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Annulment and amelioration of cadmium toxicity through dietary countermeasures

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SUMMARY

Background: Cadmium (Cd) is an environmental toxin that penetrates most parts of the environment and causes significant health hazards when it accumulates in the human body. Chronic Cd exposure, particularly in individuals with metabolic disorders like diabetes, leads to oxidative stress, inflammation, and organ damage. **Purpose:** This study aimed to establish whether dietary herbs, present in the polluted regions, can neutralize and reverse Cd-induced toxicity. **Methodology:** Main focus to assess the efficiency of the herbs in reducing Cd toxicity and enhancing biological health indices. *Enhydra fluctuans* (Lour) is the dietary herb used. Using 20 rats of either sex exposed to Cd and then treated with selected edible herbs known for their detoxifying properties, a controlled laboratory experiment was conducted. Compared to controls, the treated groups' Cd levels significantly decreased, and the related harmful effects improved. **Results:** *E. fluctuans*-treatment group showed significant decreases in blood glucose levels and normalization of liver enzymes (AST, ALT, ALP, bilirubin). Kidney function tests showed improvement in serum creatinine, BUN, uric acid, and urine protein levels. Histological studies confirmed preserved cellular architecture of the liver, kidney, and pancreas. **Conclusion:** *E. fluctuans* presents potent antidiabetic, antioxidant, hepatoprotective, and nephroprotective effects to help ameliorate systemic toxicity from Cd exposure. **Contribution:** The finding of the study supports the potential of *E. fluctuans* as an affordable, natural dietary response to heavy metal contamination, especially in environmentally exposed and metabolically compromised and metabolic stress, as well as providing meaningful contributions to the specific area of herbal toxicology and public health nutrition.

Keywords: Cadmium toxicity; dietary herb; *Enhydra fluctuans*; detoxification.

RESUMEN

Anulación y mejora de la toxicidad del cadmio mediante medidas dietéticas

Antecedentes: El cadmio (Cd) es una toxina ambiental que penetra en la mayor parte del medio ambiente y causa importantes riesgos para la salud al acumularse en el cuerpo humano. La exposición crónica al Cd, especialmente en personas con trastornos metabólicos como la diabetes, provoca estrés oxidativo, inflamación y daño orgánico. **Objetivo:** Este estudio tuvo como objetivo determinar si las hierbas dietéticas presentes en regiones contaminadas pueden neutralizar y revertir la toxicidad inducida por Cd. **Metodología:** El objetivo principal fue evaluar la eficacia de las hierbas para reducir la toxicidad del Cd y mejorar los indicadores de salud biológica. La hierba dietética utilizada fue *Enhydra*

fluctuans (Lour). Se realizó un experimento de laboratorio controlado con 20 ratas de ambos sexos expuestas al Cd y posteriormente tratadas con hierbas comestibles seleccionadas conocidas por sus propiedades desintoxicantes. En comparación con los controles, los niveles de Cd de los grupos tratados disminuyeron significativamente y los efectos nocivos relacionados mejoraron. **Resultados:** El grupo tratado con *E. fluctuans* mostró una disminución significativa de los niveles de glucosa en sangre y la normalización de las enzimas hepáticas (AST, ALT, ALP, bilirrubina). Las pruebas de función renal mostraron una mejoría en los niveles de creatinina sérica, nitrógeno ureico en sangre (BUN), ácido úrico y proteínas en orina. Los estudios histológicos confirmaron la conservación de la arquitectura celular del hígado, el riñón y el páncreas. **Conclusión:** *E. fluctuans* presenta potentes efectos antidiabéticos, antioxidantes, hepatoprotectores y nefroprotectores que ayudan a mejorar la toxicidad sistémica por exposición al Cd. **Contribución:** Los hallazgos del estudio respaldan el potencial de *E. fluctuans* como una respuesta dietética natural y asequible a la contaminación por metales pesados, especialmente en personas con exposición ambiental y metabolismo comprometido, así como en personas con estrés metabólico, además de realizar contribuciones significativas al área específica de la toxicología herbaria y la nutrición en salud pública.

Palabras clave: Toxicidad por cadmio; hierba dietética; *Enhydra fluctuans*; desintoxicación.

RESUMO

Anulação e melhora da toxicidade do cádmio por meio de medidas dietéticas

Contexto: O cádmio (Cd) é uma toxina ambiental que penetra na maior parte do ambiente e causa riscos significativos à saúde quando se acumula no corpo humano. A exposição crônica ao Cd, particularmente em indivíduos com distúrbios metabólicos como diabetes, leva ao estresse oxidativo, inflamação e danos aos órgãos. **Objetivo:** Este estudo teve como objetivo estabelecer se as ervas dietéticas, presentes em regiões poluídas, podem neutralizar e reverter a toxicidade induzida pelo Cd. **Metodologia:** O foco principal foi avaliar a eficiência das ervas na redução da toxicidade do Cd e na melhoria dos índices biológicos de saúde. *Enhydra fluctuans* (Lour) é a erva dietética utilizada. Utilizando 20 ratos de ambos os sexos expostos ao Cd e posteriormente tratados com ervas comestíveis selecionadas, conhecidas por suas propriedades desintoxicantes, foi conduzido um experimento controlado em laboratório. Em comparação com os controles, os níveis de Cd dos grupos tratados diminuíram significativamente e os efeitos nocivos relacionados diminuíram. **Resultados:** O grupo tratado com *E. fluctuans* apresentou reduções significativas nos níveis de glicemia e normalização das enzimas hepáticas (AST, ALT, ALP, bilirrubina). Os testes de função renal mostraram melhora nos níveis séricos de creatinina, ureia, ácido úrico e proteína na urina. Estudos histológicos confirmaram a preservação da arquitetura celular do fígado, rins e pâncreas. **Conclusão:** *E. fluctuans* apresenta potentes efeitos antidiabéticos, antioxidantes, hepatoprotetores e nefroprotetores para ajudar a amenizar a toxicidade sistêmica da exposição ao Cd. **Contribuição:** Os achados do estudo corroboram o potencial de *E. fluctuans* como uma resposta dietética natural e acessível à contaminação por metais pesados, especialmente em indivíduos expostos ao ambiente e com comprometimento metabólico, além de fornecer contribuições significativas para a área específica de toxicologia de ervas e nutrição em saúde pública.

Palavras-chave: Toxicidade por cádmio; erva dietética; *Enhydra fluctuans*; desintoxicação.

1. INTRODUCTION

Cadmium (Cd) is a metallic compound that belongs to the XIIth group of the periodic table. It is a soft, silvery-white metal that is similar to zinc and mercury in both chemical and physical properties [1]. Over the past century, exposure to Cd has been determined to take place in an extensive number of ways as a result of several human activities [2]. Cd is widely utilized in

several industrial sectors as a corrosive reagent and as a stabilizing agent in PVC products, dyes, and Ni-Cd batteries. Activities like this are the main causes of cadmium pollution [3]. Cd is also present in facilities for recycling electronic waste and non-ferrous metallic smelters. The increase in Cd concentration in soil, water, and atmosphere is also due to the gradual erosion and abrasion of rocks, volcanic activities, and forest fires. This metal contaminates soil and is released into the environment by even zinc, lead, and copper miners [4].

Absorption through the epidermis is quite rare; the respiratory and gastrointestinal systems absorb Cd to a lesser extent. Through albumin and erythrocytes, Cd enters the bloodstream and is then deposited in the kidneys [5], liver, and intestines [6]. Cd is gradually removed from the body through the kidneys, milk, saliva, and urine when nursing. Human exposure to Cd can cause several adverse effects, such as testicular damage, osteomalacia, renal and hepatic dysfunction, pulmonary edema, and damage to the adrenal glands and hemopoietic system [7]. Urine and Blood Additionally connected to atherogenic lipid profile changes, peripheral artery disease, coronary heart disease, and stroke were levels of Cd exposure. Cd has cytotoxic effects that can result in necrotic or apoptotic processes, and it is also known to cause cancer in humans [8].

Cd is known to exhibit strong environmental toxicity, an agent significantly known to induce diabetes and other metabolic disorders. It exerts its harmful effects through oxidative stress, inflammation, and disruption of cellular functions, impairing especially pancreatic β-cells and insulin signaling pathways [9]. In contrast to in-depth studies related to the adversities of its impacts, lesser attention has been paid to natural dietary remedies that can counterbalance these impacts. In the most contaminated areas of water, soil, and air with high Cd toxicity, humans and animals are frequently exposed to chronic Cd toxicity [10]. However, several individuals living in such contaminated areas remain healthy, probably due to their unintentional intake of dietary bioactive compounds that may neutralize Cd toxicity [11]. Among the promising natural remedial measures, one is the aquatic herb *Enhydra fluctuans* (Lour), largely consumed by several populations. Bioactive phytochemicals and antioxidants are abundant in *E. fluctuans* plants. Therefore, this study analyses the variations that might be a viable dietary intervention that helps remove Cd, reduce oxidative stress, and preserve metabolic efficiency.

1.1. Pharmacology of *Enhydra fluctuans* (Lour)

Marshy terrain is where *Enhydra fluctuans* (Lour) has been reported to grow. India, Nepal, Bangladesh, Sri Lanka, Myanmar, Thailand, Vietnam, and Malaysia are among the nations that use the plant as food. *E. fluctuans* occurs natively in India on ponds, riverbanks, wetlands, and marshes throughout the country [12]. It is noteworthy that it occurs in the Sundarbans of West Bengal, the marshy lands of Kerala, and Assam's marshes. In Sri Lanka, it grows in wetlands, paddy fields, and along riverbanks among the aquatic and marshy habitats [13]. Particular places are the wetlands of Anuradhapura and Polonnaruwa, as well as the coastal areas of Mannar and Jaffna. *E. fluctuans* can also be found in Southeast Asian countries such as Bangladesh, Myanmar, and Thailand. It blooms in wetland conditions, such as riverine, marshy, and swampy environments. The following are some specific locations the Brahmaputra River in Bangladesh and the Ayeyarwady River in Myanmar [14].

1.1.1. Botanical classification of E. fluctuans [14]

Kingdom: Plantae. Division: Magnoliophyta. Class: Magnoliopsida. Order: Asterales. Family: Asteraceae. Genus: Enhydra. Species: fluctuans.

1.1.2. Vernacular names used for E. fluctuans [14]

Table 1 shows the common vernacular names of *E. fluctuans*

Table 1. Common vernacular names of *E. fluctuans*

Languages	Names
Hindi	Raktakarabi, Harkuch, Matsayaakshi
English	Marsh herb, Watercress
Sanskrit	Achari, Jalabramhi, Bramhi, Shankhadhara, Chakrangi, Helanchi, Hilamochika, Vishaghni, Himamocika, Mambi, Trinittaparni, Matsyakshi, Matsyangi, Mochi, Rochi, Sasasrutih
Tamil	Karunkal Nerunjil
Malaya-lam	Kanakanti
Gujarati	Jalkand
Punjabi	Raktakarabi
Urdu	Raktakarabi
Bengali	Jalkarabi, Hingcha, Hincha

1.2. Pharmacological action of *E. fluctuans*

1.2.1. Analgesic and anti-inflammatory action

The analgesic activity of *E. fluctuans* extract is studied by Patra *et al.* on the experimental models. A researched the analgesic activity of *E. fluctuans* extract on experimental models utilizing a variety of pain assessment tests [15], such as the acetic acid-induced writhing test, the tail immersion test, the hot plate test, and the formalin-induced paw-licking test. Because of the reduced paw-licking reaction in the formalin test, raised pain tolerance in heat tests, and fewer trembles, the results showed a substantial decrease in discomfort. These findings, therefore, indicate that *E. fluctuans* influences the pain pathways through its analgesic activity [16]. In the same way, further supported these results as they showed that the extract possessed a great level of acetic acid-induced writhing inhibition [17], which might mean it would modulate pain perception. Besides, the extract is anti-inflammatory and could be a mechanism of how it mediates analgesia through the prevention of pain induction by inflammation as illustrated by its inhibition of carrageenan-induced paw edema [18].

1.2.2. Anti-diarrheal activity

Numerous investigations have examined the pharmacological characteristics *of E. fluctuans* and its application as a treatment for diarrhea. In an investigation by Uddin *et al,* aqueous and methanolic extracts of *E. fluctuans* proved to have highly significant anti-diarrheal efficacy against castor oil-induced diarrhea in mice. During the test, both the methanolic and aqueous extracts were administered orally at 250 mg/kg body weight in mice. An inhibition rate of 67.07% is shown in the methanolic extract and an inhibition rate of 41.18% is shown in the aqueous extract of *E. fluctuans*. As compared to this, an 84.70% inhibition rate was found in the standard medicine loperamide. Also, the methanolic extract has shown its action against *Shigella flexneri, Shigella dysenteriae*, and *Shigella boydii*. The anti-diarrheal action of methanolic extract may be related to prostaglandin inhibition [19].

1.2.3. Anticancer activity

The presence of *E. fluctuans* has been attributed to antioxidant activity from flavonoids such as baicalein 7-O-diglucoside and baicalein 7-O-glucoside. High ROS levels result in cellular damage, which includes mitosis, hence raising the possibility of DNA mutation [20]. The suppression of Ehrlich's ascites carcinoma (EAC) in Swiss albino mice provides evidence of this

plant's anticancer properties. By measuring the tumor's size, number of cells, and proportion of viable and non-viable cells, Sannigrahi *et al.* evaluated the anticancer efficacy. The flavonoids improved life expectancy, restored hematological indicators such as malondialdehyde concentration and antioxidant enzyme activity, and dramatically reduced tumor volume [21]. Stefani *et al.,* from their experiment, have recommended that flavonoids are effective in cancer prevention either through modulation of the defense enzyme system or lipid peroxidation [22].

1.2.4. Cytoprotective activity

The cytoprotective activity demonstrated by *E. fluctuans* aqueous extracts protected against heavy metal toxicity [23]. In particular, the aqueous extract restored lead acetate-induced cell viability reduction in hepatocytes and defended against cytotoxic effects caused by NaAsO2 in hepatocytes. These effects included the counteraction of protein carboxylation, alterations in transcription protein levels, lipid peroxidation, and a decrease in glutathione levels in hepatocytes. Besides, the water extract was proven to have cytoprotective potential against arsenic bioaccumulation, relieving arsenic-induced abnormalities in hematological constraints and redox imbalance in mouse liver. Moreover, exposure to the water extract considerably reverses CdCl2-induced decreased cell viability. Studies show that the aqueous extract of *E. fluctuans* has remarkable anti-oxidant properties against oxidative stress and Cd bioaccumulation in the kidney, liver, heart, brain, testes of mice, and brain [24].

1.2.5. Hepatoprotective activity

Phytoconstituents present in the plant *E. fluctuans* conferred hepatoprotective activity. Assays against carbon-tetrachloride-induced oxidative damage in rats significantly reduced the levels of alkaline phosphatase, total bilirubin, SGOT, and SGPT with ethyl acetate, petroleum ether, chloroform, and extracts of ethanol from the aerial parts of the plant. It also caused protection against extensive necrosis and steatosis that occurred after exposure to carbon tetrachloride [25]. Protection mechanisms include the enhancement of the enzymatic defense mechanism towards a restorative biological parameter, the inhibition of lipid peroxidation, and tissue integrity.

1.2.6. Anti-helminthic activity

Kuri *et al.* analyzed the anti-helminthic activity of *E. Fluctuans* via methanolic extraction, exhibiting its paralytic action on the earthworm species *Pheretima posthuma*. The extract's various concentrations were assessed and contrasted with the common anti-helminthic medication albendazole. The findings indicated that *E. fluctuans* extract significantly exceeded that of Albendazole by length of paralysis and time to death of the earthworms, illustrating that *E. Fluctuans* is a rich source of active compounds that could act as an excellent anti-helminthic drug besides providing an alternative to parasitic infestations without conventional treatments.

1.2.7. Anti-microbial activity

Bhakta *et al.* have demonstrated the promising antimicrobial activity of a methanolic extract from *E. Fluctuans*., most importantly against *Staphylococcus aureus* [26]. In addition, the extract shows moderate antibacterial effects towards numerous Gram-negative and Gram-positive bacteria, which could indicate broad-spectrum antibacterial potential [27]. Moreover, *E. fluctuans* presented strong antifungal activity by inhibiting *Aspergillus niger, Fusarium sp.,* and *Aspergillus fumigatus*; this, therefore has the use as a potential natural antifungal agent. Besides, bioactive phytochemicals isolated from *E. fluctuans* using High-Performance Liquid Chroma-

tography (HPLC) were studied for their antibacterial activity [28]. Certain compounds identified as responsible for the inhibition of growth in extracts show antibacterial properties; thus, expanding knowledge of the bioactive properties of the plant and how it could be used to fight microbial diseases. These results support the development of natural antimicrobial agents from *E. fluctuans* [29].

1.2.8. Thrombolytic activity

E. fluctuans methanolic extract has shown high thrombolytic activity, which may act as a plasminogen activator. According to Kuri *et al*., at a concentration of 10 mg/mL, the extract showed 31% thrombolytic activity than that of streptokinase, the standard thrombolytic agent. The thrombolytic impact increased in tandem with the methanolic extract's dosage rise, according to their study. This means that *E. fluctuans* could have potential therapeutic applications for disorders that require a breakdown, such as in the treatment of thromboembolic disorders. The extract may also have the capacity to activate the plasminogen to become part of the natural alternative thrombolytic agents [30].

1.2.9. Antioxidant activity

E. fluctuans' antioxidant activity has significant therapeutic potential because it has been demonstrated to guard against illnesses linked to oxidative stress. The action results from the abundance of phenolic substances, including flavonoids and phenolic acids, which are strong scavengers of free radicals and decrease oxidative stress [31]. Flavonoids like apigenin, luteolin, kaempferol, and quercetin can act as powerful antioxidants since they are known to suppress lipid peroxidation, thus protecting cells from oxidative damage [32]. Besides the inhibitory effect on oxidative stress-related enzymes such as xanthine oxidase and acetylcholinesterase which minimized the production of reactive oxygen species, the *E. fluctuans* extracts showed appreciable total antioxidant capacity through DPPH and FRAP assays in neutralizing free radicals [33]. In addition, *E. fluctuans* extracts have demonstrated cytoprotective effects, protecting the cells against oxidative damage and antioxidant enzyme function in cellular models.

2. MATERIALS AND METHODS

This study uses a rat model of diabetes to investigate how dietary treatments protect against Cd-induced damage. Induced diabetes in the rat model is done specifically with streptozotocin (STZ) and nicotinamide-induced diabetes. The experiment was conducted using twenty rats of both sexes that weighed between 160 g and 210 g, bred in the animal facility of Shri Pharmaceutical Institute Rawatpura, Kumhari, Durg, Chhattisgarh, India. According to earlier methods, STZ was administered intra-peritoneally at a dosage of 40 mg/kg to cause diabetes. To guarantee successful induction of diabetes, nicotinamide was directed at a dosage of 80 mg/kg before the administration of STZ. HI Media, Thane, Maharashtra, was the source of STZ, while Molychem, Mumbai, provided nicotinamide and Cd chloride. The study will evaluate diabetic rats exposed to Cd and assess possible protective impacts from dietary treatments. For this purpose, the work will monitor all the mentioned bioindicators of oxidative stress, inflammation, and organ functionality throughout the study to assess the therapeutic outcome.

Rats were first split up into four groups to assess the impacts of Cd poisoning and the effectiveness of a protective therapy. Group 1 was taken as diabetic control, only STZ and

nicotinamide were given to them to induce diabetes. In group 2, the treatment of STZ, nicotinamide, and the effect of Cd toxicity was assessed using Cd chloride in a diabetic model. Group 3 was administered STZ, nicotinamide, and Cd chloride. A protective treatment, aimed at reducing Cd toxicity, was given to all of them. Finally, Group 4 was taken as the reference control where metformin was administered as an antidiabetic drug. All groups received STZ and nicotinamide on day 0 to induce diabetes. Cd chloride 8 mg/kg was administered intraperitoneally from day 1 to day 7, prepared in saline, and given to Groups 2 and 3. Meanwhile, Group 3 had the protective treatment on the same schedule. This experimental set-up allowed a comparative study of the effects of Cd versus the protective treatment on toxicity induced by diabetes.

The experimental rats' blood glucose levels were monitored using the GLUCO-One BG-03 Blood Glucose Meter by Dr. Morepen, New Delhi, on days 1, 4, and 7 of the study to track glycemic changes associated with treatments. On day 7, the rats were euthanized to enable organ harvesting for blood sampling and analysis. The kidneys and livers were dissected meticulously with care and preserved in 10% formalin solution, as this would ensure effective fixing for histopathological studies. The experiments aimed at explaining the structural changes and pathological alterations caused by diabetes and Cd toxicity. The treatment given to protect the rats was also indicated in the study. Blood samples were taken for a comprehensive biochemical evaluation, which included liver function tests, renal function tests, and amylase tests to determine the systemic effects of the treatments. These evaluations provide crucial information regarding the physiological and biochemical effects of Cd toxicity and whether there is any protective efficacy of the tested intervention.

Assessing the consequences of Cd-induced toxicity in a diabetic rat model and figuring out if the preventive medication successfully lessens the harmful effects of Cd are the goals of the study. Comparison will be drawn between Group 2 which received only Cd chloride, Group 3 which received Cd chloride, STZ, and nicotinamide oral administration of *Enhydra fluctuans* ethanol extract, which was administered. This dose was established based on toxicity studies and evidence in the literature. And Group 4 is treated with Metformin, used here as a positive control for antidiabetic response by serving as a standard against which the glycemic effects of *E. fluctuans* could be assessed, and does not serve as a control for Cd toxicity. The study aims to investigate the potential of protective treatment in reducing Cd-induced toxicity and its associated complications in diabetic conditions through analysis of differences in biochemical, histopathological, and physiological parameters. This investigation mainly deals with the capability of protective treatment in disease progression prevention, vital organ protection, and counteraction of oxidative stress and inflammation caused by Cd exposure. This work is likely to provide important insights into Cd toxicity management strategies within diabetic models, leading eventually to therapeutic approaches protecting from heavy metal-induced damage in at-risk populations.

The test plant used for this study is *Enhydra fluctuans* (Lour) which is identified from the herbal garden of Mahaveer College of Ayurvedic Sciences, Rajnandgaon, Chhattisgarh. Dry plant material was powdered under shades at the Rasayanshala of the same institute. Cold maceration with defatting as an initial step was the process that was followed for extraction. In this, the powdered material was treated with petroleum ether to remove the fats and impurities. The ethanol extract was obtained by macerating the plant powder in ethanol for seven days with continuous stirring involved in the process to completely extract the bioactive compounds present in the plants. This mixture was then filtered at the end of the extraction time to separate the plant residue, and the solvent was left to evaporate to gain the dried ethanol

extract. This was screened for phytochemical content to identify the active constituents present, thus providing key information for an understanding of the plant's therapeutic potential.

3. RESULTS

3.1. Microscopic images

The images represent histological sections of normal cells, Streptozotocin and nicotinamide-induced Rat cells, and Cd-induced Rat cells of (liver, kidney, and pancreas). Various experimental conditions, stained with hematoxylin and eosin (H&E) at appropriate magnification. These panels depict structural alterations across control and treated groups. Figures 1 to 3 show histopathological examination of liver, kidney, and pancreas in rat models.

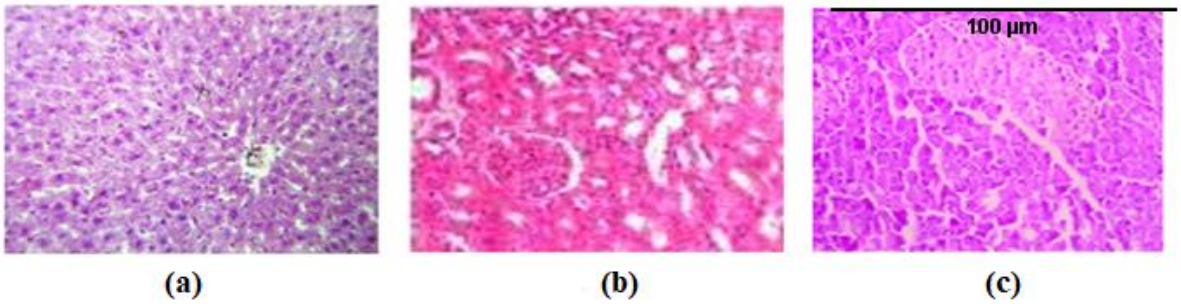

Figure 1. Normal cells of rat models: a) liver, b) kidney, c) pancreas.

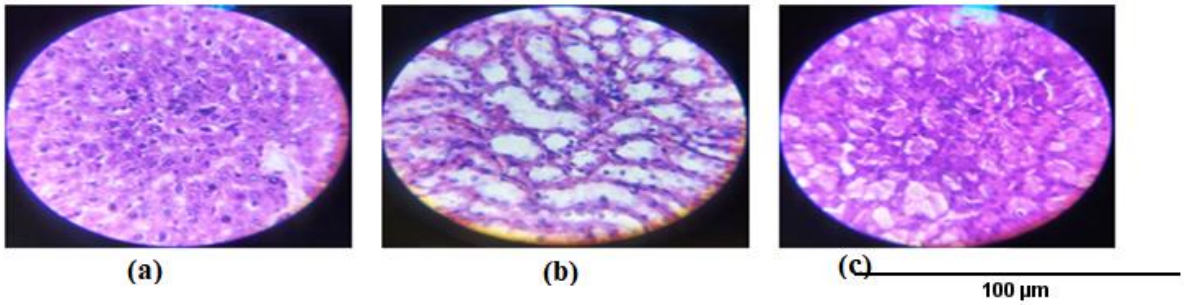

Figure 2. Streptozotocin and nicotinamide-induced rat cells: a) liver, b) kidney, c) pancreas.

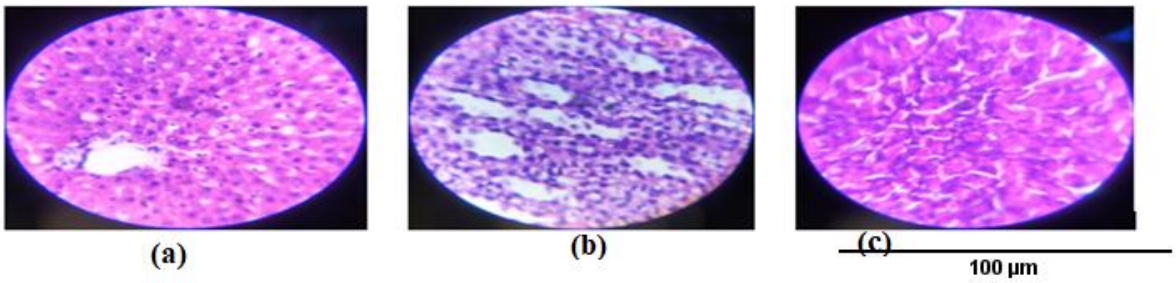

Figure 3. Cd-induced rat cells: a) liver, b) kidney, c) pancreas

3.2. Blood glucose level test

Table 2 shows Group 1 (STZ + Nicotinamide): The blood glucose levels in this group were significantly elevated (400-450 mg/dL), confirming the induction of diabetes by STZ in combination with nicotinamide. This increase is attributed to the destruction of pancreatic β-cells by STZ, leading to insulin deficiency and hyperglycemia.

Table 2. Blood glucose level test results

Group	Treatment	Blood glucose levels (mg/dL, mean±SD)
Group 1	Streptozotocin + Nicotinamide	425±12.5
Group 2	Streptozotocin + Nicotinamide + Cd Chloride	475±12.5
Group 3	Streptozotocin + Nicotinamide + Cd Chloride + Protective treatment (*E. fluctuans*)	325±12.5
Group 4	Metformin (Control)	110±5.0

Group 2 (STZ + Nicotinamide + $CdCl_2$): This group exhibited even higher blood glucose levels (450-500 mg/dL) compared to Group 1, indicating the exacerbation of hyperglycemia due to Cd chloride toxicity. $CdCl_2$ is known to induce oxidative stress and further damage β-cells, leading to aggravated hyperglycemia.

Group 3 (STZ + Nicotinamide + $CdCl_2$ + *E. fluctuans*): Notably, the rats in this group displayed significantly lower blood glucose levels (300-350 mg/dL) compared to Group 2. This suggests that *E. fluctuans* has a protective effect against Cd-induced toxicity, likely due to its antioxidant properties, which help to preserve β-cell function and reduce hyperglycemia.

Group 4 (Metformin control): As expected, the control group treated with metformin, a standard antidiabetic drug, maintained normal blood glucose levels (100-120 mg/dL), serving as a benchmark for effective glucose regulation.

Figure 4 shows the impact of various treatments on blood glucose levels in different experimental groups. Diabetes was induced with streptozotocin in combination with nicotinamide, and the effects revealed significant hyperglycemia. The further addition of Cd chloride worsened these effects, thus suggesting that the metal aggravates oxidative damage and β-cell injury. Notably, in terms of the group that received a combination of *E. fluctuans* along with Cd chloride, they manifested lower blood glucose levels, meaning there existed a protective as well as antihyperglycemic potential of this herb. The control receiving metformin had normal levels of blood glucose, setting it at par for standard glucose handling. These observations, hence, indicate *E. fluctuans* as a potentially good defensive agent against Cd-induced hyperglycemia.

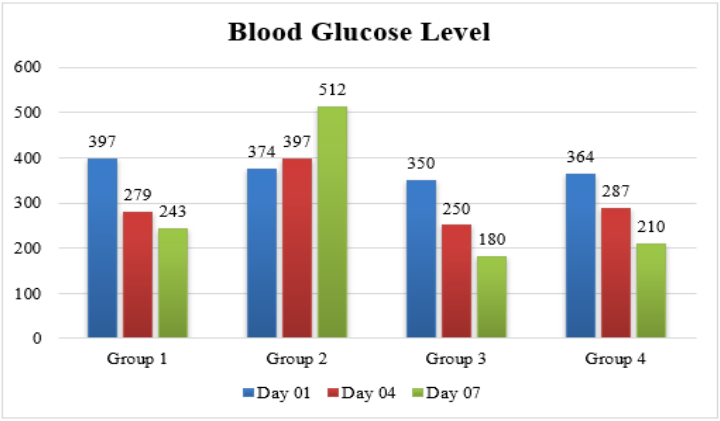

Figure 4. Graph of blood glucose level

3.3. Liver Function Test

Hepatotoxicity caused by Cd Cl_2 was shown by the drastically elevated levels of liver enzymes (AST, ALT, and ALP) in Group 2. On the other hand, Group 3, which was given *E. fluctuans*,

had lower levels of these enzymes, indicating that the preventive therapy lessened liver damage. *E. fluctuans* hepatoprotective impact is demonstrated by Group 3's near-normal enzyme levels when compared to Group 4's control is shown above the table 3.

Table 3. Liver function test results

Group	AST (U/L)	ALT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)
Group 1	150-180	70-90	200-250	0.8-1.2
Group 2	200-250	100-130	300-350	1.5-2.0
Group 3	130-160	60-80	180-220	0.7-1.0
Group 4	80-100	30-50	100-150	0.3-0.7

3.3.1. Total Bilirubin: Similarly, total bilirubin levels were highest in Group 2, reflecting impaired liver function due to $CdCl_2$. The reduction in bilirubin levels in Group 3 indicates the restoration of liver function, further supporting the protective role of *E. fluctuans*.

3.4. Kidney Function Test

Table 4 explains the Group 2 exhibited elevated serum creatinine and BUN levels, indicating renal impairment due to $CdCl_2$ toxicity. The reduced levels observed in Group 3 suggest that *E. fluctuans* offers renal protection, likely by combating oxidative stress and preserving renal function.

Table 4. Serum-based kidney function parameters

Group	Serum creatinine (mg/dL)	BUN (mg/dL)	Uric acid (mg/dL)
Group 1	1.0-1.2	25-35	2.0-2.5
Group 2	1.5-2.0	40-50	3.0-4.0
Group 3	0.8-1.0	20-30	1.5-2.0
Group 4	0.5-0.7	15-25	1.0-1.5

Uric Acid: Elevated uric acid levels in Group 2 further indicate renal dysfunction, while the reduction in Group 3 points to the efficacy of *E. fluctuans* in ameliorating $CdCl_2$-induced nephrotoxicity.

3.5. Renal Function Test

Table 5 explains the Group 2 showed increased proteinuria, a sign of kidney damage, which was significantly reduced in Group 3, indicating the shielding effect of *E. fluctuans* on renal function.

Table 5. Urine-based renal function parameters

Group	Urine protein (mg/24h)	Urine volume (mL/24h)	Creatinine clearance (mL/min)
Group 1	20-30	15-20	1.2-1.5
Group 2	40-50	10-15	0.8-1.0
Group 3	15-25	18-22	1.3-1.6
Group 4	10-15	20-25	1.5-1.8

Urine volume and creatinine clearance: Reduced urine volume and creatinine clearance in Group 2 reflect impaired renal function, whereas Group 3 showed near-normal values, further confirming the renoprotective role of *E. fluctuans*.

4. DISCUSSION

The current study's results match previous studies showing the ability of antioxidants derived from plants to reduce toxicity caused by Cd. For instance, a study on the efficacy of *Phyllanthus emblica* against Cd-induced oxidative stress and hyperglycemia in diabetic models with special emphasis on the potential of phenolic compounds to preserve pancreatic beta-cell functions and reduce oxidative stress [34]. Similarly, the outcomes found in Group 3 of the present study, wherein the *E. fluctuans* drastically decreased the concentration of blood glucose in contrast to the Cd-treated Group 2, imply that bioactive compounds from the plant flavonoids and phenolic acids are of vital significance in searching free radicals and defending the beta cells from oxidative injury.

The hepatoprotective effects noted in this study are also associated with research studies conducted on other antioxidant-rich plants. A study showed that extracts of *Curcuma longa* reduce Cd-induced liver injury through decreases in the levels of hepatic enzymes and markers of oxidative stress [35]. The present investigation showed that there was a significant reduction in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin levels of Group 3 treated with *E. fluctuans* which suggests similar mechanisms of action that may involve inhibition of lipid peroxidation and stabilization of cellular membranes. This leads to the fact that the action of *E. fluctuans* might involve pathways similar to other well-established plants for hepatoprotection [36].

The reno-protective findings of this study are reliable with that research done before indicating that *Moringa oleifera* reduces renal damage induced by Cd when its antioxidant enzyme activity and serum creatinine and urea levels were enhanced. In the current study, group 3 showed improved kidney function markers by lowering blood urea nitrogen, serum creatinine, and uric acid, with normalization of urine volume and creatinine clearance. These findings are similar to those that have been demonstrated by *Moringa oleifera*. The antioxidant and anti-inflammatory properties of *E. fluctuans* probably mediate the above effects, as the same herb has been demonstrated to reduce oxidative stress in several tissues.

These comparisons strengthen the potential of *E. fluctuans* as a natural protective agent against Cd toxicity. The similarity in effectiveness to other medicinal plants of well-studied medicines underscores the significance of exploiting bioactive compounds in less utilized herbs. This work adds to a growing number of evidence indicating that plant-based therapies offer multilevel protection against heavy metal-induced injury, especially under conditions of co-existing metabolic disorders such as diabetes. Further studies, especially on the molecular level and clinical levels, are required to further elucidate its therapeutic mechanisms and validate its clinical utility in *E. fluctuans*.

5. CONCLUSION

This study thus revealed that *Enhydra fluctuans* (Lour) has significant promise as a defensive agent in combating Cd-induced toxicity in a rat model with diabetics. It reduced the elevated blood glucose level due to Cd toxicity and improved critical biochemical markers of liver and kidney function in animals treated with *E. fluctuans*. These results further emphasize that the herb has the potential to counteract the toxic actions of Cd, in particular its ability to mediate oxidative stress, considered one of the major damage mechanisms due to Cd. Antioxidant, hepatoprotective, and cytoprotective characteristics of *E. fluctuans* seem to be the focal point for protection, through improved function of organs with reduced levels of toxicity in treated

groups in comparison to those given Cd alone. The research points towards the possibility of this herbal remedy as a natural food intervention, particularly for residents in areas of high exposure to environmental Cd exposure.

In addition to discussing Cd toxicity, this research provides broader implications within the public health and toxicology environment. The alleviation of oxidative damage in the body and the preservation of critical organ functions make *E. fluctuans* a good prospect for further research in a detoxification process involving heavy metals. The results lead the way to the performance of clinical trials with human subjects to assess the human subjects' efficacy and tolerance toward the bacteria. Identification and characterization of bioactive compounds could result in the discovery of novel therapeutic agents for managing heavy metal toxicity. This research contributes to the significance of herbal remedies in addressing environmental health issues and recommends integrative studies to harness their complete and affordable utilization for better health worldwide.

CONFLICTS OF INTEREST

All authors declare that there are no conflicts of interest.

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