the experiment: plastic cages, syringes and needles, plain bottles, rat feed, sensitive weighing balances, cotton wool, dissecting sets, measuring cylinders, flasks, test tubes, surgical gloves, scalpel blades, heparinised bottles, soap, surgery pins, oral cannulas, buckets, dissecting boards, sponges, mortars and pestles, blenders, centrifuge machines, microscope slides, improved Neubauer haemocytometers, refrigerators and cover slips.

2.2 Experimental Animals and Care

The experiment utilised twenty-five adult male rats, with an average weight of 132 grams (± 10g). The rats were obtained from the Animal Facility of Bright Farm, Owode Ede, Osun State, Nigeria. The rats were bred in the animal house of the facility of Basic Medical Sciences, Osun State University, Osogbo, Osun State; under the light and dark cycle at room temperature 35℃. The implementation of wire gauze and a plastic cage ensured adequate aeration. The Health Research Institute Ethics Committee (HREC) at Osun State University, Nigeria, approved the procedures employed in this study. In the course of the study, rodent diets were procured from Top Feed Mills in Osogbo, Nigeria, and unfiltered drinking water was provided ad libitum. Prior to the administration of the experimental substances, the rats were randomly allocated to five groups and housed in separate cages. They were acclimatized to the experimental room for a period of one week prior to the commencement of the experiments.

2.3 Experimental Design

A total of 25 adult male albino Wistar rats were randomly allocated to five groups, designated A, B, C, D and E, with five rats (n=5) assigned to each group. The groupings and dosage of treatments are as follows;

- Group A - Control group (physiological saline and feed).
- Group B - Induced with 50mg/kg reserpine only.
- Group C - Induced with 50mg/kg reserpine and co-treated with citalopram (40mg/kg).
- Group D - Induced with reserpine (50mg/kg) and co-treated with riboceine (30mg/kg).
- Group E - Induced with reserpine and co-treated with citalopram(40mg/kg) and riboceine (30mg/kg).

With the exception of the animals which constituted the control group, all other animals were subjected to the induction of reserpine. Animals in Group C were administered citalopram and reserpine, while those in Groups D and E were administered riboceine and reserpine following a week of acclimatisation.

2.4 Drugs and Reagents

Reserpine (Calbiochem–506238) and citalopram (Calbiochem–506130) were procured from the United States. Riboceine (Cellgevity–703327642433) was procured domestically in Nigeria. The chemicals, materials, drugs and reagents utilized in this study, including distilled water, formaldehyde, normal saline and others, were obtained from local suppliers and are of analytical grade.

2.5 Ethical Approval

All experimental procedures were conducted in accordance with the stipulated requirements of the Health Research Ethics Committee (College of Health Sciences, Osun State University, Osogbo, Nigeria) and in compliance with the guidelines of the National Institute of Health Guide for the Care and Use of Laboratory Animals. The research was conducted in the Animal House facility of Osun State University, which is located in Osogbo, Osun State, Nigeria.

2.6 Drug Preparation and Administration

The volume administered was calculated using the stock solutions and the average body weight (ABW). In order to ascertain the volume gain, it is necessary to multiply the average body mass by 1000 and then divide this by the dosage (in milligrams per kilogram) and the stock solution. The mean body weight was recorded as 132 kg. Following this measurement, the following pharmaceuticals were administered: reserpine, citalopram and riboceine. The stock solution of reserpine was prepared by means of the following procedure. A quantity of 54.5 mg of the drug was dissolved in 10 ml of distilled water, thus yielding a solution containing 5.45 mg of the drug per ml. The stock solution of citalopram was prepared by the dissolution of 245.6 mg of the substance in 10 ml of distilled water, yielding a concentration of 24.56 mg/ml. The stock solution of Riboceine was prepared by means of dissolving 630 milligrams of the substance in 10 milliliters of distilled water, thus yielding a concentration of 63 milligrams per milliliter.

Volume of Reserpine administered =132/1000×50/545 = 0.1ml
Volume of Citalopram administered = 132/1000 × 40/2456 = 0.1ml
Volume of Riboceine administered = 132/1000 × 30/630 =0.1ml
Volume of Reserpine was 0.2 ml for group E.
Volume of citalopram was 0.2ml for group E.
Volume of Ribociene was 0.2ml for group E.

2.7 Animal Sacrifice and Tissue Processing

The rats were euthanized with an intramuscular injection of ketamine (20 mg/kg) for the purpose of a histological assessment, which was conducted 12 hours after the final treatments. Blood was extracted from the left ventricle and transferred into heparinized bottles. Transcardial perfusion was then initiated, commencing with a 50-ml flush of 0.1 M phosphate-buffered saline (PBS; pH 7.4). Thereafter, 500 ml of 4% paraformaldehyde (PFA) was infused via cardiac puncture. The excision and fixation of the liver in 4% paraformaldehyde (PFA) for 24 hours was followed by storage in 30% sucrose at 4°C. A histological demonstration was conducted on sections that had been embedded in paraffin wax. These sections were then stained with Hematoxylin and Eosin in order to demonstrate general cytoarchitectural features.

2.8 Routine Histology

2.8.1 Hematoxylin and Eosin Staining Procedure

The sections were initially deparaffinized in two changes of xylene, each lasting three minutes, followed by rehydration in two changes of descending grades of alcohol, including absolute I, absolute II, 90%, 70%, and 50% ethanol, for two minutes each. Following a rinse in distilled water for a period of three minutes, the sections were subjected to staining with ion hematoxylin for a duration of 10 to 15 minutes. Subsequently, the excess stain was removed by washing the sections in running tap water for a period of five minutes. Following this, the sections were differentiated in 1% acid alcohol for a duration of one minute. Subsequently, the sections were subjected to counterstaining with eosin for a period of two minutes. The samples were then dehydrated through ascending grades of alcohol, with each grade being applied for a period of two minutes. Following this, the samples were cleared in two changes of xylene and mounted in a synthetic resin medium (D.P.X).

2.9 Biochemical Assay

2.9.1 Estimation of Liver Function Markers

The blood samples collected were subjected to a centrifugation process at 3000 RPM for a duration of 15 minutes, with the objective of effecting the separation of the serum. Subsequently, an automated biochemical analyzer was employed to ascertain the levels of ALP, AST, and ALT in the serum. The manufacturer's instructions for sample loading and analysis were strictly followed, and the results were recorded in appropriate units for each enzyme.

2.10 Photomicrography

The sections were observed using a Leica DM750 research microscope equipped with a Leica ICCS50 digital camera. Photomicrographs of the tissue sections were captured at multiple magnifications.

2.11 Statistical Analysis

The biochemical examination results were analyzed quantitatively using GraphPad Prism (version 8) software. The statistical analysis comprised one-way Anova and Tukey's multiple comparison test, with a significance level of $p<0.05$.

3. Results

3.1. Effect of Riboceine on serum Aspartate Transferase level in Reserpine treated Rats

As demonstrated in Figure 1, serum AST levels increased significantly ($P<0.05$) in rats that received reserpine only (Dep) with a mean value of 69.40±2.71, as well as rats treated with reserpine and citalopram (Dep + AntiDep) with a mean value of 70.12 ± 1. In comparison with the control group (51.60±2.11), the mean serum aspartate transaminase (AST) level of rats in groups D and E was significantly ($P>0.05$) modulated by riboceine supplementation (69.40±2.71). This was a significant difference when compared with the mean serum AST levels of rats in groups B and C.

3.2. Serum Alanine Transaminase Concentration was modulated by Riboceine Regimen

In the present study, a significant increase in serum ALT profile was observed in rats administered reserpine only (Group B), with a mean value of 26.61±2.34, as compared with the control group (18.20±4.21). A similar increase was also observed in rats treated with reserpine and riboceine (Group D+Sulp; 18.10±1.71). Concomitant treatment with reserpine, citalopram, and riboceine (group E; 19.31±3.25) also elicited a significant reduction in the level of serum ALT when compared to the reserpine only group (Figure 2).

3.3. Effects of Reserpine, Citalopram, and Riboceine on Serum Alkaline Phosphate Concentration

As illustrated in Figure 3, no statistically significant variation was detected in the serum alkaline phosphate level among the various experimental groups.

3.4. Histological Evaluation of the Liver

As demonstrated in Figure 4, rats in Group B, which received a single dose of reserpine, exhibited a distinct histomorphological presentation (indicated by red arrows) when compared to Group A. This alteration is characterized by the presence of necrotic hepatocytes, hepatocytes exhibiting poor staining, and ruptures in the walls of hepatic vessels. Moreover, rats administered citalopram and reserpine (group C) exhibited mild pathological alterations. Nonetheless, the overall presentation was analogous to that of the control group. Rats in groups D and E, which had been administered riboceine, exhibited a liver microarchitecture that was consistent with that of the control group.

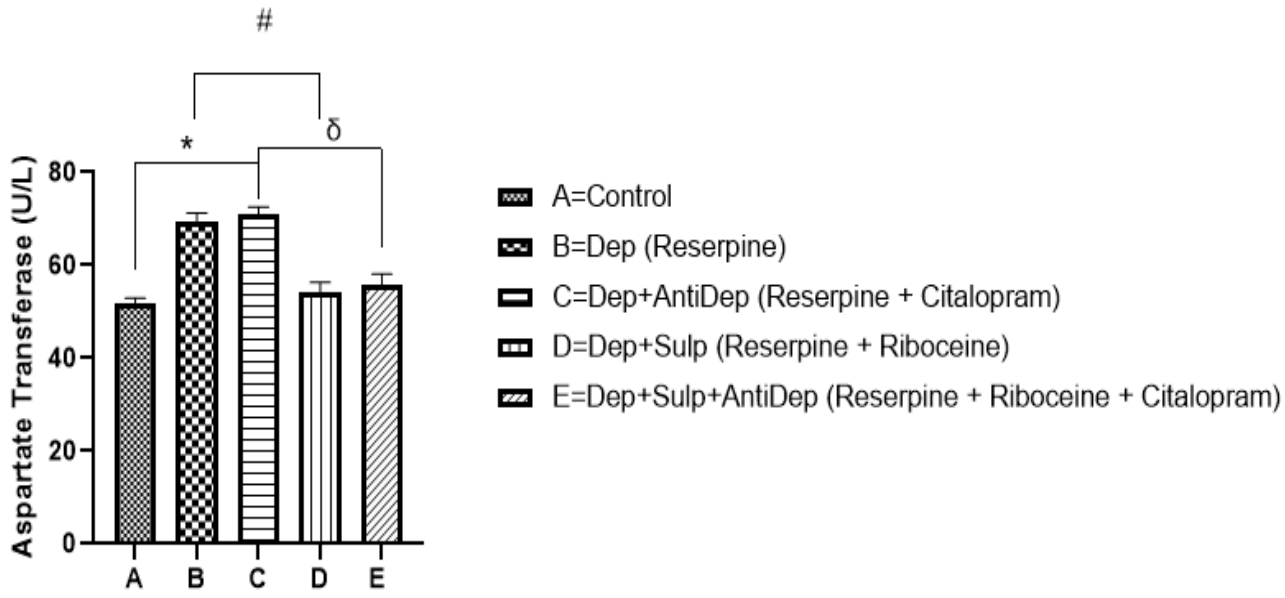

Figure 1. AST level across all groups.*represent significant difference when compared with group A; # represent significant difference when compared with group D; δ represent significant difference when compared with group E.

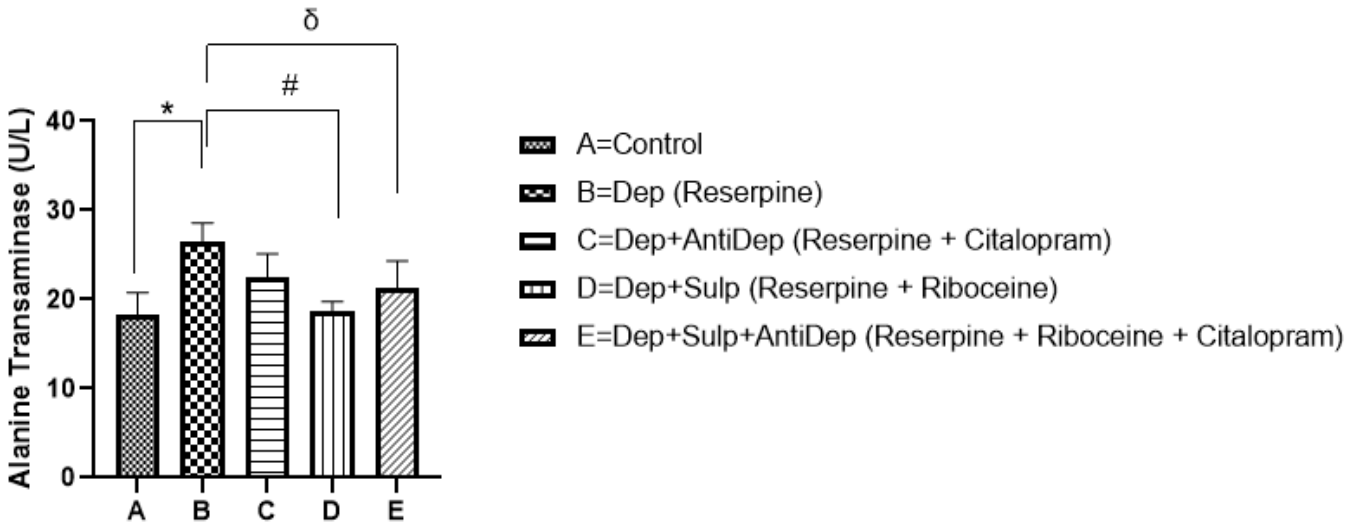

Figure 2. ALT Levels across the experimental groups. *represents significant difference when compared with group A; # represent significant difference when compared with group D; δ represent significant difference when compared with group E.

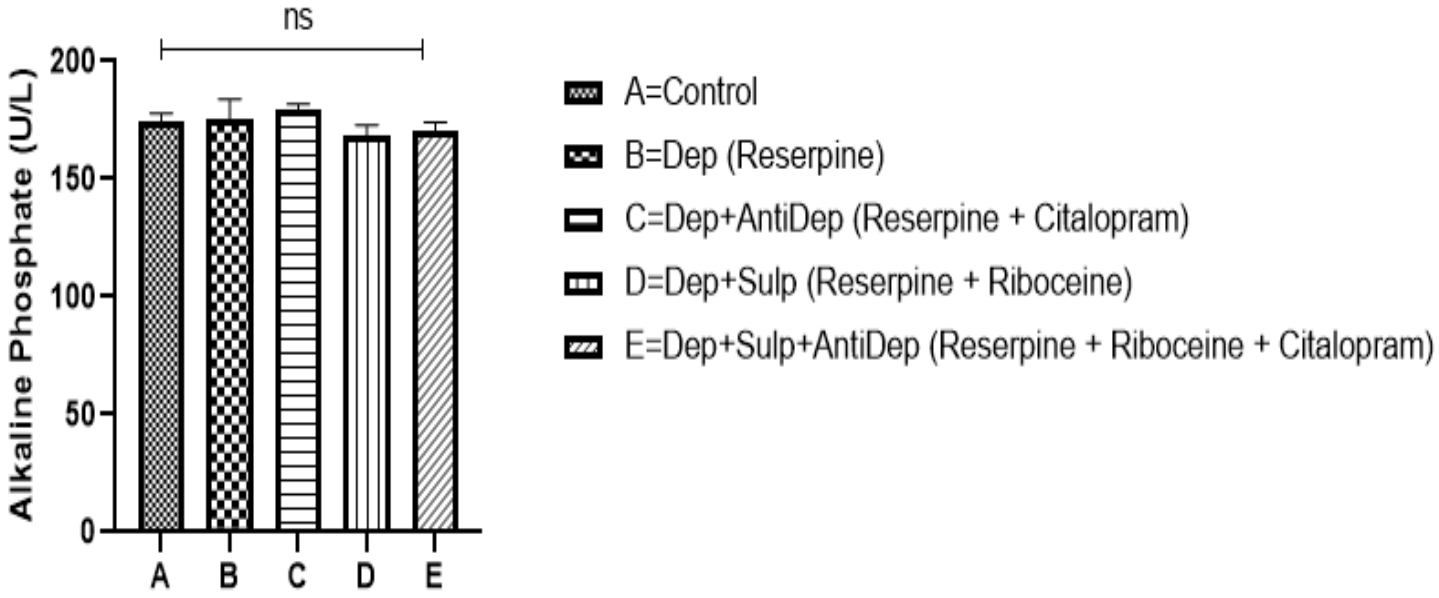

Figure 3. ALP Level across the experimental groups.*represent significant difference when compared with group A; # represent significant difference when compared with group D; δ represent significant difference when compared with group E.

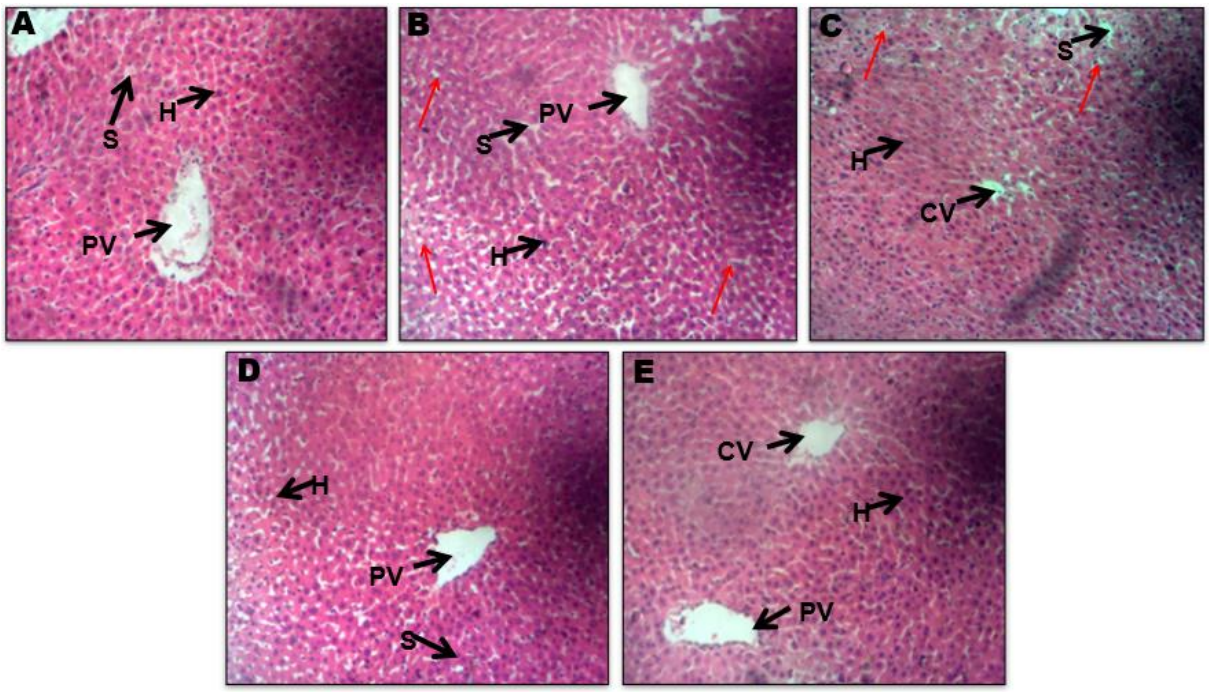

Figure 4. Photomicrographs of the liver general micromorphological presentation across the study groups (A-E). Hematoxylin and Eosin stain (×100). The hepatocytes (H), Portal vein (PV), central vein (CV) and stroma (S) are well outlined across the micrographs.

4. Discussion

The objective of this study was to examine the potential protective effect of a riboceine regimen against reserpine-induced hepatotoxicity in adult male Wistar rats. Reserpine, an antipsychotic and antihypertensive medication, has been associated with hepatotoxic effects, leading to liver damage and dysfunction (Weir, 15). The liver plays a crucial role in metabolism, detoxification, and protein synthesis, rendering it susceptible to drug-induced injury (16). The findings of this study demonstrated that the administration of a riboceine regimen effectively mitigated the hepatotoxic effects of reserpine, as evidenced by the modulation of key liver function markers in the experimental animals. The following markers are widely utilised in clinical practice for the assessment of liver health and the detection of liver injury: alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP). In this study, the rats treated with reserpine alone exhibited a significant increase in ALT and AST levels compared to the control group, thus confirming the hepatotoxic effect of reserpine. Elevated serum levels of ALT and AST are indicative of hepatocellular damage (ref.). The hepatotoxicity of reserpine observed in this study can be attributed to its ability to induce excess free radical production and oxidative stress, which are consistent with the findings of Khushboo et al. (6). The results of this study demonstrated that citalopram treatment had no significant effect against reserpine-induced hepatotoxicity. This phenomenon may be attributable to the mechanism of action in question, which has been demonstrated to exclusively involve the nervous system (18). In contrast, rats that received the riboceine regimen in conjunction with reserpine exhibited a significant attenuation of the reserpine-induced hepatotoxicity, as evidenced by the substantial reduction in ALT and AST levels. This observation is consistent with the findings of Mega Obukohwo et al. (5), which suggest that riboceine exerts a hepatoprotective effect, thereby preventing or reducing liver cell damage induced by reserpine. Riboceine has been demonstrated to enhance the synthesis of glutathione (GSH), a pivotal intracellular antioxidant that plays a substantial role in the neutralisation of free radicals and the protection of cells from oxidative stress (19). Reserpine-induced hepatotoxicity is frequently associated with increased oxidative stress (20), and the enhanced GSH production by riboceine (21) may counteract this damaging effect, leading to a reduction in liver cell injury (22). Furthermore, it has been demonstrated that hepatotoxicity is frequently accompanied by inflammation in the liver tissue (23). Riboceine has been reported to possess anti-inflammatory properties (5), which could contribute to its protective effects against reserpine-induced liver injury. Furthermore, riboceine has been demonstrated to modulate specific cell signaling pathways involved in liver injury and repair, thereby leading to a restoration of normal liver function (5). The precise molecular mechanisms underlying the hepatoprotective

action of riboceine have yet to be fully elucidated. However, there is a possibility that several potential mechanisms are responsible for its beneficial effects, which include a significant reduction in malondialdehyde (MDA) and C-reactive protein levels in liver cells, thereby protecting them from oxidative and inflammatory injury (24). The histological examination of photomicrographs from the various treatment groups is consistent with the liver function test findings previously discussed. Rats that had been administered reserpine exhibited significantly compromised hepatic morphology, as indicated by the presence of necrotic plaques and ruptured hepatic vessels (20). Nevertheless, rats treated with riboceine exhibited normal behavior and morphology, which was comparable to the control group. This finding serves to further substantiate the beneficial role of riboceine in circumventing hepatic perturbations induced by reserpine. The protective effect of riboceine, as observed in this study, carries significant implications for its potential clinical applications. Riboceine has been identified as a potential hepatoprotective agent, suggesting its potential to prevent or reduce drug-induced liver injury caused by reserpine and possibly other hepatotoxic substances. However, further studies are required to validate these results in human subjects and to explore the optimal dosing and treatment duration of riboceine for the purpose of hepatoprotection. In conclusion, the findings of this study indicate that a riboceine regimen effectively circumvents reserpine-induced hepatotoxicity in adult male Wistar rats. The modulation of key liver function markers, including ALT, AST, and ALP, supports the potential hepatoprotective role of riboceine. This research paves the way for further investigations into riboceine as a therapeutic strategy to safeguard liver health and mitigate drug-induced liver injury in clinical settings. Nevertheless, it is important to exercise caution when extrapolating these findings to human subjects until further clinical evidence is available.

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Authors' Contribution
Study concept and design: A.O.S.
Acquisition of data: J.O.F., A.O.O.
Analysis and interpretation of data: A.0.S., B.I.O., O.A.O.
Drafting of the manuscript: I.0.B., A.O.O.
Critical revision of the manuscript: A.O.S., I.O.B., B.I.O., O.A.O.
Statistical analysis: J.O.F.

Ethics
It is declared that all ethical considerations were taken into account in the preparation of the submitted manuscript.

Conflict of Interest
The authors declare that they have no conflict of interest.

Data Availability
The data that support the findings of this study are available on request from the corresponding author.

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