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Hepatoprotective Effect of Lantana camara L. Flower Extracts Against Acetaminophen-Induced Liver Injury in Wistar Rats

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Abstract

Background and Objective: Acetaminophen (APAP) overdose is a leading cause of acute liver failure worldwide. Lantana camara possesses antioxidant and membrane-stabilizing properties suggesting potential hepatoprotective activity. This study investigates the hepatoprotective effects of L. camara flower extracts against APAP overdose induced liver damage in rats.The study was conducted at National Veterinary Research Institute, Vom from August 1st, 2022 to November 15th, 2022. Dried L. camara flowers were extracted in methanol. Hepatotoxicity was induced in Wistar rats weighing 125±25g, with 750 mg/kg APAP on day 6 and pretreated for 5 days with 100, 300 or 500 mg/kg of methanolic L. camara flower extracts (n=5 per group). The rats were then sacrificed and evaluated for prophylactic effect against alterations in liver enzymes (ALT, AST, ALP), albumin, bilirubin and total protein. Histopathological examination of liver was also carried out.The groups treated with L. camara flower extracts exhibited dose-dependent prophylactic activity. The 500 mg/kg extract dose showed maximal efficacy with significant ($p<0.05$) reduction of AST by 63%, ALT by 105%, and ALP by 80%, and near-normalization of bilirubin and protein levels, compared to APAP control. Histology revealed normal hepatic architecture with only mild hepatomegaly at 500 mg/kg dose.L. camara flower extract exhibited remarkable protective effects against APAP-induced liver damage as evidenced by biochemical and histological parameters. The 500 mg/kg dose conferred optimal hepatoprotection, validating its potential as an alternative therapy for APAP toxicity.

1. Introduction

The liver is a vital organ that carries out over 500 essential functions including metabolism, nutrient storage, and detoxification. It plays a central role in maintaining normal physiology and overall health. Acute liver injury or disease poses serious health risks and threatens survival if not addressed promptly.[1]

Acetaminophen (APAP), commonly known as paracetamol, is one of the most widely used over-the-counter analgesic and antipyretic drugs worldwide due to its excellent safety profile at therapeutic doses. However, an overdose, even slightly higher than the recommended limit, can cause acute liver failure which may require liver transplantation or can even be fatal.[2] The mechanism of APAP hepatotoxicity is complex but involves metabolic bioactivation by cytochrome P450 enzymes like CYP2E1 to form the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI).[3] At therapeutic doses, NAPQI formed is effectively detoxified by conjugation with glutathione (GSH). However, an overdose overwhelms the liver's detoxifying capacity leading to GSH depletion. The excess unconjugated NAPQI accumulates and binds covalently to cellular proteins causing oxidative stress, mitochondrial dysfunction and ultimately cell death via necrosis or apoptosis.[4] Other factors like generation of reactive oxygen species and impaired protein clearance have also been implicated in potentiating APAP hepatotoxicity.[5] Considering the increasing global burden of APAP toxicity and limitations of current antidotal therapies, there is an urgent need to explore alternative hepatoprotective agents.[6]

Lantana camara L. (Verbenaceae) is a widely distributed invasive shrub native to tropical regions of America. It has naturalized and become established in many parts of Asia, Africa and Australia.[7] In traditional medicine systems, various parts of L. camara have been employed for the treatment of infections, inflammation, wounds and diabetes.[8]

Previous studies have demonstrated wound healing,[9] antidiabetic,[10] analgesic and anti-inflammatory[11] activities of L. camara extracts. Regarding hepatoprotection, L. camara leaf extracts alleviated carbon tetrachloride-induced liver toxicity in rats.[12] However, scientific data on the hepatoprotective potential of L. camara flowers against acetaminophen-induced liver injury are lacking. Considering the antioxidant-rich composition and ethnomedicinal uses of L. camara flowers, we sought to evaluate if pre-treatment with L. camara flower extracts can protect against subsequent APAP overdose induced liver damage in rats. This study was undertaken due to the rising global burden of APAP hepatotoxicity and the need for alternative therapeutic approaches..

2. Materials and Methods

2.1. Experimental Animals

In this study, [25] male Wistar rats, weighing 100-150 g were procured from National Veterinary Research Institute, Vom, Plateau State. The animals were housed under standard room temperature and 12 hours of light/dark cycle and fed with commercial pellet diet and water ad libitum. The study protocol was approved by the Research Ethics Committee of Modibbo Adama University, Yola (UAEC/YMAU/YL/0753) as per prescribed guidelines by National Health Research Ethics Committee of Nigeria NHREC[13], Hepatotoxicity was induced by a single oral dose of 750 mg/kg of Acetaminophen. The acetaminophen was suspended in 1% carboxymethyl cellulose and given via oral gavage at a volume of 10 mL/kg body weight.

2.2. Plant Materials and Extraction

The fresh flowers of Lantana camara was collected from wild sources in National Veterinary Research Institute, Vom, Nigeria. Taxonomic identification and authentication were performed by O. E. Agyeno, a Botanist from the Department of Plant Science Technology, University of Jos, Plateau State where a voucher specimen (Herbarium No. UJH19000291) was deposited. The collected flowers (100 g) were shade-dried, pulverized to powder and subjected to extraction with 80% methanol (1 L) using maceration method as described by Araya[14]. The powdered plant sample was infused in methanol for 72 hours and filtered using Whatman Filter Paper No.1. The filtrate was concentrated using a rotary evaporator, dried at 50 ℃ in a water bath and stored at room temperature.

2.3. Phytochemical Screening

Preliminary phytochemical screening of the extract was performed to identify major chemical constituents using standard procedures.[15] Qualitative and quantitative evaluation of the phytochemical constituent was carried out.

2.4. Experimental Design

For a duration of 6 days, five groups of Wistar rats, each containing 5 rats, underwent different treatments. Group I, known as the normal control, was given distilled water orally at a dosage of 10

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mL/kg. Group II, referred to as the acetaminophen control, was administered distilled water for the first 5 days, followed by acetaminophen (750 mg/kg), as adopted from [16] on the 6th day to induce hepatotoxicity.[17] Group III was treated with L. camara flower extract (100 mg/kg) for 5 days, then given acetaminophen (750 mg/kg) on the 6th day. Group IV received L. camara flower extract (300 mg/kg) for 5 days, followed by acetaminophen (750 mg/kg) on the 6th day. Group V was treated with L. camara flower extract (500 mg/kg) for 5 days, then given acetaminophen (750 mg/kg) on the 6th day. The vehicle, extracts and acetaminophen were all administered daily by oral gavage in a volume of 10 mL/kg body weight. On the final day of treatment, rats were euthanized humanely by cervical dislocation under anaesthesia. Blood samples were collected immediately via cardiac puncture for biochemical analysis. Small section of each liver was excised and fixed in 10% formalin for histopathological examinations.

2.5. Biochemical Analysis

The serum levels of ALT and AST were gauged using standard calorimetric methods at 546 nm employing Randox kits (Randox Laboratories Ltd., UK) according to principles by Reitman and Frankel [18]. ALP activity was measured calorimetrically at 410 nm using p-Nitrophenylphosphate as substrate.[19] The levels of total and direct bilirubin were also assessed calorimetrically at 578 nm using Randox assay kits. In an alkaline environment, direct bilirubin and diazotized sulphanilic acid interact to form a blue complex. Total bilirubin was gauged by reacting with diazotized sulphanilic acid in the presence of caffeine, which liberated albumin-bound bilirubin.[20] Furthermore, total protein was gauged based on the principles put forth by Weichselbaum [21], which involved the creation of a coloured biuret complex, and albumin level was determined calorimetrically using Randox kits (Randox Laboratories Ltd., UK) based on the method by Doumas et al., [22].

2.6. Percent Hepatoprotection

Percent hepatoprotection from acetaminophen-induced changes in biochemical markers by L. camara flower extract in a pretreatment model was determined using method described by Kolakota et al., [23]. The percentage protection was determined using the formula:

$$\%\ Protection = \frac{Negative\ control - Treatment}{Negative\ control - Normal\ control} \times 100 \quad (1)$$

2.7. Histopathological Studies

The histopathological analysis of liver tissues was carried out as described by Choji et al., [24]. The liver from each mouse was surgically removed, rinsed with normal saline and preserved in 10% formalin. The tissue fixed in formalin was then washed with tap water. Following this, the tissue underwent dehydration through a series of ethanol treatments and was cleared with xylene. The tissue, now cleared with xylene, was embedded in paraffin wax. From the block of paraffin-embedded tissue, sections of 5 microns thickness were cut and stained with hematoxylin and eosin for histopathological examination. Slides for microscopic examination were prepared and scrutinized under a microscope. Images were captured using an Olympus DP12 CCD camera.

2.8. Statistical Analysis

Data were evaluated by SPSS version 27 software using one-way Analysis of Variance (ANOVA) followed by Tukey's post hoc test to separate the means that are statistically different. $P < 0.05$ was considered to be statistically significant.

3. Results and Discussion

3.1Phytochemical Analysis

The phytochemical analysis revealed the presence of several bioactive compounds in the methanolic flower extract of Lantana camara (Table 1). Qualitative screening detected the presence of saponins, tannins, flavonoids, alkaloids and phenols. Quantitative estimation showed that tannins were the most abundant compound (6.01%), followed by flavonoids (5.81%), phenols (3.91%), alkaloids (3.11%) and saponins (1.40%). However, terpenoids, glycosides and steroids were absent in the extract.

Table 1: Qualitative and quantitative phytochemical composition of the methanolic extract of L. camara flower.

Phytochemicals	Qualitative	Quantitative (%)
Saponins	+	1.40
Tannins	+	6.01
Terpenoids	–	–
Flavonoids	+	5.81
Alkaloids	+	3.11
Glycosides	–	–
Steroids	–	–
Phenols	+	3.91

(+) present, (–) absent.

3.2.Effect of Treatment on Liver Enzymes

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AST levels (Figure 1) were significantly heightened ($p<0.05$) in the acetaminophen control group (93.87 ± 4.17 U/L) compared to normal control (63.4 ± 3.63 U/L), indicating considerable liver damage. Pre-treatment with 100 mg/kg extract led to a small non-significant decrease in AST (89.57 ± 2.9 U/L). However, the 300 mg/kg and 500 mg/kg extract doses showed significant ($p<0.05$) reductions in AST levels (85.14 ± 2.44 U/L and 74.64 ± 2.83 U/L respectively) in a dose-dependent manner. Similarly, serum ALT levels (Figure 1) were significantly elevated ($p<0.05$) in acetaminophen control (45.61 ± 1.81 U/L) versus normal control (22.61 ± 2.01 U/L). The 100 mg/kg extract pre-treatment only marginally decreased ALT levels (33.39 ± 1.57 U/L). But 300 mg/kg extract led to significant ($p<0.05$) decline (27.04 ± 0.93 U/L) and 500 mg/kg extract showed maximum reduction (21.32 ± 0.93 U/L) close to normal control. Serum ALP levels (Figure 1) demonstrated significant ($p<0.05$) increases in acetaminophen control (131.56 ± 6.08) compared to normal control (90.98 ± 4.41 U/L). The 100 mg/kg extract pre-treatment non-significantly reduced ALP (124.9 ± 1.94 U/L). However, 300 mg/kg and 500 mg/kg flower extracts exhibited marked significant ($p<0.05$) dose-dependent decreases in elevated ALP levels, confirming protective effects.

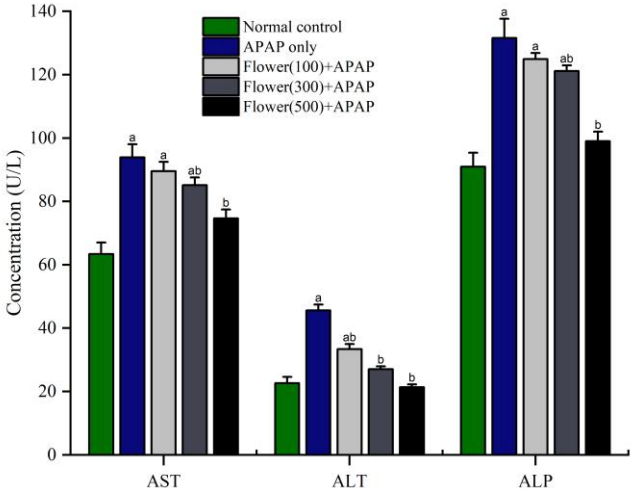

Figure 1: Effect of L. camara extract on liver enzymes in acetaminophen-induced liver toxicity in Wistar rats. 'a' $p < 0.05$ higher from normal control. 'b' $p < 0.05$ lower from APAP only.

3.3. Effect of Treatment on Total Protein, Albumin and Bilirubin

Serum albumin levels (Figure 2) were not significantly ($p<0.05$) affected by acetaminophen or the treatment extract. However, total serum protein levels were significantly reduced ($p<0.05$) in acetaminophen control group (47.77 ± 0.73 g/L) versus normal control (63 ± 1.41 g/L) suggesting impaired protein synthesis. But 100 mg/kg, 300 mg/kg and 500 mg/kg extract doses showed significant ($p<0.05$) dose-responsive increases in total protein (58.99 ± 1.31 g/L, 62.49 ± 1.61 g/L and 64.9 ± 2.78 g/L respectively) indicating maintained liver function. Total and direct serum bilirubin levels (Figure 2) were significantly ($p<0.05$) elevated in acetaminophen control group compared to normal control suggesting impaired bilirubin metabolism and excretion. However, Lantana camara flower extracts demonstrated significant ($p<0.05$) dose-dependent reductions in both total and direct bilirubin levels.

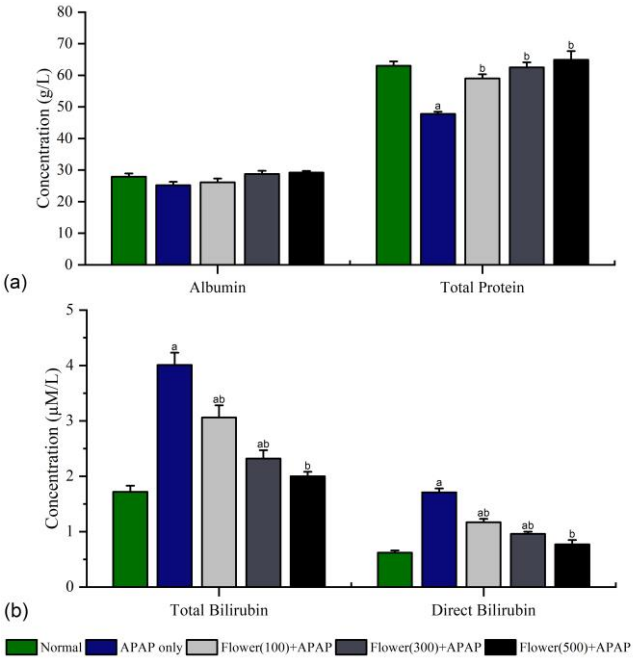

Figure 2: Effect of L. camara extract on (a) serum albumin and total protein, (b) total and direct bilirubin in acetaminophen-induced liver toxicity in Wistar rats. 'a' $p < 0.05$ from normal control, 'b' $p < 0.05$ from APAP only.

3.4 Percentage Protection

The percent protection conferred by different doses of Lantana camara flower extract against acetaminophen-induced alterations in some liver indices is shown in Figure 3. The 100 mg/kg extract dose showed moderate percent protection against AST (14.11%), ALT (53.13%), ALP (16.41%), total protein (73.67%), total bilirubin (41.48%) and direct bilirubin (49.54%). The 300 mg/kg extract exhibited improved protection over 100 mg/kg with percentage protection of 28.65% for AST, 80.74% for ALT, 25.6% for ALP, 96.65% for total protein, 73.8% for total bilirubin and 68.81% for direct bilirubin. However, the 500 mg/kg flower extract dose displayed

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maximum percent protection across all parameters - 63.11% for AST, 105.61% for ALT, 80.26% for ALP, 112.48% for total protein, 87.77% for total bilirubin and 86.24% for direct bilirubin. Notably, the high ALT and ALP protection percentages of 105.61% and 80.26% respectively with 500 mg/kg extract signify that enzyme levels were brought down below normal control by the extract dose.

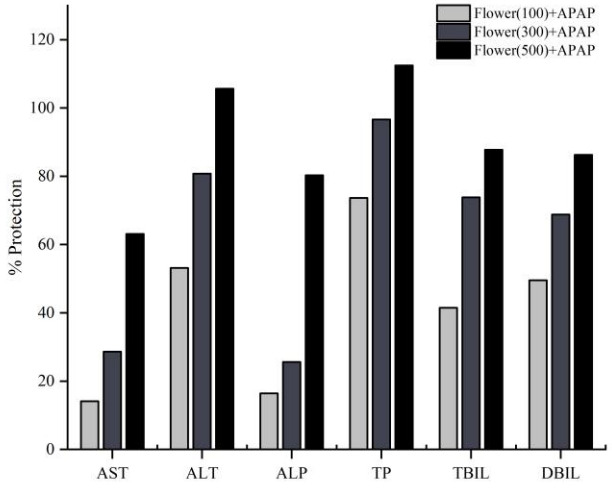

Figure 3: Percent protection of the L. camara extract against acetaminophen-induced toxicity on serum liver markers.

3.5. Histopathological Analysis

Histopathological examination of the liver tissues revealed marked differences between the treatment groups (Figure 4). The liver section from the normal control group (A) showed normal hepatocyte morphology with intact nuclei surrounded by intact cytoplasm and clearly defined cellular outlines. In contrast, the acetaminophen control group (B) exhibited severe hepatic damage characterized by extensive hepatic cord atrophy, cellular vacuolation with naked nuclei, disrupted cellular boundaries appearing as strands and mild hemorrhage. While the lowest extract dose of 100 mg/kg (C) still showed considerable cellular degeneration, the 300 mg/kg dose (D) aided in reducing inflammation and tissue disorganization. the 500 mg/kg dose (E) produced near-normal histology with only mild hepatomegaly and alleviated hepatic vacuolation.

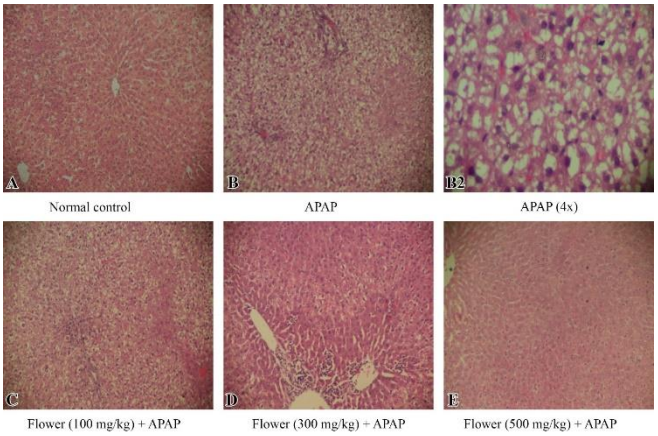

Figure 4: Photomicrographs of the Haematoxylin-Eosin-stained liver sections. (A) Normal control; (B) APAP only; (C-E) Pretreated with 100, 200 and 300 mg/kg of the L. camara flower extract respectively, before APAP overdose.

4.Discussion

The aim of this study is to investigate the potential protective effect of Lantana camara methanolic flower extract against acetaminophen-induced liver toxicity. The rich phytochemical profile (Table 1) which include tannins and flavonoids are polyphenolic antioxidants that can scavenge free radicals and exhibit anti-inflammatory activities.[25] The high tannin and flavonoid content of the L. camara extract likely contributes to its antioxidant and hepatoprotective potential. Alkaloids have been reported to demonstrate a wide range of pharmacological activities including antimicrobial, antidiabetic, anticancer, etc.[26] Phenols exhibit a wide range of biological properties including antioxidant, anti-inflammatory, antimicrobial, immunomodulatory and tissue protective effects.[25] The phenolic compounds in L. camara flowers can scavenge free radicals, chelate redox-active metals and attenuate lipid peroxidation and protein carbonylation induced by toxins like APAP.[27] This may significantly contribute to its observed hepatoprotective activity

The substantial elevations of serum AST, ALT and ALP levels (Figure 1) in the acetaminophen control group confirm significant liver injury induced by the overdose, consistent with previous reports.[17] The dose-dependent reductions of these enzyme levels by Lantana camara flower extracts provide evidence on its hepatoprotective effects against APAP-triggered damage.

The attenuation of serum AST levels by the flower extracts indicates maintained integrity of liver cell membranes to prevent cytosolic AST leaking into circulation.[28] This suggests the extracts likely prevent acetaminophen-induced oxidative damage

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and stabilize hepatocellular membranes to restore function.

The progressive dose-dependent decline and normalization of ALT levels also clearly demonstrate extract-mediated hepatoprotection through inhibiting cell membrane disintegration to block ALT release.[29] The significant alleviation of elevated ALP by flower extracts, particularly 500 mg/kg dose, confirms mitigation of cholestasis and improved bile flow. This also indicates lesser biliary epithelial injury and regeneration by the extracts through reducing APAP-induced oxidative stress and restoration of glutathione levels. [4,29]
The repairs of cell membrane, cytosolic contents leakage and biliary function cumulatively confer reversal of acetaminophen hepatotoxicity.
The slight decline in serum albumin and significant declines in total protein levels upon acetaminophen overdosage (Figure 2) indicate considerable impairment of liver's synthetic capacity. Albumin constitutes the highest proportion of serum proteins produced by the liver. Hence, hypoalbuminemia signifies the severity of hepatocellular damage. [30] Total proteins also represent the functional state of the liver. The dose-responsive increases in albumin and protein levels by the flower extracts therefore clearly demonstrate enhanced functional hepatocyte mass and recovered protein synthesis ability of the regenerating liver.[31] Moreover, significant hyperbilirubinemia marked by high total and direct bilirubin levels was observed upon acetaminophen toxicity, denoting serious liver injury. This suggests inhibition of bilirubin metabolism and transport function of hepatocytes by the reactive metabolites of acetaminophen overdose.[32] However, flower extract pretreatment conferred marked alleviation of hyperbilirubinemia even at the lowest dose of 100 mg/kg. The progressive decline and near-normalization of bilirubin levels substantiate improved structural integrity of hepatic cells, restored expression of bilirubin metabolizing enzymes and transporters.[33]
The percentage protection calculations (Figure 3) provide further quantitative evidence on the excellent hepatoprotective efficacy exhibited by Lantana camara flower extracts, especially at higher doses of 300 mg/kg and 500 mg/kg body weight. The 500 mg/kg dose displayed outstanding protection of over 80% against acetaminophen-triggered elevations in ALP and ALT levels, suggesting remarkable restoration of biliary function and maintenance of hepatocellular membrane integrity respectively.[34] Maximum percent reductions were also achieved with this dose for AST, total protein and bilirubin levels, substantiating its potent curative effects against acetaminophen hepatotoxicity. The considerable protection percentages against AST elevation additionally indicate stabilized cytosolic contents and cytoskeletal structures alongside membrane integrity.28 Enhanced total protein and lowered bilirubin levels further validate recovered synthetic and excretory capacity of regenerating hepatic tissues.[4]
The photomicrographs (Figure 4) provide direct validation on the excellent protective effects of L. camara flower extracts against acetaminophen hepatotoxicity. The loss of cellular architecture seen in acetaminophen control liver sections is attributable to membrane damage and oxidative injury triggering cell death pathways.[5]
This leads to the observable distorted tissue patterns, vacuolations and haemorrhage along with compromised functional capacity as evidenced through elevated enzymes and bilirubin. However, sequential improvements were clearly documented in extract treated groups with 100 and 300 mg/kg doses still showing inflammatory signs which were completely absent in the 500 mg/kg group. The extracts likely confer protection via free radical scavenging, restoration of glutathione levels and prevention of covalent binding mediated organellar dysfunctions as reflected through retained cytological integrity.[4]
The findings strongly validate enhanced structural and functional regeneration of hepatic tissues to near normalcy by flower extracts through mitigation of APAP-induced damage in a dose-dependent manner.
The study provides substantial evidence on the hepatoprotective efficacy of Lantana camara flower extracts against acetaminophen-induced liver injury in an experimental rat model. The extracts exhibited significant dose-dependent amelioration of biochemical and histological indices of acute liver damage triggered by acetaminophen overdose.

4. Conclusion

This study provides the first scientific report on promising therapeutic potentials of Lantana camara flower extracts against APAP overdose-mediated hepatotoxicity. Using a comprehensive panel of functional biochemical markers and histological indicators, significant dose-dependent amelioration of acute liver damage in rats by the methanolic extract was demonstrated. 500 mg/kg dose conferred maximal reversal of biochemical alterations viz. up to 105% restoration of serum

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ALT and 80% recovery of alkaline phosphatase levels alongside normalizations of albumin, bilirubin and AST. Histological examinations also evidenced remarkable structural and morphological recoveries. The results establish significant hepatoprotective efficacy of Lantana camara flowers mediated through maintenance of membrane integrity, metabolic and excretory functions as well as tissue architecture.

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Authors' Contributions
Conceptualization: HS, BB; Data curation, Formal analysis, Methodology, Project administration, Software, Writing-original draft: HS; Funding acquisition, Investigation, Resources, Supervision, Validation, Visualization, Writing-review & editing: HS, BB, UAA.

Conflict of interest
The authors declared that there was no conflict of interest.

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