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Launaea taraxacifolia Ameliorates Cisplatin-Induced Hepato-renal Injury

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Authors' contributions

This work was carried out in collaboration between all authors. Author ASA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors OFA and JOO managed the analyses of the study and assisted in the literature searches. Author ORO prepared histological slides, Author AMA provided the cisplatin used. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: The protective potential of aqueous leaf extract of *Launaea taraxacifolia* against Cisplatin-induced hepato-renal damage in Wistar rats.
Study Design: Randomized controlled experiment
Place and Duration of Study: Experimental Animal Unit and Department of Anatomy, University of Ibadan between July and September, 2013.
Methodology: Thirty rats were randomly divided into 6 groups of 5 rats each. Group A- control; Group B- cisplatin (CIS) alone; Group C and D- *Launea taraxacifolia* (LT) 100 mg and 400 mg respectively and Group E and F- treated with LT 100 mg and 400 mg respectively and then given CIS. Kidney and liver sections were taken for histopathological evaluations. Serum samples were taken for alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin [BIL], total protein (TP), albumin [ALB], blood urea nitrogen (BUN) and creatinine (CREAT) level assessments. The remaining tissues were processed for the assessment of biochemical markers of oxidative stress:

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Lipid peroxidation (LPO), Superoxide dismutase (SOD), Catalase (CAT) and Glutathione (GSH).
Results: Hepatorenal histological toxicities were observed in rats exclusively exposed to cisplatin while dose-dependent ameliorations of these histopathologies were seen in those with combined exposure (Groups E and F) with the aqueous extract of *Launaea taraxacifolia* and virtually normal histoarchitecture was seen in extract alone treated rats. The hepatic (ALT, AST, BIL) and renal (BUN and CREAT) injury markers significantly ($p<0.05$) increased in groups exclusively exposed to cisplatin with less severity in co-treated (E and F) groups. The oxidative stress markers, LPO, SOD and CAT levels which were significantly elevated ($p<0.05$) in cisplatin exclusively exposed Group B, were not altered in other groups when compared with control. However, glutathione level significantly decrease ($p<0.05$) in GSH levels in kidney and liver tissues of (Group B) cisplatin alone relative to control.
Conclusion: *Launaea taraxacifolia* provides protection against cisplatin-induced hepatorenal damage through its antioxidant activities.

Keywords: Launea taraxacifolia; cisplatin; liver; kidneys; antioxidant and rats.

1. INTRODUCTION

Cisplatin (*cis*-diamminedichloroplatinum (II), CDDP) is an effective cytotoxic drug commonly used for cancer treatments [1]. However, its use is restricted by its undesirable severe toxic side effects at therapeutic doses. One-third of patients experience decline in renal functions at low therapeutic doses because of its selective renal parenchymal accumulation [2-4]. Hepatotoxicity occurs at much higher doses [5,6]. Cisplatin-induced toxicity is mediated through generation of reactive oxygen species [ROS] with consequent depletion of glutathione and inhibition of the activities of antioxidant enzymes in kidney and liver tissues [7-11]. Quite a number of antioxidants synthetic drugs have been shown to protect non malignant cells and organs against cisplatin-induced cytotocity [12] but recently there has been a shift of interest to phytochemicals in plants as origin of natural antioxidants [13,14].

Launaea taraxacifolia (Willd) is an annual herb of Western Tropical Africa typically known as wild lettuce. It is locally called *efo yanrin* in South Western Nigeria [15]. The plant is often grown for its leaves [16]. Several studies have shown that wild lettuce is nutritionally important due to high levels of vitamins, minerals, proteins, essential fatty acid**s** and fibre contents [16,17]. *Launaea taraxacifolia* is also a good source of flavonoids which are renown antioxidants. [16,18]. Anecdotal claims suggested that the plant is very useful in the management of various health challenges [19]. There is no data on the protective effect of *L. taraxacifolia* against Cisplatin-induced hepatorenal toxicities, this study then seeks to investigate this possibility.

2. MATERIALS AND METHODS

2.1 Plant Material Collection and Authentication

The fresh leaves of *Launea taraxifolia* were harvested from Precious farm, Ibadan, Nigeria and authenticated by Mr. Esimekhuai Donatus of the Department of Botany, University of Ibadan where UIH-22370 was assigned as the voucher specimen and deposited in the departmental herbarium.

2.2 Plant Extract Preparation

Two thousand (2000g) grams of *Launea taraxifolia* leaves were dried (at 40ºC for 4 days), powdered and soaked in 8litres of distilled water for extraction and was kept at 60ºC for 24 hours after which they were filtered using filter papers. The resultant filtrate was concentrated using a rotary evaporator to give a residue. The dosage of the dried extract to be administered was then calculated.

2.3 Chemicals

The Chemicals used were purchased from Sigma-Aldrich Chemical Co. (St. Louis, Missouri, USA): nicotinamide adenine dinucleotide phosphate (NADP); glucose-6-phosphate; l-γ-glutamyl-3-carboxyl-4-nitronilide; glycylglycine; epinephrine; glutathione (GSH); 5, 50-dithio-bis-2-nitrobenzoic acid; hydrogen peroxide; thiobarbituric aid and 1-chloro-2, 4-dinitrobenzene. Cisplatin was procured from Korea United Pharm. Inc. (Naojang, Chungnam, Korea). All other reagents were of analytic grade and were obtained from the British Drug Houses (Poole, Dorset, UK).

2.4 Animal Protocol

Male Wistar rats weighing 200 ± 10 g, obtained from the Animal house, Faculty of Veterinary medicine, University of Ibadan, Nigeria, were kept in well-ventilated plastic cages, provided with rat pellets, water ad libitum and subjected to a 12:12 light-to-dark photoperiod. The Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health was the basis of the humane care of all the experimental animals used. The contents of the University of Ibadan Ethical Committee for the protection of animal welfare during experiments were used as the Institutional reference for ethical regulation.

2.5 Experimental Design

Thirty pathogen free adult male Wistar rats were divided into six groups of five rats each as follows:

A. Control: Rats in this group received water (5 ml/kg body weight; orally) and saline (5 ml/kg body weight; intraperitoneally as single dose on day 21 only) as described by Amin [38].
B. Cisplatin (CIS) alone: Rats in this group were given a single dose of cisplatin (CIS) intraperitoneally at 10 mg/kg b.wt as previously used by Amin [38].
C. Launea taraxacifolia (LT) 100 mg: Rats in this group received 100 mg/kg b.wt of *Launea taraxacifolia* orally for 21 days.
D. LT 400 mg: Rats in this group were given 400 mg/kg of *Launea taraxacifolia* orally for 21 days.
E. LT 100 mg + CIS: Rats in this group received 100 mg/kg b.wt of *Launea taraxacifolia* orally plus cisplatin (10 mg/kg b.wt; intraperitoneally) on the 21st day.
F. LT 400 mg + CIS: Rats in this group were orally pre-treated with 400 mg/kg of *Launea taraxacifolia* plus cisplatin (10 mg/kg b.wt; intraperitoneally) on the 21st day. Five days after the administration of CIS, the rats were sacrificed for the evaluation of biochemical and histological variations in liver and kidneys.

2.6 Sample Collection

Each animal in the experimental groups was weighed. Two millilitres (2 ml) of blood was taken from the medial canthus of the eye into Lithium-heparinized test tubes for haematological studies. Blood sample was also collected into sterile plain tubes and allowed to clot. The serum was separated from the clot and centrifuged into clean tubes for biochemical analysis. The liver and left kidneys of the various groups were fixed in 10% buffered formalin in labeled bottles.

2.7 Biochemical Assays

The total protein was determined using Biuret reaction while albumin was measured by spectrophotometric estimation using the Sigma diagnostics albumin diagnostic reagent (Sigma Diagnostic, U.K.), which contained bromocresol green (BCG). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were determined spectrophotometrically as described by Toro and Ackermann [20] and Duncan [21]. The bilirubin level was determined by diazo reaction [22-24]. Serum urea and creatinine levels were determined as described by Toro and Ackermann [20] and Coles [25]. Portions of liver and kidneys were homogenized in 50 mM Tris–HCl buffer (pH 7.4) containing 1.15% potassium chloride. The homogenate was centrifuged at 10,000g for 15 min at 4ºC. The supernatant was collected for the estimation of superoxide dismutase (SOD) by the method described by Misra and Fridovich [26]. GSH was determined at 412 nm using the method described by Jollow [27]. Lipid peroxidation was quantified as MDA according to the method described by Farombi [28] and expressed as µm MDA/g tissue. Catalase activities were assessed by the method of Clairborne [29].

2.8 Histopathological Preparations of the Tissues

Formalin fixed kidney and liver tissues were routinely processed and stained with haematoxylin and eosin for light microscopy at X400 magnification.

2.9 Statistical Analysis

The data was statistically analysed using one-way analysis of variance (ANOVA) and Duncan's Multiple Range Test (DMRT) was used to separate the means. The level of significance was $p<0.05$ while the results were expressed as group mean±standard error of mean.

3. RESULT

3.1 Relative Weights of Organs

The relative weight (Table 1.) of kidneys of rats given Cisplatin only (Group B) increased significantly ($p<0.05$) relative to all other groups. Also, the RWK of rats in Group E and F (0.79±0.10; 0.72±0.04) though higher than in the control and Group C and D was significantly lower ($p<0.05$) than Group B (0.91±0.06). The RWL was not significantly different ($p>0.05$) in all the treatment groups (Table 1).

Table 1. Effect of *Launea taraxacifolia* extracts on the relative weight (%) of kidney and liver of rats exposed to cisplatin

	CONTROL	CIS ALONE	LT (100mg)	LT (400mg)	LT 100mg)+ CIS	LT (400mg)+ CIS
RWK(%)*	0.65± 0.02[a]	0.91± 0.06[c]	0.59±0.14[a]	0.63±0.03[a]	0.79±0.10[b]	0.72±0.04[b]
RWL (%)	3.17±0.24	2.90±0.30	3.01±0.12	3.20±0.27	3.34±0.27	3.15±0.03

*Values in the same row with different superscripts are significantly different; *p<0.05*
RWK - Relative weight of kidney, RWL - Relative weight of liver

3.2 Histopathology

Cisplatin administration precipitated vacuolar degeneration of the renal tubular epithelium with numerous tubular casts in Group B rats (Fig. 1.), however, the Group E and F showed moderate and mild renal histopathologies respectively. The kidneys architecture (Fig. 1.) was normal in the control and Group C and D. Fig. 2. Shows no visible lesions in the liver of the control, Group C, D and F rats. However, Group B and E rats show marked hepatic congestion.

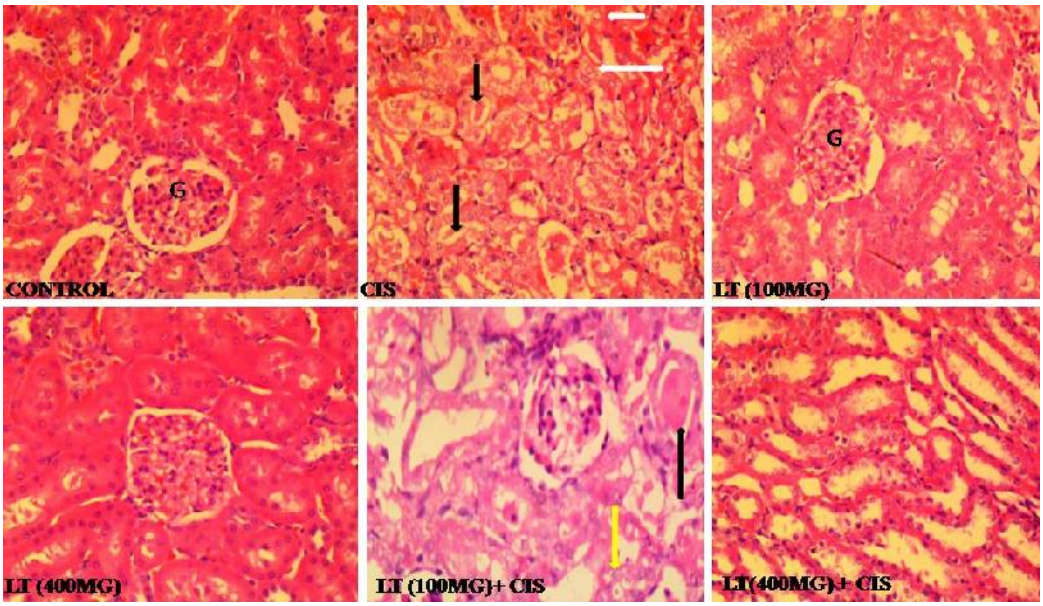


Fig. 1. Photomicrographs of the kidneys of rats

Control: No visible lesion; Cisplatin alone (CIS): widespread vacuolar degeneration of the tubular epithelium (white arrow); with numerous tubular casts (black arrow); Launea taraxacifolia (LT) 100 mg : renal architecture appear normal; Launea taraxacifolia (LT) 400 mg : No visible lesion; Launea taraxacifolia (LT) 100 mg+CIS: severe acute tubular necrosis and sloughing off of the tubular epithelium (yellow arrow) with formation of intra-luminal eosinophilic casts (black arrow); Launea taraxacifolia (LT) 400 mg+CIS: moderate thinning/flattening of the epithelium of tubules in the renal medulla Magnification: X400; Stain: H&E

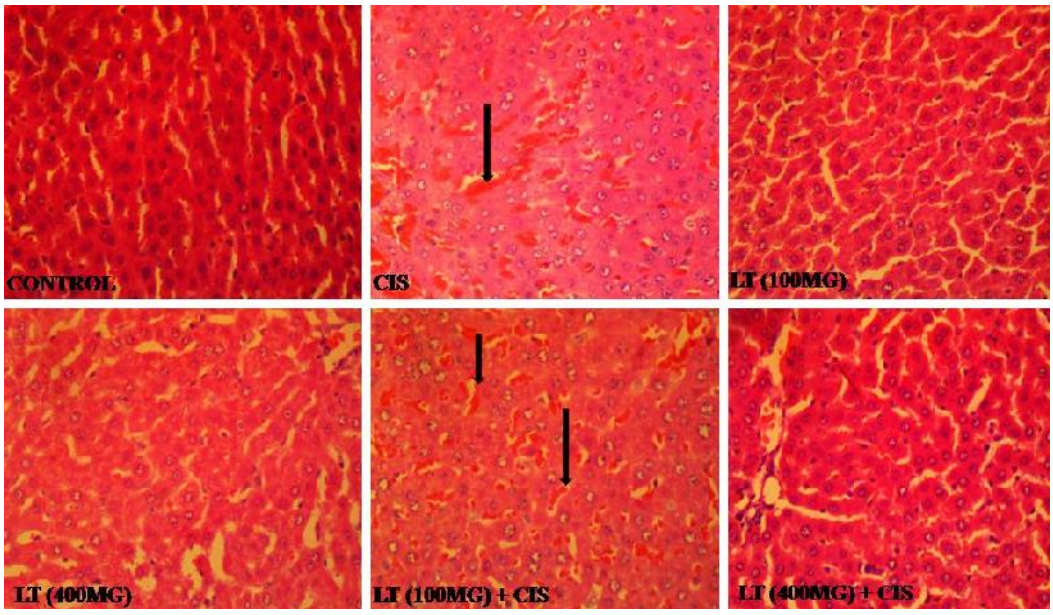


Fig. 2. Photomicrographs of the liver of rats

Control: No visible lesion; Cisplatin alone (CIS): marked congestion of the hepatic sinusoids (black arrow); Launea taraxacifolia (LT) 100 mg: No visible lesion; Launea taraxacifolia (LT) 400 mg: normal hepatic architecture; Launea taraxacifolia (LT) 100 mg + CIS: marked congestion of the hepatic sinusoids (black arrow); Launea taraxacifolia (LT) 400 mg + CIS: normal hepatic architecture. Magnification: X400; Stain: H&E

3.3 Serological Parameters

The effects of pretreatment with LT against cisplatin induced variations on serological parameters (Table 2). The Mean values of hepatic injury markers; serum ALT (21.80±1.07), AST (28.20±1.46) and bilirubin (2.26±0.25) significantly increased ($p<0.05$) with accompany decreased TP (5.12±0.10) and albumin (3.26±0.07) in Group B rats relative to control (7.80±1.16; 10.80±1.50; 0.50±0.16; 6.90±0.18; 3.78±0.10). Similarly, renal function indicators; BUN (168.40±5.20) and CREAT (2.20±0.07) mean values significantly increased ($p<0.05$) in Group B rats compared to control (29.20±5.78; 0.56±0.10). Pre-treatment with *Launea taraxacifolia* in Group E and F rats significantly ($p<0.05$) ameliorated the levels of their serological parameters to cisplatin toxicity relative to Group B. However, TP, ALB, BIL and AST levels in Group E were not significantly different ($p>0.05$) from values in Group B rats. Interestingly, both hepatic and renal function markers (TP, ALB, BIL, AST, ALT; UREA and CREAT) were not significantly different ($p>0.05$) between the control and Group C and D rats.

Table 2. Effect of *Launea taraxacifolia* extracts on the serological parameters of rats exposed to Cisplatin

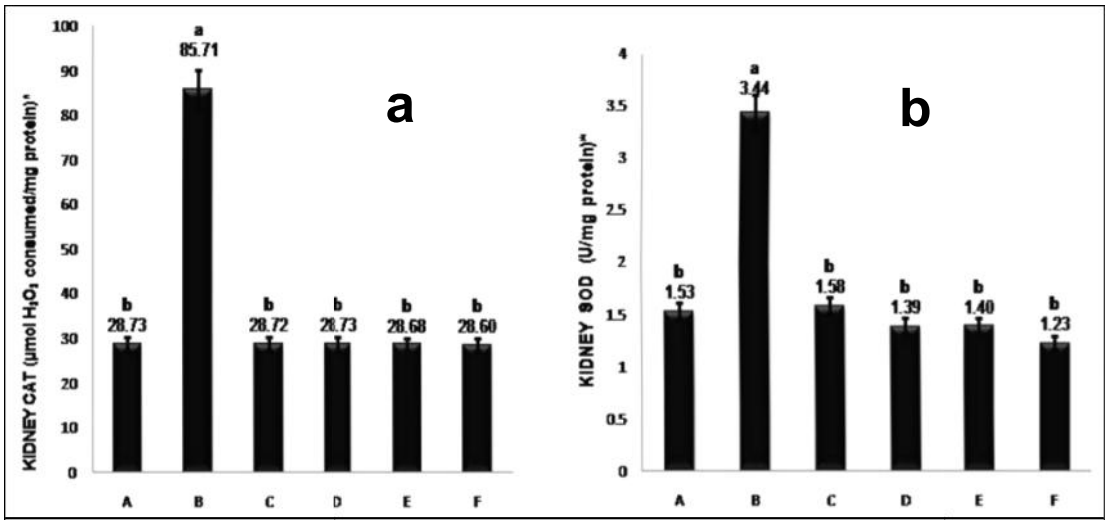
GROUP	CONTROL	CIS	LT (100mg)	LT (400mg)	LT (100mg) + CIS	LT (400mg) + CIS
ALT (IU/L)*	7.80±1.16^{a}	21.80±1.07^{c}	6.00±0.63^{a}	6.60±0.81^{a}	19.80±0.37^{b}	19.20±0.58^{b}
AST (IU/L)*	10.80±1.50^{a}	28.20±1.46^{c}	7.60±0.75^{a}	8.20±0.97^{a}	27.00±0.45^{c}	21.60±0.81^{b}
TP (g/dl)*	6.90±0.18^{a}	5.12±0.10^{c}	6.86±0.11^{a}	7.06±0.11^{a}	5.18±0.11^{c}	5.82±0.21^{b}
ALB (g/dl)*	3.78± 0.10^{a}	3.26±0.07^{c}	3.90±0.12^{a}	3.80±0.11^{a}	3.32±0.04^{c}	3.58± 0.06^{b}
BIL (mg/dl)*	0.50± 0.16^{a}	2.26±0.25^{c}	0.62± 0.07^{a}	0.54±0.08^{a}	2.18±0.21^{c}	1.28±0.12^{b}
BUN (mg/dl)*	29.20±5.78^{a}	168.40±5.20^{d}	21.60±1.09^{a}	36.40±3.17^{a}	139.80±4.91^{c}	123.00±3.14^{b}
CREAT(mg/dl)*	0.56±0.10^{a}	2.20±0.07^{c}	0.48±0.14^{a}	0.60±0.07^{a}	1.70±0.13^{b}	1.60±0.10^{b}

*Values in the same row with different superscripts are significantly different; *p<0.05 TP – Total protein, ALB – Albumen, BIL – Bilirubin (total), AST - aspartate aminotransferase, ALT- alanine aminotransferase, CREAT – Creatinine, BUN – Blood Urea Nitrogen*

4. BIOCHEMICAL ASSAYS

Figs. 3-4 shows the data on the effects of pretreatment with LT against cisplatin induced damaged on antioxidant systems and lipid peroxidation in kidney and liver. Cisplatin exposure significantly ($p<0.05$) elevated CAT and SOD enzymes in the renal tissues of Group B rats compared to control (Figs. 3a and b). These enzymes, however, were not significantly ($p>0.05$) different in rats pretreated with graded doses of LT (Group E and F) and the control. Also, a significantly elevated ($p<0.05$) lipid peroxidation (LPO) was accompanied by a concomitant reduced intracellular GSH activity in the Group B relative to other groups (Figs. 4a and b). The LPO and GSH levels of Group E and F were not significantly different ($p>0.05$) from the control.

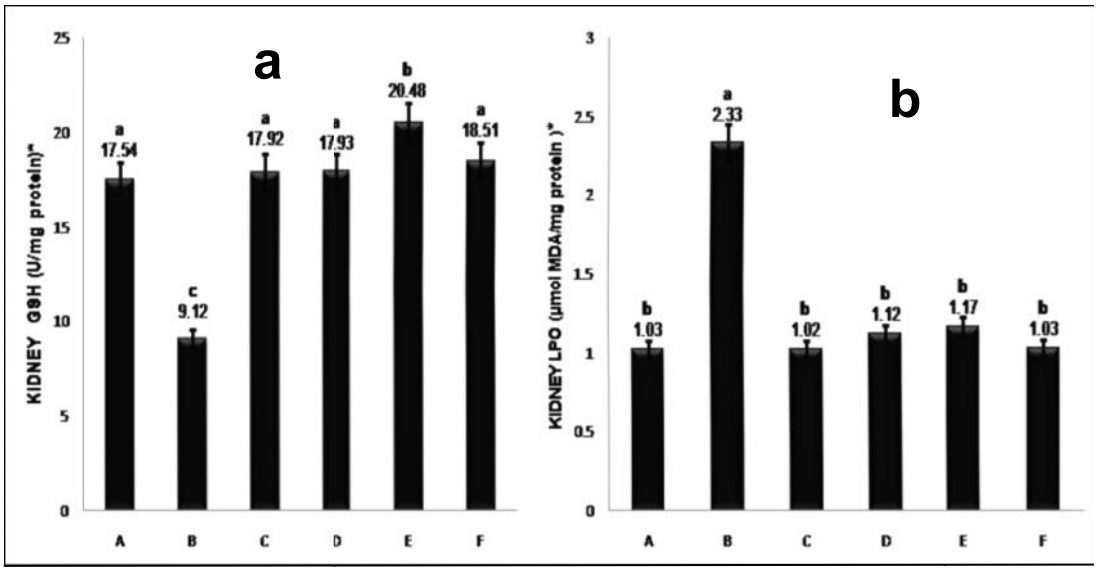
The biochemical assay of the hepatic tissues (Figs. 5-6.) presented a similar picture to the data on kidney's assay. The CAT and SOD enzymes increased significantly ($p<0.05$) in the cisplatin exclusively (Group B) exposed rats compared to control (figs. 5a and b). The profiles of CAT and SOD enzymes in the liver of Group E and F were not significantly ($p>0.05$) different from the control value. The LPO level significantly increased ($p<0.05$) in the Group B relative to other groups. This was, however, accompanied by a concomitant reduced GSH activity (Figs. 6a and b). The pre-treatment with LT in Groups E and F exhibited an insignificantly different ($p>0.05$) concentrations of LPO and GSH compared to the control.



Figs. 3a and b. Effect of Launea taraxacifolia extracts on cisplatin-induced alterations in (a) catalase (CAT) and superoxide dismutase (SOD) in kidneys

*Bars with different superscripts are significantly different; *p < 0.05*

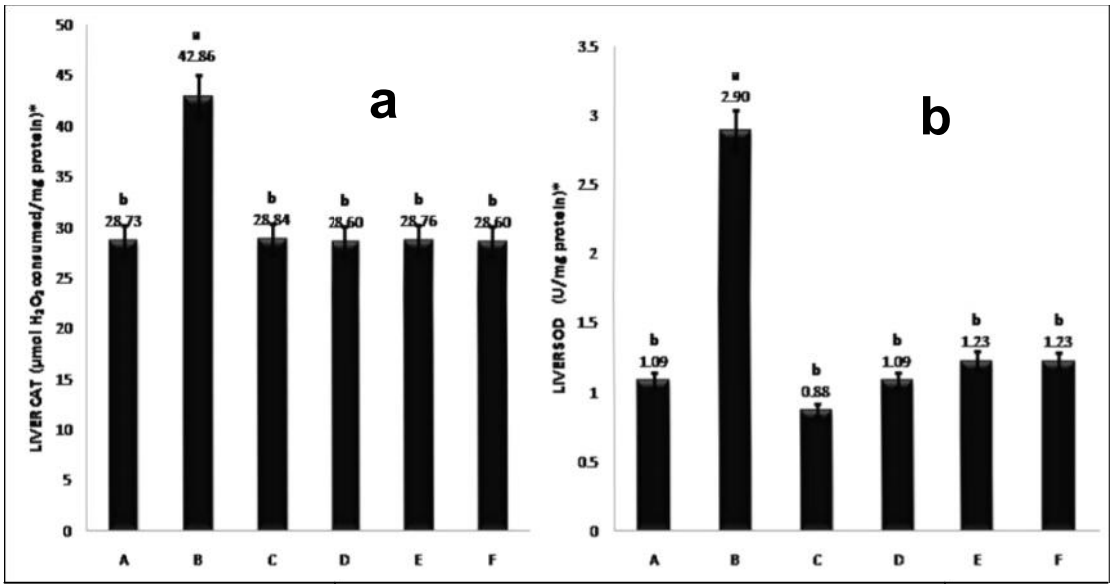
A = Control group, B= Cisplatin (10 mg/kg), C= Launea taraxacifolia (LT) 100 mg, D= LT (400 mg), E= LT (100 mg) + CIS, E= LT (100 mg) + CIS



Figs. 4a and b. Effect of Launea taraxacifolia extracts on cisplatin-induced alterations in (a) Glutathione (GSH) and (b) lipid peroxidation levels in kidneys

*Bars with different superscripts are significantly different; *p < 0.05*

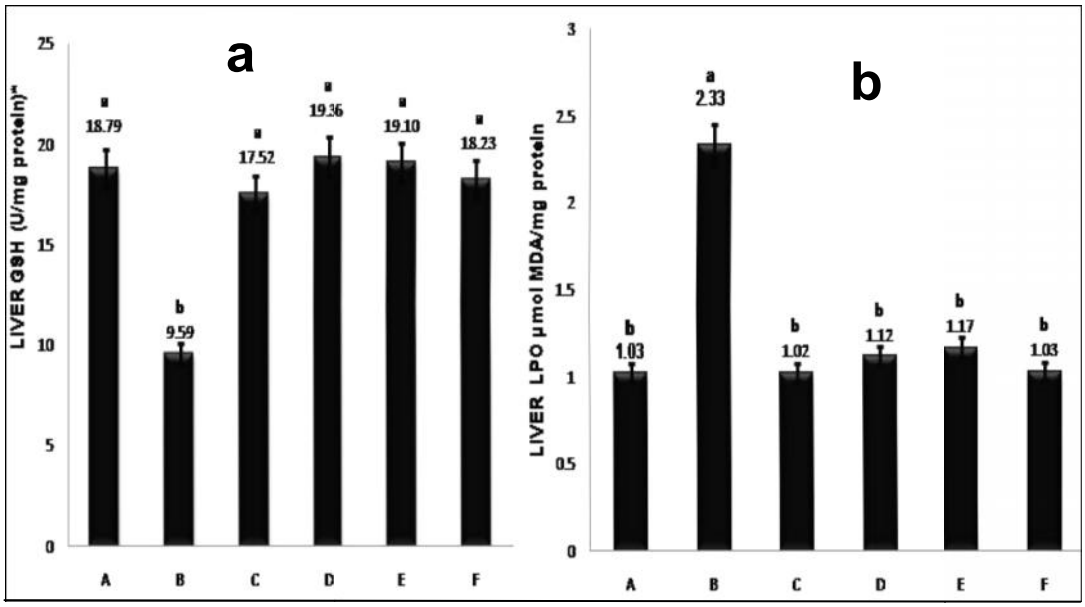
A = Control group, B= Cisplatin (10 mg/kg), C= Launea taraxacifolia (LT) 100 mg, D= LT (400 mg), E= LT (100 mg) + CIS, E= LT (100 mg) + CIS



Figs. 5a and b. Effect of Launea taraxacifolia extracts on cisplatin-induced alterations in (a) Catalase (CAT) and superoxide dismutase (SOD) in liver

*Bars with different superscripts are significantly different; *p < 0.05*

A = Control group, B= Cisplatin (10 mg/kg), C= Launea taraxacifolia (LT) 100 mg, D= LT (400 mg), E= LT (100 mg) + CIS, E= LT (100 mg)+CIS



Figs. 6a and b. Effect of Launea taraxacifolia extracts on cisplatin-induced alterations in (a) Glutathione (GSH) and (b) lipid peroxidation levels in liver

*Bars with different superscripts are significantly different; *p < 0.05*

A = Control group, B= Cisplatin (10 mg/kg), C= Launea taraxacifolia (LT) 100 mg, D= LT (400 mg), E= LT (100 mg)+CIS, E= LT (100 mg) + CIS

5. DISCUSSION

Cisplatin is a commonly used cytotoxic drug for the treatment of a wide variety of tumors. However, studies have shown that it has both dose-dependent and duration dependent nephrotoxic and hepatoxic [4-6] side effects. The generation of reactive oxygen species and the decrease in the antioxidant enzymes may characterized cisplatin–induced tissue toxicity [30;6]. The observed increased reno-somatic index and reno-parenchymal lesions in the cisplatin exposed rats are in consonance with Mansour [30] reports on cisplatin-induced alteration to kidneys architecture and reno-somatic index. The increase in the kidney mass as percent of body mass is a result of acute renal parenchyma oedema.

Liver enzymes (ALT and AST) are biochemical indicators of acute hepatocellular damage. Their increase serum levels reflect the degree of hepatocellular membrane damage and leakage [31]. The changes in the serum levels of bilirubin and the serum proteins are biochemical indicators of the morphological integrity of the hepatocytes [25;32]. This work shows that cisplatin treatment significantly elevates serum hepatic enzymes (ALT and AST), bilirubins and reduces albumen and total proteins levels which are indicators of hepatocellular dysfunction as previously documented by Mansour [8]. It is noted that the serum levels of these biochemical markers of hepatocellular injury significantly improved in Group E and F that have combined exposure. This protection could be ascribed to the high flavonoids content (an antioxidative agent) in the aqueous extract of *Launea taraxacifolia* [16,18].

The levels of blood urea nitrogen and creatinine which are indicators of renal dysfunction were elevated in cisplatin exposed rats probably due to the ability of cisplatin to inhibit

protein synthesis in the tubular cells [33] or the initiation of lipid peroxidation and free radical generation [34,35] in renal tubular cells. These results agree with previous documentation on the cisplatin-induced nephrotoxicity [30,36]. However, these biochemical evidences of nephrotoxicity appear to be markedly improved in co-treated rats in Groups E and F. This apparent phytoprotective activity of *Launea taraxacifolia* could be ascribed to the high flavonoids content (an antioxidative agent) of the aqueous extract [16,18].

An antioxidant becomes oxidized when it destroys a free radical. Therefore, the antioxidant resources must be constantly restored in the body. Superoxide dismutase and catalase are primary enzymes and GSH (an intermediate metabolite) involved in direct elimination of reactive oxygen species namely superoxide radical and hydrogen peroxide [37]. Superoxide (SOD) constitutes the first line of defense against oxygen derived radicals and plays the role of dismuting superoxide radicals to H2O2, while CAT proceeds by metabolically eliminating H2O2 from the intracellular environment and in a way supporting the course of scavenging the hydrogen peroxide and hydroxyl radical generation and thus interrupting the propagation of the lipid peroxidation reaction [38]. The level of which is quantified by a measure of LPO status. Glutathione (GSH) chief role against oxidative stress is to scavenge hydroxyl radicals and singlet oxygen directly [38]. The increase SOD and CAT levels in the hepatic and renal tissues in exclusively cisplatin treated Group B rats is an acute biochemical response to cisplatin precipitated oxidative stress. These elevated endogenous enzymes levels is due to a transient adaptive mechanism initiated by the defence system which probably after two weeks or more would be overwhelm by free radical attacks. These finding agrees partially with Amin et al. [39] report of exclusive rise in SOD level of cisplatin exposed rats. However, it contrast reports of decrease in the antioxidant enzymes typifying cisplatin –induced tissue toxicity [30;6]. The concomitant decrease in GSH activity of both the liver and kidney tissues in cisplatin group was a consequence of increased oxidative stress and cellular damage. This result concur with Florea [40] who further reported cisplating-alterations linkage to increase cytochrome P 450 and decreased cytochrome b(5) levels. Additionally, the increased LPO in cisplatin exclusively treated rats is due to the attack by reactive oxygen on cellular components of polyunsaturated fatty acid residues of phospholipids, which are exceptionally sensitive to oxidation [41].

However, the stable status of the endogenous enzymes (SOD and CAT) observed in the co-treated animals (Group E and F), the marked reduction in LPO and a higher GSH levels suggest that LT at doses of 100 and 400 mg/kg b.wt fortified the antioxidant defense system and prepared the animals to withstand the damaging effects of cisplatin administration probably through its flavonoid contents.

6. CONCLUSION

This study has demonstrated that *Launaea taraxacifolia* ameliorates cisplatin induced hepatorenal injury via its antioxidative activities.

CONSENT

Not applicable.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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