Original Article

Ethanol Extract of *Senecio biafrae leaves* Ameliorates Mercury Chloride-induced Hepatic Parenchymal Cell Damage in Adult Wistar Rats

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ABSTRACT

Background: Mercury chloride ($HgCl_2$) is a pervasive environmental toxin with well-documented hepatotoxic effects, primarily attributed to its ability to induce oxidative stress and disrupt cellular integrity. This study assessed the effects of ethanol extract of *Senecio biafrae* leaves (EESBL) on the histoarchitecture of adult Wistar rats following mercury chloride-induced hepatic injury.

Methods: Thirty-five adult Wistar rats were assigned to seven groups of five rats each. All groups except the control received 4 mg/kg of mercury chloride orally for 21 days, while the control received distilled water. Group 2 rats were sacrificed after mercury exposure; group 3 rats underwent a 21-day recovery. Group 4 rats received 2 mg/kg of Silymarin, and groups 5–7 received 200, 400, and 600 mg/kg of *Senecio biafrae* leaves extract, respectively, orally for 21 days. After treatment, rats were euthanized, and liver tissues were weighed, processed via paraffin wax embedding method, and stained with hematoxylin and eosin for demonstration of general histoarchitecture. Data collected were analyzed using One-way ANOVA, followed by Tukey's post hoc test for multiple comparisons. Results were expressed as mean ± standard error of mean, with a level of significance set at $p<0.05$.

Results: Histological analyses revealed that mercury chloride caused marked damage in the rats' liver histoarchitecture, showing varying degrees of cellular degeneration, hepatocyte vacuolation, congested central vein, and necroinflammation around the periportal zone. However, ethanol extract of *Senecio biafrae* leaves reversed most changes in a dose-dependent manner comparable to the silymarin-treated group.

Conclusion: The study concluded that the EESBL has an ameliorative potential in stabilizing hepatic tissue architecture and supporting structural restoration in the liver following mercury chloride-induced hepatotoxicity.

Keywords: Mercury chloride, *Senecio biafrae* leaves, Hepatic injury, Hepatocytes, Hepatic Acinus, Silymarin

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INTRODUCTION

Environmental contamination by heavy metals, especially mercury, presents a major global health concern due to their pervasive nature and toxicological impacts on human and animal health. [1, 2] Mercury chloride, a potent inorganic mercury compound, induces hepatotoxicity by generating reactive oxygen species (ROS), leading to oxidative stress, lipid peroxidation, and cellular injury. [3, 4] The resultant oxidative stress, inflammation, and cellular damage disrupt hepatic function, manifesting as elevated liver enzyme levels and histological abnormalities. [5, 6] Exposure to mercury chloride occurs through industrial effluents, contaminated water, and dietary sources, leading to accumulation in the liver. [7].

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The liver, a central organ in metabolism and detoxification, is particularly vulnerable because of its zonal organization, where different hepatocyte regions exhibit varying susceptibility to toxic insults. [8, 9] Recent research has emphasized the role of phytochemicals in mitigating heavy metal-induced toxicity. [10, 11] *Senecio biafrae* ("African spinach") is a leafy vegetable widely consumed in West Africa, valued for its nutritional and medicinal properties, and possesses antioxidant and anti-inflammatory compounds. [12, 13] However, its efficacy against heavy metal-induced hepatic injury remains underexplored. This study explores the hepatoprotective effects of the ethanol extract of *Senecio biafrae* leaves against mercury chloride-induced liver toxicity, providing insights into its potential medicinal application.

MATERIALS AND METHODS

Chemicals and Drugs

Mercury Chloride in its white crystalline form, 500 ml Diethyl ether (⩾ 99.8%), products of British Drug Home Limited, Poole, England, was supplied. Silymarin (Silybon-70®; tablets 70 mg) was manufactured by Micro Labs Limited, India.

Plant Collection and Authentication

Fresh leaves of *Senecio biafrae* were obtained from Fia market, Iyanfoworogi, via Ile–Ife, and were authenticated by a taxonomist in the Department of Botany, Obafemi Awolowo University, Ile–Ife; a voucher specimen number IFE/18215 was assigned, and the plant specimen was deposited in the Departmental herbarium for future references.

Preparation of Ethanol Extract of *Senecio biafrae* Leaves

The fresh leaves of *Senecio biafrae* were air-dried, weighed, and pulverized. The pulverized leaves of *Senecio biafrae* were extracted three times with 80% ethanol, with continuous stirring at room temperature for 24 hours each using a magnetic stirrer. The extract was filtered using Whatman number 1 filter paper, and the filtrate was concentrated *in vacuo*, using a vacuum rotary evaporator, and later freeze-dried in a lyophilizer. The ethanol extract was stored in a desiccator for future use. [14] Ethanol extraction offers broad phytochemical recovery but may alter compound stability and selectivity, leading to variability in yield, purity, and bioactive composition.

Animal Care and Management

Ethical clearance was obtained from the Health Research and Ethics Committee (HREC) of the Institute of Public Health, Obafemi Awolowo University, Ile–Ife (IPH/OAU/12/2543).

Thirty-five adult Wistar rats weighing between 130 g – 150 g were used for this study. They were procured from the Animal House of the College of Health Sciences, OAU, Ile–Ife. The rats were housed in plastic cages, kept under standard laboratory conditions of temperature, humidity, and light; fed on standard laboratory rat chow (Ace feed, Osogbo, Osun State, Nigeria) and given free access to clean water.

Experimental Design

The rats were assigned to seven groups of five rats each (thirty-five rats). Rats in group 1 (normal control) were administered 2 mL/kg distilled water for 42 days, while groups 2 – 7 rats received 4 mg/kg of mercury chloride dissolved in distilled water, orally, for 21 days. Twenty-four hours after the last administration of mercury chloride, group 2 rats were sacrificed immediately, group 3 rats were observed for the next 21 days, group 4 rats received 2 mg/kg of Silymarin, 12 hourly, orally for 21 days while, group 5, 6 and 7 rats were treated with 300, 400 and 600 mg/kg of ethanol extract of *Senecio biafrae* leaves respectively, orally for 21 days.

Determination of Percentage Body Weight Change

The weight of the rats was measured twice a week using a top loader weighing balance. Body weight change was expressed as the difference between the final and initial body weights divided by the initial weight, multiplied by one hundred.

$$\text{Body Weight Change (\%)} = \frac{\text{final weight} - \text{initial weight}}{\text{Initial weight}} \times 100$$

Sacrifice of rats

Twenty-four hours after the last administration, the rats were sacrificed under diethyl ether anesthesia. A midline incision on the anterior body wall was made. The whole liver was excised, weighed on a top loader weighing balance. The median lobes of each liver were dissected, and all samples were taken from a carefully dissected median lobe to maintain uniformity and remove contrary reports, as previous reports showed that liver lobes respond to hepatotoxic agents differently. [15]

Determination of Relative Liver Weight

The relative liver weight was expressed as the ratio of liver weight to final body weight multiplied by one hundred.

$$\text{Relative Liver Weight} = \frac{\text{liver weight}}{\text{final body weight}} \times 100$$

Histological Procedure

The median lobe of the rats was fixed in 10 % neutral buffered formalin (NBF) for the demonstration of general histoarchitecture, by total immersion for 48 hours, and were trimmed to about 4 – 6 mm thick. Liver tissues were processed via the paraffin wax embedding method of Drury and Wallington (1980), [16] for light microscopic examination, and 5 µm sections were produced on a rotary microtome (Laboid: LBM – RM2) and were stained with Hematoxylin and Eosin (H&E) to demonstrate general histoarchitectural features.

Photomicrography and Image Analysis

The stained sections were examined under a LEICA research microscope (DM750) connected to a digital camera (LEICA ICC50), and permanent photomicrographs were taken. Scale bars were merged on each micrograph taken.

Assessment of Hepatotoxicity

Histological scoring of the micrographs was determined by adopting the method described by Amber, [17] which involved cell counting using a computer running image analysis software (ImageJ® NIH, US) according to the manufacturer's specifications. The ImageJ® cell counter plugin tool for the analysis of specific cells of the micrographs was employed. The cell counts were obtained, means were computed and analyzed. For quantifying hepatotoxicity, hepatocytes were counted in 7 high-power fields (400x) of H and E-stained sections, taking account of the following morphological criteria: increased eosinophilia, cell swelling and lysis, intranuclear vacuolation, pyknosis, karyorrhexis, around zone 1, 2, and 3 of hepatic acini. [18, 19] Intact hepatocytes were defined as those with round nuclei with prominent nucleoli. All specimens were examined for these features. The percentage of degenerating changes observed was estimated by evaluating the number of microscopic fields with cellular degenerative changes compared to the whole histologic sections. Severity of cellular degenerating changes was graded as depicted in Table 1, following a modification of a previously reported method. [20,21]

Statistical Analysis

Data obtained were analyzed using GraphPad Prism (*version 9.3*), and results were expressed as mean ± standard error of mean (SEM). The presence of significant differences among means of the groups was determined using one-way analysis of variance (ANOVA) with *Tukey post hoc test*. Alpha level of 0.05 was taken as significant.

RESULTS

Effects of EESBL on percentage weight change and relative liver weight of rats with mercury chloride-induced hepatic injury

Mercury chloride caused significant weight loss of the rats across the groups, with significant decrease in mercury chloride induced group only, when compared with normal control group 1 rats ($p < 0.0001$), as depicted in Fig. 1. However, in a dose-dependent manner, EESBL significantly restored weight loss in the graded doses of extract treated groups ($HgCl_2$ + 300, 400, 600 mg/kg EESBL, respectively) when compared with group 2; with the greatest increase observed in group 7 rats, while silymarin-treated group 4 rats ($p < 0.0001$) also had a significant weight gain when compared with group 2 rats. [$F = 32.00$; $p < 0.0001$].

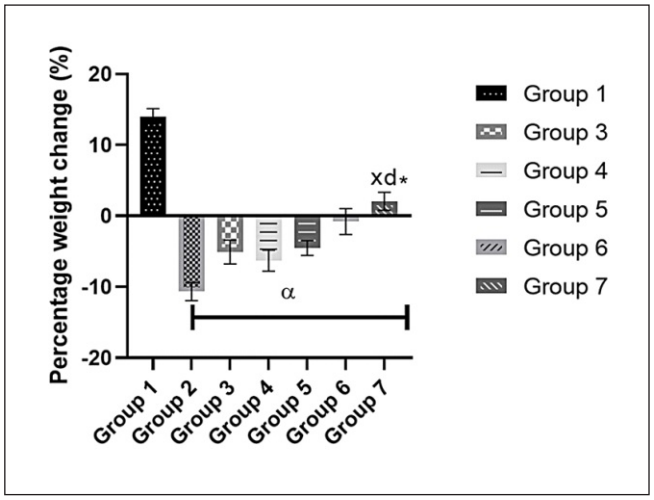

Figure 1: Effects of EESBL on percentage weight change of Wistar Rats exposed to $HgCl_2$ toxicity.
Each bar represents Mean ± SEM. The bars with superscript (α) are significantly different from the normal control, while (x) is significantly different from group 4 rats, (d) is significantly different from the low dose of EESBL, and (*) is insignificantly different from the medium dose of EESBL using one-way ANOVA, Tukey test at $p < 0.05$.

Table 1: Quantification of Cellular Degenerating Changes in the Hepatic Zones.

Percentages of occurrence	Grades	Grades indication
0	0	None
<20	1+	Mild
20 – 70	2+	Marked
>70	3+	Severe

Naiki-Ito *et al.*, 2010 (modified).

Table 2: Absolute and Relative (to body weight) Liver Weights of Wistar Rats following 3 Weeks of Daily Exposure to HgCl2 Orally and 3 weeks Post Treatment with EESBL and Silymarin.

Group (n = 5)	Treatment	Final body weight (Mean) (g)	Absolute liver weight (g)	Relative liver weight (%)
1	2 mL/kg distilled water	162.94	3.76 ± 0.10	2.31 ± 0.11
2	4 mg/kg $HgCl_2$	124.16	2.51 ± 0.22^{a}	2.02 ± 0.19^{b}
3	4 mg/kg $HgCl_2$ + Withdrawal	133.92	4.46 ± 0.16^{bx}	3.33 ± 0.14^{ax}
4	4 mg/kg $HgCl_2$ + 2 mg/kg of Silymarin	129.48	5.60 ± 0.05^{ax}	4.33 ± 0.05^{ax}
5	4 mg/kg $HgCl_2$ + 300 mg/kg EESBL	135.34	4.86 ± 0.24^{ax}	3.60 ± 0.21^{ax}
6	4 mg/kg $HgCl_2$ + 400 mg/kg EESBL	138.32	4.92 ± 0.28^{ax}	3.55 ± 0.17^{ax}
7	4 mg/kg $HgCl_2$ + 600 mg/kg EESBL	144.24	4.99 ± 0.35^{ax}	3.46 ± 0.24^{ax}
			F = 21; p = <0.0001	**F = 22; p = <0.0001**

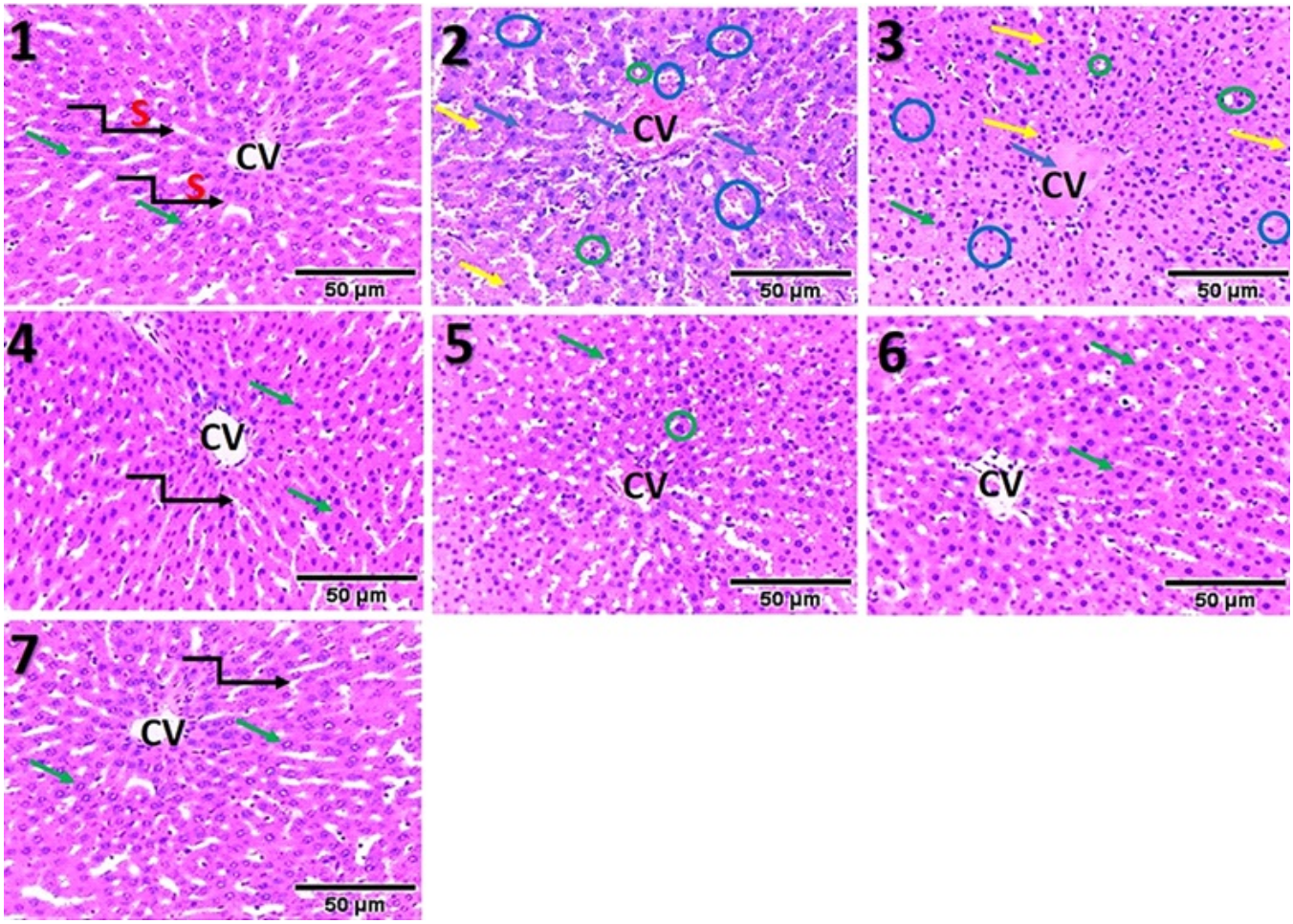

Figure 2: [1 – 7] Representative light micrographs of Sections of liver subjected to H&E stain at zone 3.
Observe [1] Hepatocytes (H) polyhedral in shape with prominent central vein (cv), eccentrically placed rounded euchromatic nuclei with prominent nucleoli (green arrow) & endothelial cells (EC) lining the radially apparent sinusoids (S) [2][3][5] shows features cell degeneration; pyknosis (yellow arrow), and hepatocellular vacuolation (Green circle), hemorrhagic congestion in the central vein and sinusoidal dilatation (blue arrow), also seen are areas of necrosis (red circle) [4][6][7] features are similar to control with rounded nuclei and prominent nucleoli (black arrow) and radially apparent sinusoids (S). Scale bars – 50μm.

Table 3: Histological Scores of Liver Damages induced by HgCl2 and the Effects of EESBL and Silymarin treatments on cellular degeneration at Zone 1, 2, and 3 of hepatic acinus

Groups	Treatments	0	1+	2+	3+
1	2mL / kg distilled water	7 (100)	0 (0)	0 (0)	0 (0)
2	4 mg/kg $HgCl_2$ only	0 (0)	0 (0)	6 (86)	1 (14)
3	4 mg/kg $HgCl_2$ + recovery	0 (0)	0 (0)	6 (86)	1 (14)
4	4 mg/kg $HgCl_2$ + silymarin	0 (0)	4 (57)	3 (43)	0 (0)
5	4 mg/kg $HgCl_2$ + 300 mg/kg bw EESBL	0 (0)	0 (0)	6 (86)	1 (14)
6	4 mg/kg $HgCl_2$ + 400 mg/kg bw EESBL	3 (43)	2 (29)	1 (14)	1 (14)
7	4 mg/kg $HgCl_2$ + 600 mg/kg bw EESBL	5 (71)	1 (14)	1 (14)	0 (0)

Numbers of high-power fields are shown, with percentages enclosed within parenthesis. n = 5.

Grade indication: no change (0), mild (1+), marked (2+), severe (3+).

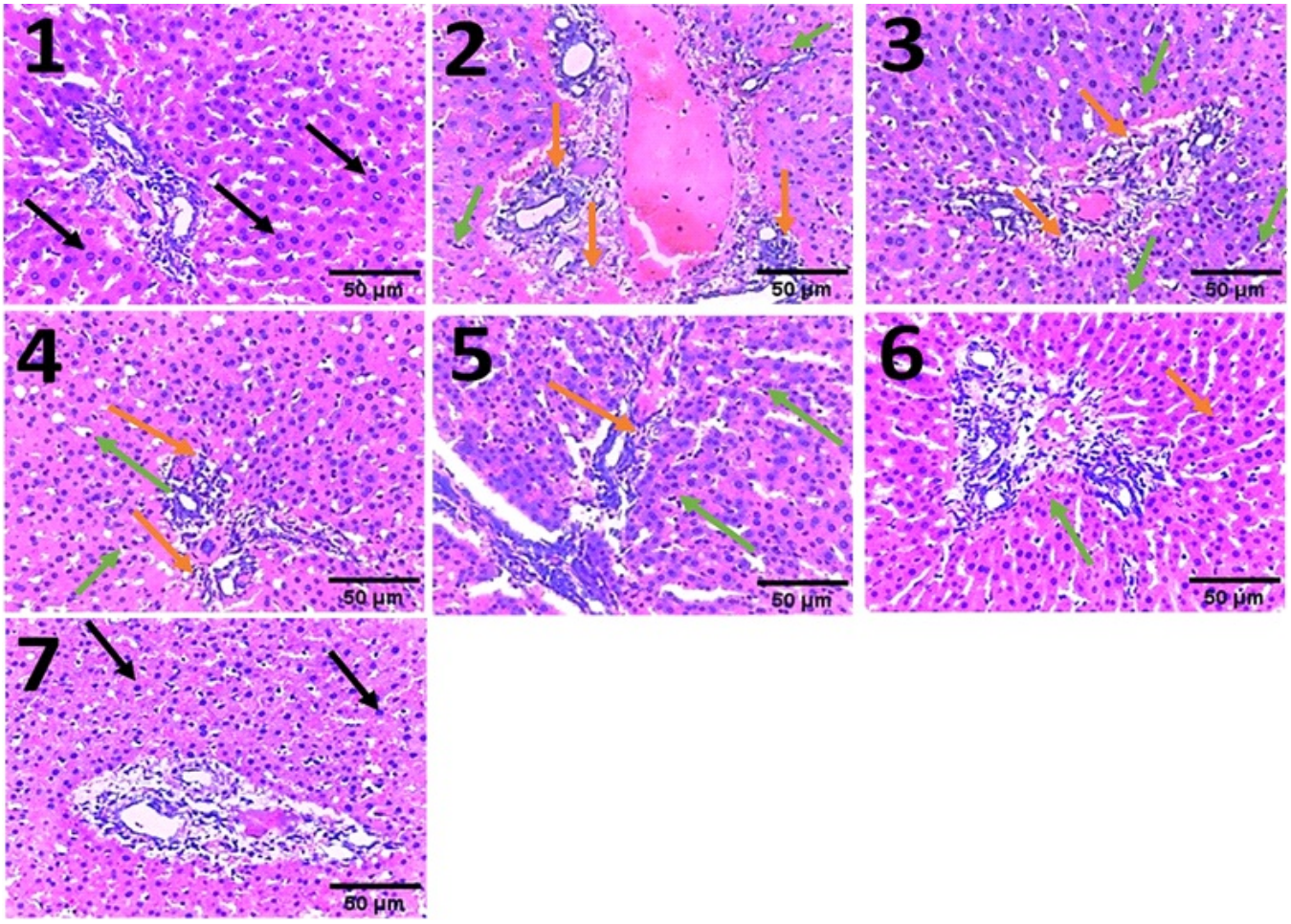

Figure 3: [1 – 7] Representative light micrographs of Sections of liver subjected to H&E stain at zone 1: Observe [1] polyhedral hepatocytes, their round nuclei with prominent nucleoli (black arrow) [2][3][5] tissue degeneration with periportal and diffuse lobular necroinflammation (orange arrow). Also seen is Kupffer cell hyperplasia (green arrow). [1][4][6][7] shows preserved architecture and reparative changes. Scale bars – 50μm.

There was a significant effect of mercury chloride and EESBL on the relative liver weight of rats across the groups when compared with the normal control, as shown in Table 2.

Values were expressed as mean ± SEM of five rats in each group**.** Groups with the superscript a are significantly different from the normal control group. In contrast, superscript b is not significant to the normal control group, superscript x is significantly different from the observed, Silymarin-treated, low dose, mid dose, and high dose of EESBL groups, when compared to the negative control group using one-way ANOVA, Tukey test at $p < 0.05$.

Histological Observation

Results of histological observation of Wistar rats' liver stained with Hematoxylin and Eosin (H&E) sections around zones 1, 2 and 3 of hepatic acinus revealed the following as depicted in fig. 2 and 3, the centrilobular zone (zone 3) of the hepatic acinus of control rats produced intact morphological features, some of which include polyhedral hepatocytes, with characteristically round euchromatic nuclei with prominent nucleoli and normal radiating sinusoids. Most of these characteristics of the normal liver features were also observed in the rats treated with medium and high doses of EESBL in the same manner as presented by silymarin-treated rats. However, mercury chloride induced areas of necrosis with numerous cytoplasmic and nuclear necrotic morphological changes in groups 2 and 3 rats. These groups also showed disheveled architecture, intranuclear vesiculations and vacuolations, hemorrhagic congestion in the central vein and sinusoidal dilatation. Rats treated with low-dose EESBL also presented some of these abnormal morphological features, as shown in Fig. 2.

As depicted in Fig. 3, the periportal zone (zone 1) of the hepatic acinus, the normal control group 1 rats revealed a well–preserved hepatic architecture, the portal triad was distinct, comprising a centrally located portal vein, a smaller hepatic artery, and a bile ductule lined by cuboidal epithelium. The sinusoids were lined with endothelial cells and Kupffer cells, without evidence of congestion or structural disruption. No necroinflammation, cytoplasmic vacuolations, or fibrosis was observed. Rats in group 2 induced with mercury chloride produced tissue degeneration with periportal and diffuse lobular necroinflammation; the portal triad appeared congested, with dilated portal veins and inflammatory cell infiltration. This is also mildly shown with rats in groups 3 and 5 with inflammatory foci, primarily composed of macrophages and lymphocytes, which were scattered throughout the lobules. The rats treated with medium dose and high dose of EESBL show preserved architecture and reparative changes comparable to the normal control group and silymarin-treated group, as shown in Fig. 3.

Histological Scoring of Cellular Degeneration Changes in the Hepatic Acinus Zones 1, 2, and 3

The histological scores of liver damage induced by mercury chloride and the effects of EESBL and Silymarin treatments on cellular degeneration at zones 1, 2, and 3 in the seven experimental groups as shown in Table 3. The normal control group 1 rats showed prominent intact hepatocyte nuclei and no degenerative changes. However, mercury chloride induced significant cellular degeneration in negative control rats of groups 2 and 3 rats with a high number of necrotic hepatocytes across the 7 seven high-power fields considered, when compared with the normal control group 1 rats. However, EESBL significantly reduced these cellular degenerating features with fewer necrotic hepatocytes and more percentage of intact hepatocytes in a dose-dependent manner in groups 5, 6, and 7 rats, which is similar to what was observed in silymarin-treated rats, when compared with the negative control group 2 rats [$p < 0.0001$].

DISCUSSION

Liver injury is a significant pathological condition that impairs hepatic function, disrupts metabolic homeostasis, and predisposes individuals to severe systemic complications. [22, 23] It can result from various etiologies, including exposure to toxicants, drug-induced damage, viral infections, and metabolic disorders. [24] Among environmental toxins, heavy metals such as mercury chloride are a potent hepatotoxin, which has long been known for its ability to disrupt liver function, often leading to systemic issues such as weight loss and liver enlargement. [25] Understanding the mechanisms of liver injury and identifying potential therapeutic interventions are crucial for ameliorating hepatic damage and preserving liver function. The effects of the ethanol extract of *Senecio biafrae* leaves against mercury chloride-induced hepatic injury can be attributed to its multifaceted mechanisms of action. Phytochemical analyses have identified flavonoids, polyphenols, saponins, and alkaloids in the leaves of *Senecio biafrae*, which exhibit antioxidant, anti-inflammatory, and hepatoprotective properties. [14, 26] These bioactive compounds in *Senecio biafrae* contribute to maintaining hepatic cellular integrity and supporting the liver's structural stability against mercury chloride-induced damage. [21, 27]

Body weight is a critical indicator of overall health in experimental animals. [28] In this study, at the beginning of the experiment, there was no significant difference in body weight among the various groups of rats, which suggests that the experimental design was robust and that each group started from a comparable baseline. This is consistent with typical toxicology research practices that aim to eliminate confounding variables. [29] However, rats exposed to mercury chloride (groups 2 – 7) exhibited a significant reduction in body weight, reflecting the well-documented toxic effects of mercury chloride when compared with the normal control group rats. The loss of body weight seen in this study corroborates the findings from other research that highlights the ability of mercury chloride to cause metabolic disruptions and reduce nutrient absorption, thus leading to systemic weight loss. [30]

The liver plays a central role in energy metabolism, and hepatic injury often leads to impaired protein and lipid metabolism, further causing weight loss. [31]

However, this study focused on how treatment with EESBL and silymarin influenced the recovery of body weight. Although the rats treated with EESBL and silymarin did show an increase in weight, the recovery was inconsistent, fluctuating throughout the experimental period. This

inconsistent weight gain might suggest that while both EESBL and silymarin have therapeutic potential, their ability to restore body weight after severe liver toxicity may be limited or require a longer recovery period. The observation that EESBL caused a dose-dependent increase in body weight, especially at higher doses, aligns with existing research on the therapeutic properties of *Senecio biafrae*. [32]

This study demonstrated a significant increase in both absolute and relative liver weight in groups (3-7) in Wistar rats treated with silymarin, EESBL, and the withdrawal group following exposure to mercury chloride. This increase was notably higher compared to the control group; this is suggestive of hepatocellular hypertrophy. Cellular hypertrophy observed in this study suggests adaptive hypertrophy rather than adverse hepatomegaly, which is an adaptive response to toxic injury and regeneration stimuli in the liver. [33] Following toxicant withdrawal, such as mercury chloride or therapeutic intervention (silymarin, EESBL), the liver initiates a regenerative response aimed at restoring tissue integrity and function. [34] In the situation where mitotic activity is delayed or limited, hypertrophic growth of surviving hepatocytes often serves as a compensatory mechanism. [34] This phenomenon is characterized by increased cytoplasmic volume, nuclear enlargement, and organelle content, allowing hepatocytes to sustain metabolic functions and tissue repair. [35] In this study, the increased liver weights in the silymarin and EESBL-treated groups likely reflect such a hypertrophic response. In the mercury chloride-treated group, absolute and relative liver weight decreased, indicating hepatocellular necrosis and tissue degeneration. [36] Hepatotoxic agents often induce hepatocyte swelling, congestion, and inflammatory infiltration, contributing to increased liver weight.

Histopathological evaluation of liver sections from the mercury chloride-treated rats in this study revealed marked structural alterations, confirming significant hepatocellular damage. It provided crucial insights into the extent of hepatic damage, tissue integrity, and the hepatoprotective potential of EESBL. The liver parenchymal cells (hepatocytes) are organized within the hepatic acinus into three metabolic zones based on proximity to the portal triad and oxygen supply. [37] Mercury chloride-induced hepatotoxicity disrupts this zonal organization, leading to hepatocellular damage, sinusoidal congestion, and inflammatory infiltration. Histological analyses of mercury chloride-induced liver revealed marked histological abnormalities, including widespread hepatocyte degeneration, ballooning, sinusoidal congestion, and intense inflammatory cell infiltration. The sinusoidal and endothelial damage, marked by congestion and Kupffer cell hyperplasia, further compromises hepatic microcirculation, worsening hepatocellular necrosis. [38] Also, Mercury chloride exposure impairs bile canaliculi, contributing to cholestasis and portal inflammation. [39] These findings confirm the hepatotoxic effects of mercury chloride and its capacity to induce significant structural alterations in the liver. The necrotic changes observed in this study are consistent with the findings of a recent study, [40] which reported similar nuclear alterations, including pyknosis, in the liver tissues of rats treated with mercury chloride. Hepatocellular vacuolation, a prominent histopathological alteration observed in this study, reflects intracellular edema resulting from cellular injury and impaired ion transport mechanisms, leading to disrupted hepatic parenchymal architecture. [41] This is a well-documented response to toxicant exposure; in contrast, liver sections from groups 4, 5, 6, and 7, respectively, demonstrated significant improvements. Hepatocyte morphology was largely preserved, with reduced evidence of degeneration and necrosis. Sinusoidal congestion and inflammatory cell infiltration were notably reduced, indicating a stabilization of hepatic microvascular architecture and a moderated immune cell response following EESBL treatment. The dose-dependent ameliorative effect of EESBL observed in this study suggests that higher doses of the extract enhance the preservation of hepatic parenchymal cells and mitigate the severity of mercury chloride-induced histopathological alterations, as confirmed by the improved liver architecture at the highest dose of 600 mg/kg, which is comparable to the silymarin-treated group, indicating the safety of EESBL at the administered dose. The control group exhibited normal liver histoarchitecture, including the characteristic appearance of hepatic lobules, well-arranged hepatocytes, and intact central veins. The liver tissue appeared healthy, with well-organized anastomosing plates of hepatocytes radiating from the central vein and clearly defined sinusoids. This normal liver architecture is essential for optimal liver function, including metabolism, detoxification, and the synthesis of vital proteins and enzymes; [42] EESBL helps maintain cellular integrity and prevents hepatocellular damage. Additionally, the hepatoprotective effects of EESBL are evident in its ability to preserve liver parenchymal cells and histoarchitecture by reducing inflammatory cell infiltration, cytokine production, and limiting structural disruptions.

CONCLUSION

The study concluded that mercury chloride-induced hepatotoxicity disrupts hepatic histoarchitecture, causing hepatocyte degeneration and inflammatory infiltration. However, EESBL ameliorated these alterations, preserving liver morphology, stabilizing hepatic tissue architecture, and supporting structural restoration in the liver. These findings highlight the structural-functional relationship of the liver and the importance of hepatic zonation in toxicant susceptibility and repair.

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Conflict of Interest: The authors declare no conflict of interest.

Criteria for Inclusion of Authors: Prof. D.O. Adeyemi and Mr. A.O. Ibitoye conceived and designed the study; AO, Ibitoye analyzed and interpreted the data. DO, Adeyemi, supervised the research.

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