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Histopathological Evaluation of the Effects of Siam Weed in Cadmium Induced Toxicity on the Liver of Wistar Rat

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Siam plant (*Chromolaena odorata*) is a plant with a characteristic aromatic smell, since ancient times, had been of interest for medical purposes in the local parlance and had been reported to be used in tradition medicine as antispasmodic, antiprotozoal, anti trypanosomal, antibacterial, antifungal, antihypertensive, anti-inflamatory, astringent, diuretic and hepatotropic agent. The aim of this study is to assess the histological impact of Siam weed on liver damage produced by Cadmium in adult Wistar rats. A total of twentyfive albino Wistar rats were obtained for the experiment. The rats were divided into five groups (A - E) and subjected to various treatments. At the end of administration the liver of the animals was harvested and processed histologically and photomicrographs taken. The photomicrographic images exhibits central vein (CV) and portal tract congestion, together with necrotic regions, sinusoidal space blockage, focal foci of haemorrhage (shown by an arrow), and the presence of Kupffer cells. The study revealed that the intraperitoneal

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administration of Cadmium in rats resulted in notable hepatotoxicity, as evidenced by histopathological alterations and degeneration of hepatocytes. Conversely, the oral ingestion of Chromolaena Odorata did not have any impact on the liver toxicity induced by Cadmium in rats.

Keywords: Chromolaena odorata; cadmium; liver; hepatocytes; Siam weed.

1. INTRODUCTION

The Siam plant, scientifically known as Chromolaena Odorata, is a highly aromatic plant that has been historically valued for its medicinal properties. It has been traditionally used in local medicine as an antispasmodic, antiprotozoal, antitrypanosomal, antibacterial, antifungal, antihypertensive, anti-inflammatory, astringent, diuretic, and hepatotropic agent [1]. The plant is a herbaceous, perennial, semi-woody shrub that grows into dense, tangled bushes reaching a height of approximately 1.5 to 2.0 metres. This plant is a fast-growing shrub that is native to the Americas and is known for its ability to thrive in areas with poor soil conditions. It has been introduced into several biological regions of tropical lands, originating from Southern Mexico [2]. C. odorata is known as Independence leaf, ewe Awolowo, Akintola taku by the Yoruba people, and obu inenawa by the Igbo people, who are two prominent ethnic groups in Nigeria. Siam weed is acknowledged as one of the most detrimental tropical weeds globally. The growth rate of this plant is exceptionally rapid, reaching up to 20 mm per day. Additionally, it exhibits abundant seed production [2]. The liver serves as a primary site for the accumulation of Cd and other harmful substances. Multiple studies indicate that Cd induces hepatotoxicity. The hepatotoxicity of this metal is characterised by the disruption of certain plasmatic enzymes, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and lactate dehydrogenase. Intoxication with Cd can cause various morphological alterations in hepatic tissue, as seen by Koyu et al [3]. Furthermore, Cd-induced hepatotoxicity is facilitated by the increased expression of reactive oxygen species (ROS), such as hydroxyl groups, superoxides, and hydrogen peroxides, leading to oxidative harm to lipid components of membranes. The application of metal therapy induces significant alterations in the liver, including inflammation and extensive accumulation of fat in liver cells, as well as the presence of huge fluid-filled spaces in the cytoplasm. The cytoplasm of hepatocytes exhibits vacuoles, and the nuclei display pyknotic changes with a reduced staining affinity. This is attributed to the damage caused to the hepatic cells following treatment with Cd. Furthermore, it was noted that the damage to hepatic cells escalates proportionally with the rise in dosage. Apoptosis was observed at a dosage of 10 mg/kg of Cd administered to the body weight, as reported by Gathwan et al. [4]. This finding aligns with the study conducted by Brzoska et al.[5], which found an 8% reduction in liver weight of Wistar rats after the administration of Cd, with statistical significance ($P < 0.05$). The study conducted by Mohapatra et al. [6] found that the liver tissue of mice treated with Cd showed histopathological changes. These changes included the disruption of hepatocytic plates, disintegration of hepatocytes characterised by the rupture of cell membrane, cytoplasmic vacuolization, and pycnosis of nuclei. The findings were consistent with those of El-Refaiy [7], who observed severe liver necrosis, fatty alterations, degeneration symptoms, and inflammatory cell infiltrations in rats treated with Cd. The liver's histological alterations resulting from Cd treatment may be attributed to the generation of extremely reactive radicals and subsequent lipid peroxidation. Hepatotoxicity can be caused by the accumulation of hydroperoxidase, which is linked to the peroxidation of membrane phospholipids by lipid hydroperoxidase. This is the underlying mechanism of hepatocellular injury [8]. To assess the histological impact of Siam weed on liver damage produced by Cadmium in adult Wistar rats.

2. MATERIALS AND METHODS

2.1 Location of Study

The study was conducted in the Department of Medical Laboratory Science, Faculty of Basic Medical Sciences, College of Health Sciences, Niger Delta University, located at Wilberforce Island Amassoma, Bayelsa State, Nigeria.

2.2 Procurement of Leaf (*Chromolaena odorata*)

The leaf was acquired from Amassoma, located along the new site road in Niger Delta University,

Bayelsa State and identified by Botany department of the University and samples deposited in the herbarium.

2.3 Extraction of Plant

The plant was rinsed in water severally to remove dirty particles initially before drying by subjecting it to a temperature of 50 degrees in a hot air oven and this was done aspectically. The substance was desiccated until it achieved a crisp texture, and subsequently pulverised into a fine powder. A total of 300 millilitres of pure alcohol was utilized to immerse 50 grammes of the powdered leaf, which was then kept undisturbed for a duration of 72 hours. Following a period of 72 hours, the mixture underwent filtration utilizing a sterile gauze. The extract was subsequently subjected to autoclaving and incubation until it reached a pasty consistency. The paste served as the base substance that was measured and given to the laboratory animals (Wistar rat) based on the lethal dosage of the leaf.

2.4 Experimental Animals

A total of twenty five(25) albino Wistar rats,3months old weighing 170±3.4g -220±3.0g were obtained for the experiment.The rats were from two closely related parents breed under the same condition.

2.5 Housing

The animals were kept in a hygienic laboratory animal facility at a temperature range of 27±20°C, with a twelve-hour cycle of light and darkness. The albino wistar rats were nourished with regular feed pellets from Guinea Feed Nigeria Ltd, and they were also provided with clean water.

2.6 Study Duration

The process lasted for a total of six weeks, with the first two weeks dedicated to acclimatisation and the next two weeks focused on drug administration.

2.7 Route of Administration

- Cadmium was administered intraperitoneally
- Siam leaf (*Chromolaena Odorata)* extract was administered orally using orogastric tube

2.8 Sample Collection

After the weeks of providing substances, the animals were euthanized using chloroform as an anaesthetic. The rats were dissected in order to extract the liver, which was promptly preserved using a 10% formalin solution according to the method of Eric et al [9].

2.9 Tissue Processing

The tissue underwent conventional histological tissue processing, including embedding, sectioning, and staining using the Haematoxylin and Eosin staining protocol at the Histopathology laboratory of Niger Delta Teaching Hospital (NDUTH) in Okolobiri..

2.10 Hematoxylin and Eosin Staining

Hematoxylin and eosin are the primary stains employed to see the nucleus and cytoplasmic inclusions.

Foundational concepts: Hematoxylin is a cationic dye that selectively stains the acidic component of the tissue, specifically the nucleus. On the other hand, eosin is an anionic dye that selectively stains the basic component of the tissue, specifically the cytoplasm.

2.11 Staining Protocol

The sections were treated with two rounds of xylene to remove the wax until it was completely removed.

We hydrated the sections in decreasing concentrations of alcohol, starting from 100% alcohol, then 80% alcohol, followed by 70% alcohol, and finally water.

The sections were stained with Harris Hematoxylin and subsequently washed in water. The tissue sections were differentiated in 1% acid alcohol until the nucleus retained the stain. The tissue sections were immersed in tap water containing Scot's solution for a duration of 2 minutes, resulting in a blue coloration.

Subsequently, the sections underwent counterstaining with Eosin for a duration of 2 minutes. The sections were desiccated using increasing concentrations of alcohol (two changes of 70%, 95%, and two changes of 100% alcohol).

List 1. Experimental design

Group A	Group B	Group C	Group D	Group E
Control Received only feed and water for 14 days	Received feed and cadmium(0.6ml) for 14 days	Received feed and water and cadmium (0.6ml) and high dose of *C. Odorata* extract 800mg/kg for 14 days	Received feed and water and cadmium (0.6ml) and low dose of *C. Odorata* extract 400mg/kg for 14 days	Received feed and water and *C. Odorata* extract 800mg/kg for 14 days

The tissue sections were clarified and affixed using DPX. 6. The tissue sections were observed under a microscope.

2.12 Microscopy

The specimens were examined using an Olympus binocular light microscope at a magnification of 40X. Subsequently, the sections were captured as photomicrographs using a digital Techno camera connected to the microscope.

3. RESULTS

3.1 Histology Photomicrograph

Fig.1. Shows the morphology of the liver after the administration of the various treatments for 14 days. Slide shows normal morphology of the liver,central vein (CV),hepatocytes (H) with intact sinusoidal space (S) (X10)(X40)H&E

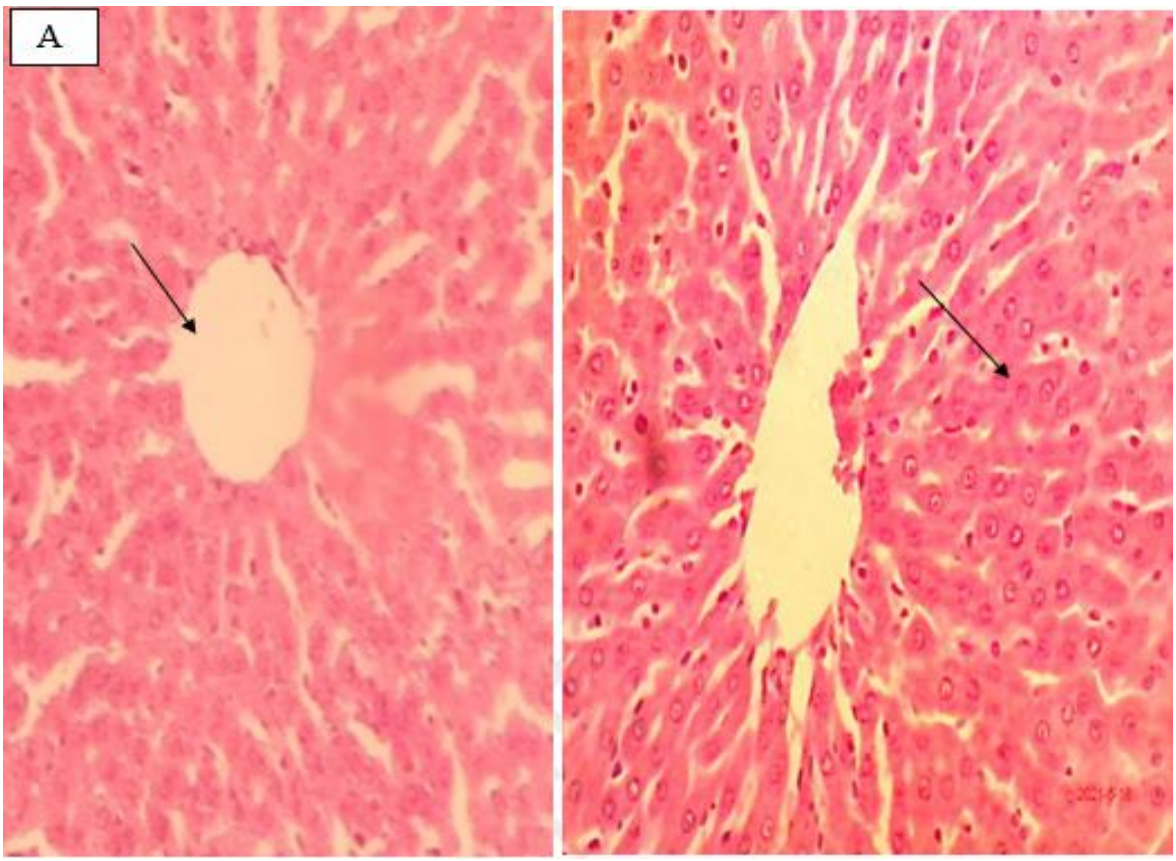

Fig. 1. Depicts the liver's morphology following the administration of different medications for a duration of 14 days. The slide displays the typical structure of the liver, including the central vein (CV) and intact hepatocytes (H) with sinusoidal space (S) visible. The magnification used for the images is X10 and X40.H&E refers to Hematoxylin and Eosin, a commonly used staining technique in histology to visualise cellular structures and tissue components

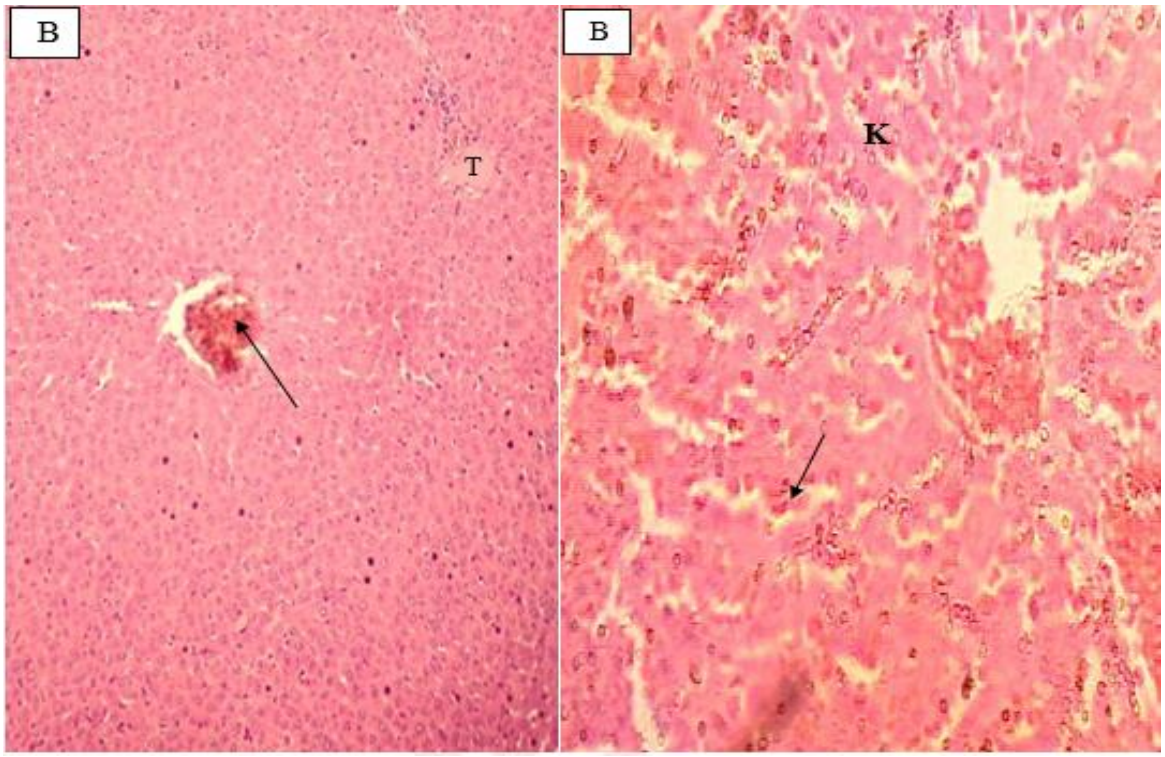

Fig. 2. Shows the morphology of the liver after the administration of the various treatments for 14 days. Slide shows congestion of central vein (CV) and portal tract(T) with areas of necrosis, occlusion of sinusoidal space and focal areas of heamorrhage(arrow), presence of Kupffer cells (K) (X10) (X40) H&E

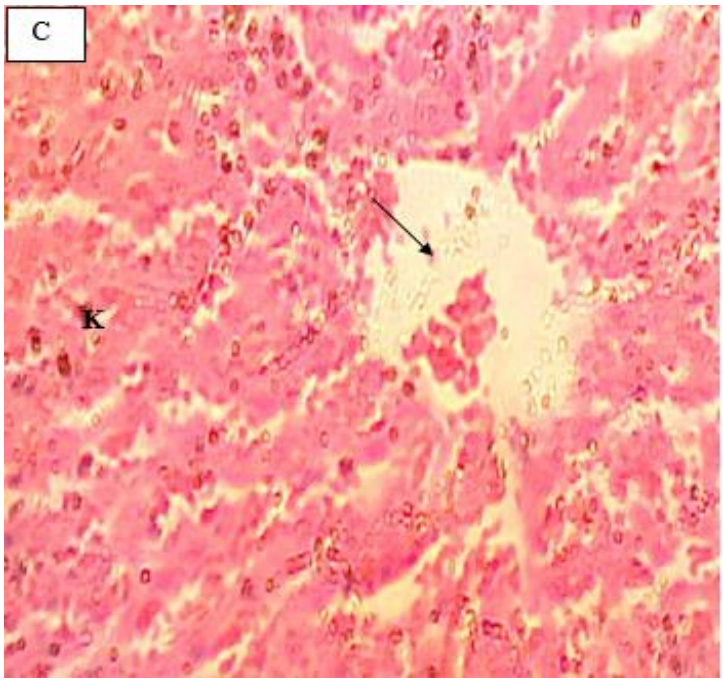

Fig. 3. Shows the morphology of the liver after the administration of the various treatments for 14 days. Slide shows the degeneration of wall of the central vein (CV) with areas of necrosis,occluded sinusoidal space with degeneration of hepatocytes(V) and presence of Kupffer cells (K) (X10) H&E

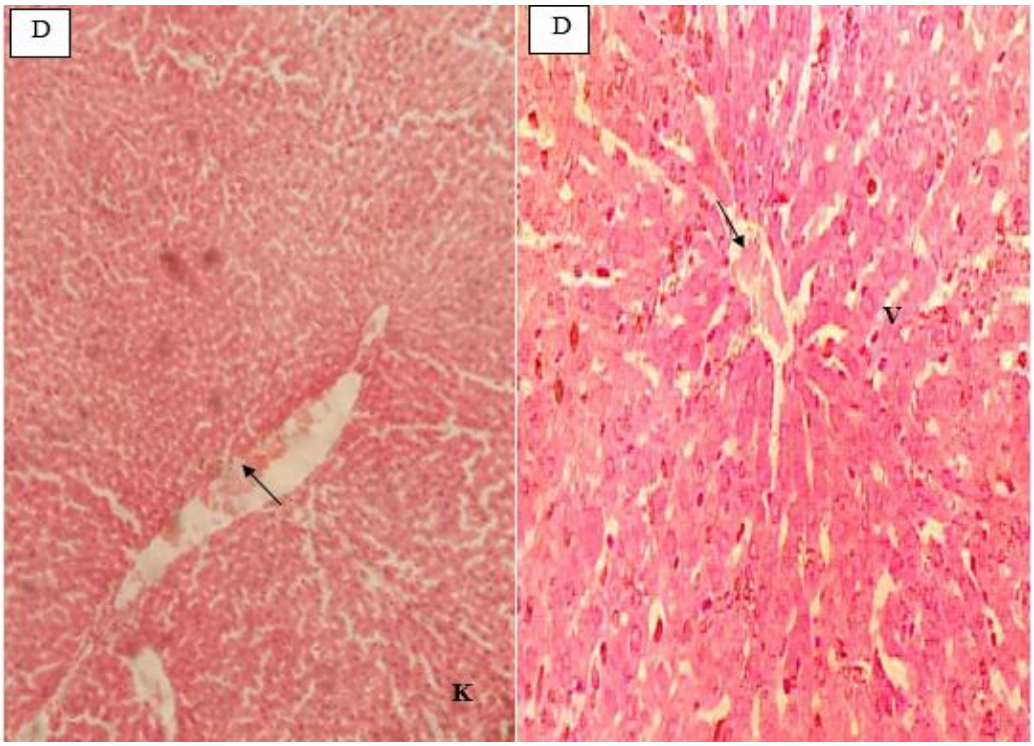

Fig. 4. Shows the morphology of the liver after the administration of the various treatments for 14 days. Slide shows the central vein (CV), occluded sinusoidal space (S) with vacuolar degeneration of hepatocytes(V) and presence of Kupffer cells (K) (X10) (X40) H&E

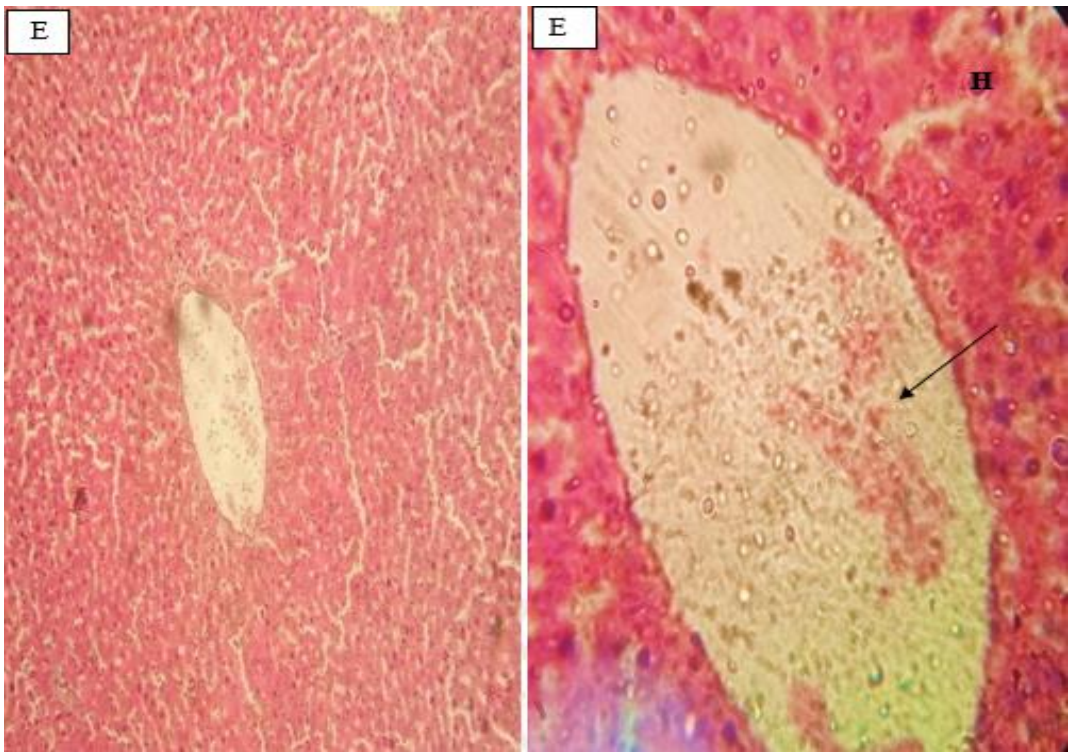

Fig. 5. Shows the morphology of the liver after the administration of the various treatments for 14 days. Slide shows normal morphology of the liver, central vein (CV), hepatocytes (H) with intact sinusoidal space (S) (X10) (X40)H&E

Fig. 2 shows the morphology of the liver after the administration of the various treatments for 14 days. Slide shows congestion of central vein (CV) and portal tract(T) with areas of necrosis, occlusion of sinusoidal space and focal areas of heamorrhage(arrow), presence of Kupffer cells (K) (X10) (X40) H&E.

Fig.3 Shows the morphology of the liver after the administration of the various treatments for 14 days. Slide shows the degeneration of wall of the central vein (CV) with areas of necrosis,occluded sinusoidal space with degeneration of hepatocytes(V) and presence of Kupffer cells (K) (X10) H&E.

Fig.4 Shows the morphology of the liver after the administration of the various treatments for 14 days. Slide shows the central vein (CV), occluded sinusoidal space (S) with vacuolar degeneration of hepatocytes(V) and presence of Kupffer cells (K) (X10) (X40) H&E.

Fig.5 Shows the morphology of the liver after the administration of the various treatments for 14 days. Slide shows normal morphology of the liver, central vein (CV)hepatocytes (H) with intact sinusoidal space (S) (X10)(X40)H&E.

4. DISCUSSION

The Siam plant, scientifically referred to as Chromolaena Odorata, is extensively utilised for its medicinal properties in traditional societies. It is renowned for its importance in the process of wound healing and treatment of many medical conditions. This study aims to evaluate the histopathological impact of Chromolaena Odorata on liver damage induced by Cadmium in adult Wistar rats. The experiment involved a total of twenty-five rats. The rats were divided into five groups (A - E) and subjected to various treatments. Fig 1-5 displays the structure of the liver following the application of different therapies for a duration of 14 days, observed at a magnification of x400. The slide designated group A depicts the experimental animals in the control group that received both food and water. The subjects assigned to group B were the ones who received cadmium, as well as feed and water. The slide designated group C displays the liver of the animals that were offered a high dose (800mg/kg) of the extract (Chromolaena Odorata), together with meal, water, and cadmium. The slides marked as group D depict animals that received a low dose (400mg/kg) of the Chromolaena Odorata extract, whereas the slides labelled as group E indicate animals that were provided with feed, water, and a higher dose (800mg/kg) of the extract.

The liver morphology of the animals in the control group (Fig 1) was undamaged. The slide displays a typical histological image of the liver, showing a central vein and hepatocytes with an intact sinusoidal area.

Fig 2 depicts the anatomical structure of the liver in rats that were given cadmium. The image exhibits central vein (CV) and portal tract congestion, together with necrotic regions, sinusoidal space blockage, focal foci of haemorrhage (shown by an arrow), and the presence of Kupffer cells. The findings were consistent with those of El-Refaiy,[7] who observed severe liver necrosis, fatty alterations, degeneration symptoms, and inflammatory cell infiltrations in rats exposed to Cadmium. The liver's histological alterations induced by Cadmium treatment may result from the generation of extremely reactive radicals and subsequent lipid peroxidation. Hepatotoxicity can occur due to the accumulation of hydroperoxidase, which leads to the peroxidation of membrane phospholipids by lipid hydroperoxidase. This process is responsible for causing damage to hepatocytes [8]. The study conducted by Mohapatra et al.,[6] found that exposure to Cadmium in mice resulted in significant histopathological changes in the liver tissue. These changes included the disruption of hepatocytic plates, disintegration of hepatocytes characterised by cell membrane rupture, cytoplasmic vacuolization, and pycnosis of nuclei. The findings were consistent with those of El-Refaiy,[7] who observed severe liver necrosis, fatty alterations, degeneration symptoms, and inflammatory cell infiltrations in rats treated with Cadmium. The liver's histological alterations caused by Cd treatment may result from the generation of extremely reactive radicals and subsequent lipid peroxidation. Hepatotoxicity can occur due to the accumulation of hydroperoxidase, which leads to the peroxidation of membrane phospholipids by lipid hydroperoxidase. This process is responsible for causing damage to hepatocytes [8]. Furthermore, several scholars have documented the presence of a significant population of Kupffer cells within the walls of the sinusoids. The presence of a higher number of Kupffer cells suggests a defensive response to Cadmium in rats, as indicated by El-Refaiy [7].

The study demonstrated that animals treated with Cadmium and a high dosage of Chromolaena Odorata leaf extract exhibited histological alterations in the liver. These changes included degeneration of the central vein wall, necrotic areas, occluded sinusoidal space, degeneration of hepatocytes, and the presence of Kupffer cells (Fig 3). Fig 4 displays the liver morphology of rats that were administered cadmium along with a low dose (400mg/kg) of Chromolaena odorata extract. Histological alterations were observed in the central vein, with the sinusoidal space being blocked and hepatocytes showing vacuolar degeneration. Additionally, Kupffer cells were present.This finding is consistent with the research by Asomugha et al.,[10]. The consumption of Chromolaena Odorata did not result in cadmium-induced liver damage in rats, even at a dosage of 800mg/kg. Cadmium has been observed to induce hepatotoxicity. The hepatotoxicity of this metal is demonstrated by the disruption in the function of certain plasmatic enzymes, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and lactate dehydrogenase. Intoxication with Cadmium can also result in various morphological alterations in hepatic tissue [3].

Fig 5 displayed the typical structure of the liver in animals treated just with Chromolaena Odorata extract, with no observed histological alterations. The slide exhibited a central vein and hepatocytes with preserved sinusoidal space, suggesting the absence of hepatotoxicity in the animals.

A comparable research done in Serbia found that both Cd dosages caused absolute lymphopenia, with a stronger impact at the higher Cd dose, when lymphopenia was accompanied with leucopenia [11]. Similar toxic effects of Cd on lymphocyte count were found following a single Cd treatment in rats [12,13], 14 days of Cd injection in male BALB/c mice [14], and four weeks of CdCl2 therapy in Wistar rats by drinking water [15,14]. Lafuente et al. [16] found significant levels of Cd in the spleen and thymus following oral CdCl2 therapy at dosages of 25-100 ppm, as well as reduced B lymphocyte counts in the spleen and thymus, implying that Cd buildup causes direct tissue harm.. Furthermore, treatment with a greater Cd dosage resulted in considerable MDA increase. These findings are similar with prior research, which found a significant rise in MDA levels in plasma after receiving a single Cd dosage orally (30 mg/kg b.w.) or i.p. (1.5 mg/kg b.w.) [17]. In this study, the two Cd dosages produced differing platelet values. The lower Cd dose (15 mg/kg b.w.) caused thrombocytosis, but the higher Cd dose (30 mg/kg b.w.) caused thrombocytopenia. The literature is rather contradictory, with some studies reporting stable levels of PLT following acute or subacute therapy [12,18], while others report a reduction in PLT(platelet) account [15,13,19]. The WBC (White Blood Cell) data support the theory that inflammation is the cause of the thrombocytosis that was seen after the lower Cd dosage was administered. Histopathological examination could not find evidence of a significant disruption of the liver's structure that would cause the release of enzymes. Accordingly, we saw no increase in the levels of AST and ALT in the serum. A few writers report a reduction in enzymes [20,21,22], but other authors report an elevation [11,12]. However another study where analyses of blood and liver samples showed that albumin and total protein levels were significantly lower, while blood and hepatic Cd levels were significantly elevated along with notable increases in alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) activities. Hepatic glutathione peroxide (GPx), catalase (CAT), superoxide dismutase (SOD), and catalase activity all considerably decreased in comparison to control. This was followed by a notable rise in malondialdehyde (MDA) levels, dysregulation of caspase, and cytokine (TNF-α, IL-6, IL-4, IL-10) levels. Nonetheless, it was shown that the levels of Cd, hepatic enzymes, MDA, TNF-α, IL-6, and caspases-3/-9 were much lower in the rats given NAR+Cd than in the Cd group. liver histopathological abrasions were significantly reduced, and there was a considerable elevation in the liver SOD, CAT, GPx, IL-4, IL-10, albumin, and total protein. When combined, these findings suggest that NAR may be a useful flavonoid for preventing hepatic Cd bioaccumulation and, as a result, reducing the effects of Cd on oxidative inflammation and apoptosis in rat liver [23].Also in another study using silymarin or DPx to treat Cd-induced liver damage significantly reduced it. The assessment of the TUNEL test demonstrated that treatment with DPx prevented the histological hepatic harm caused by Cd. In rats given Cd injections, DPx therapy dramatically decreased the expression of Bax and caspase-3. Furthermore, DPx treatment markedly raised the expressions of HO-1 and NRF2 in the livers of rats given a Cd injection.

Based on its antioxidant and anti-inflammatory properties, DPx effectively protects Cd-induced hepatotoxicity [24].

5. CONCLUSION

The study revealed that the intraperitoneal administration of Cadmium in rats resulted in notable hepatotoxicity, as evidenced by histopathological alterations and degeneration of hepatocytes. Conversely, the oral ingestion of Chromolaena Odorata did not have any impact on the liver toxicity induced by Cadmium in rats.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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