湖南大学学报（自然科学版）
Journal of Hunan University (Natural Sciences)

第 50 卷 第 3 期
2023 年 3 月

Available online at http://jonuns.com/index.php/journal/index

Vol. 50 No. 3
March 2023

Open Access Article

https://doi.org/10.55463/issn.1674-2974.50.3.15

Ameliorating Effects of *Croton Bonplandianus* Leaves against Gentamicin Induced Acute Liver and Kidney Injury: A Biochemical and Histopathological Investigation

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Received: January 10, 2023 ▪ Review: February 9, 2023 ▪ Accepted: March 6, 2023 ▪ Published: March 31, 2023

Abstract: The utilization of natural constituents for the treatment of various medical complaints is well established. The members of the Euphorbiaceae family, especially the Croton genus, are reported to be rich in diterpenoids and showing various biological activities. Many activities of *Croton bonplandianus* are still unfolded therefore, current study is designed to evaluate the ameliorative effects of aqueous extract of *C. bonplandianus* against gentamicin-induced liver and kidney injuries in rats. The aqueous extract of leaves (27-81 mg/kg) was administered to albino rats Wistar strain for eight days with concurrent administration of gentamicin (100 mg/kg) daily. The protective effect of the aqueous extracts on the liver was determined by liver function tests (SGPT, ALT, GGT, Bilirubin) and kidney functions were evaluated by assessment of plasma biomarkers including urea, creatinine, uric acid and electrolytes (sodium, potassium, chloride and bicarbonate). Histopathological studies of liver and kidney tissue were carried out by Hematoxylin and Eosin (H& E) staining confirmation of the consequences. Significant alterations in liver and kidney tissues treated groups with aqueous extracts of leaves were obtained in lower doses (27-54 mg/kg). Similarly, serum levels of SGPT, ALT, GGT, bilirubin, creatinine, and urea in the treated group were significantly reduced ($P < 0.01$) at similar doses, whereas no significant changes were founded in levels of ions and uric acids. The histological examination of the liver and kidney confirmed the biochemical changes in treated rats. The underlying results demonstrate the protective effect of aqueous leave extracts *Croton bonplandianus* on an acute liver and kidney injury rat model. The hepato and renal protective effects of *C. bonplandianus* are certainly due to the presence of diterpenoids flavonoids and polyphenols exhibiting free radical or oxygen scavenging activities.

Keywords: *Croton bonplandianus*, gentamicin, histopathological studies, nephroprotective effect.

巴豆邦普兰迪亚努斯叶对庆大霉素诱导的急性肝肾损伤的改善作用：生化和组织病理学研究

摘要：利用天然成分治疗各种医疗问题已经很成熟。据报道，大戟科植物，尤其是巴豆属植物，富含二类化合物，具有多种生物活性。巴豆的许多活性仍未展开，因此，当前的研究旨在评估巴豆水提物对庆大霉素导的大鼠肝肾损伤的改善作用。将叶子的水提取物(27-81毫克/公斤)给予白化病大鼠威斯达品系8天，同时每天给予庆大霉素(100毫克/公斤)。水提取物通过对肝脏的保护作用通过肝功能测试（血清谷氨酸-丙酮酸转氨、丙氨酸氨基转移酶、γ-谷氨转移、胆红素)确定,肾功能通过评估血浆生物标志物（包括尿素、肌酸、尿酸和电解质钠、氯、盐和盐素)。对肝脏和肾脏组织进行病理学研究，通过苏木精和伊红染色确认结果。在较低剂量(27-54毫克/公斤)的叶水提取物治疗组中，肝脏和肾脏组织发生了显著变化。同样，治疗组血清谷丙转功能、丙氨酸氨基转移、维素、维素、含微氨素素素素素素和血清素含量在相似剂量下显着降低（P<0.01），而离子水平没有显着变化和尿酸。肝脏和肾脏的组织学检查证实了治疗大鼠的生化变化。基本结果证明了巴豆叶水提取物对急性肝肾损伤大鼠模型的保护作用。巴豆的肝和肾保护作用肯定是由于二种黄酮和多 囧 的存在表现出自由基或氧清除活性。

关键词：巴豆，庆大霉素，组织病理学研究，肾保护作用。

Introduction

Pakistan showed rich and diverse plants, from which substances with distinct pharmacological activities have been identified. Moreover, the use of medicinal flora native to Pakistan is the growing area of research for scientists [1]. Wide varieties of medicinal plants have been tested and showed therapeutic potential against drug -induced liver and kidney disorders [2]. Several compounds in the plants such as flavonoids, alkaloids, terpenes, and phenolic compounds possess hepatoprotective and nephroprotective activities [3]. Drug-induced liver and kidney injuries are the main causes of drug discontinuation despite the ultimate need for therapy. *Croton bonplandianus* is a perennial herb indigenous to south Bolivia and founded in Asia. Different species of *Croton* (Euphorbiaceae) showed antiviral, anti-bacterial, anti-fungal, anti-inflammatory, anti-plasmodic, anti-proliferative, and antiseptic activities in the complementary traditional medicine [4]. Several compounds are identified in various croton species such as alkaloids, terpenoids, and saponins that have marked therapeutic activity [5].

Literature revealed that the methanolic and aqueous extracts of *C. bonplandianus* contained rutin, crotsparine and its methylated derivative phorbol, flavonoids, alkaloids and phenolic content, saponin and tannins [6, 7]. Plant material showed analgesic, anti-oxidant, anti-bacterial, anti-fungal, hepatoprotective, anti-coronary, insect repellent, and wound healing effects [8].

Liver and kidney damage are mainly caused by the used of various chemical agents, when taken in high dose or on prolong used [9]. Kidney damage is usually characterized with increased exposure to medication [10]. Non-selective NSAIDs (non-steroidal anti-inflammatory drugs), anti-cancer drugs, antibiotics, and amino glycosides are well-reported causes of renal damage [11, 12]. Gentamicin is an aminoglycoside antimicrobial used to treat several grams -negative infections but it showed severe adverse drugs such as nephrotoxicity, hepatotoxicity and ototoxicity.

The possible mechanism of hepatic injury of gentamicin is the induction of oxidative stress and inflammation that leads to the mitochondrial dysfunctioning and ultimately leads to elevation in hepatic biomarkers such as ALT, ALP, total bilirubin, and gamma GT [13, 14]. Drug-induced acute liver damage is considered as the membrane deterioration, infiltration of neutrophils, hepatocyte necrosis, release of cytokines, and production of reactive oxygen species (ROS) [9]. Similarly, gentamicin also induces kidney damage by producing reactive oxidation species and apoptosis in the renal proximal tubule [15]. Gentamicin deposits in the renal tubule, where it induces membrane damage, necrosis, inflammation, apoptosis, and release of vasoconstrictor hormone. These events affect the membrane permeability and ultimately lead to the reduction in the glomerular filtration rate (GFR) [3]. These effects make it a suitable agent for the induction of hepatic and nephrotoxicity [16].

On the basis of former research, the aqueous extracts of leaves of the *Croton bonplandianus* were selected for hepatoprotective and nephroprotective

effects against gentamicin-induced hepatic and renal injuries.

The aqueous fraction is considered safe while administered to animals for liver protective and renal protective effects comparative to methanolic extract. The detailed microscopic examination of liver and kidney tissues was conducted to ascertain the preventative effect of plant extracts on tissues of vital organs. Beside the histopathological studies biomarker related to hepatic and renal injuries were also determined to confirm the findings of the study.

1. Materials and Method

Aqueous extracts of leaves of *Croton bonplandianus* (CB) (27-81 mg/kg), paracalcitrol (PC) (100 mg/kg), gentamicin (GM) (100 mg/kg), distilled water, and feeding tubes.

1.1. Solvents

Hexane (Sigma-Aldrich), chloroform (Sigma-Aldrich), methanol (Sigma-Aldrich), ethyl acetate (Sigma-Aldrich), and distilled water.

1.2. Collection and Identification of Plant Material

Leaves of the *Croton bonplandianus* (Euphorbiaceae) were collected from the botanical garden of the University of Karachi. Leaves were authenticated by the taxonomist from the Department of Botany, University of Karachi. A voucher specimen (no. 03) was preserved and deposited in the Department of Pharmacognosy, Baqai Institute of Pharmaceutical Sciences, Baqai Medical University, Karachi.

1.3. Extraction and Fractionation of Leaves

Dried leaves (1 kg) were extracted in Methanol (7L) for 15 days at room temperature followed by filtration with Whatman filter paper (45 micron). This procedure was repeated with residual material twice and combined all filtrates. The methanolic extract was concentered using a rotary evaporator under reduced pressure and controlled temperature (40^{o}C). Then, the extract was suspended in H_2O sequentially partitioned with n-hexane, chloroform and EtOAc. All the fractions were lyophilized to obtained dried extracts and were store at 4^{o}C up to be used for pharmacological work [17, 18].

1.4. Animal Model

Adult male albino rats of wistar strain weighing 200 ± 10 g were selected for nephroprotective and hepatoprotective activity provided by Baqai Institute of Pharmaceutical Sciences, Baqai Medical University Karachi followed using Winter method [19].

Animals were kept as per the standard rule given by animal houses with maintained temperature 25 ± 2 °C for 12-hour light/dark cycle. Rats fed with a laboratory standard balance diet and water *ad libitum* [20].

1.4.1. Ethical Approval

The study was approved by the Ethical Committee of Baqai Medical University, Karachi, Pakistan Ref. # BUU-EC/2018/01.

1.5. Experimental Design

Animals were weighed and randomly divided in six groups, each of six animals and treated in the following manner:

The control group daily received only 10 ml/kg distilled water for 8 days orally.

GM group: treated with 100 mg/Kg of gentamicin intra-peritoneally daily.

GM-PC group: treated with 100 mg/Kg of gentamicin and 100 mg/Kg paracalcitriole daily.

GM-CB group rats were given three different oral doses (81, 54 and 27 mg/Kg) of aqueous extract of CB concurrent with GM at 100mg/kg daily for 8 days [4, 21].

1.6. Blood Collection and Tissue Preparation

After 24 hours after the last dose, all the animals were anesthetized. The thoracic cage was exposed and approximately 5ml of blood was collected from each rat by the cardiac puncture technique. Blood samples were then transferred to the gel tube for biochemical estimation [22]. The blood was centrifuged for 8-10 minutes at 3500 RPM. The serum was stored after separation into eppendorf tubes at -20 °C for estimation of renal and hepatic biomarkers. After that, the rats were sacrificed by cervical dislocation and their livers and both kidneys were removed immediately and kept in 10% formaldehyde for histopathological processes [23-25].

1.7. Measurement of Serum Biochemical Parameters

The hepatic biomarkers including AST, ALT, GGT and serum total, direct and indirect bilirubin were assayed using commercial reagent kits from Merck (Germany). Renal biochemical markers (creatinine, urea and uric acid) were estimated using commercial reagent kits (Sigma-Aldrich) as per the manufacturer protocol. The serum electrolyte levels were also determined by adopting standard methods.

1.8. Histopathological Examination

The isolated kidneys and liver from all groups were preserved in formalin 10% and embedded in paraffin wax as a standard protocol. Afterward 5-micron thick tissue sections were sliced, mounted on a poly-1-lysine coated glass slide, and stained with haematoxylin and eosin (H & E) for histopathological examination. Stepwise methodology are represented in fig. 1 [26].

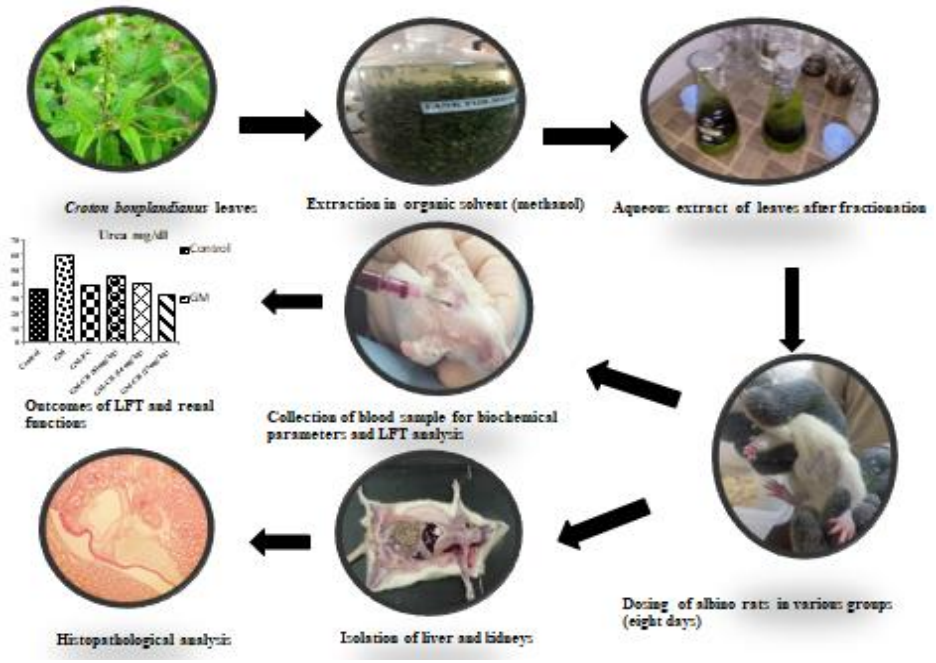


Fig. 1 Leading steps of the research methodology

2. Result

2.1. Biochemical Analysis

2.1.1. Renal Functional Biomarkers

Gentamicin (GM) induced nephrotoxic mode was used to evaluate the nephroprotective effects of plant extracts. The serum electrolyte levels, including Na^{++}, K^{+}, Cl^{-} and HCO_3 were not changed significantly. The lower dose of CB showed a greater reduction in serum uric acid levels compared to high dose. The GM-treated group showed elevated levels of urea and creatinine, while these parameters were markedly reduced in GM-PC group (standard). Concurrent administration of plant extracts in different doses with gentamicin displayed a protective role and prevented drug-induced nephropathies. The lower dose of CB showed a group maximum protective effect compared to the higher dose indicated by the marked reduction in creatinine level (Table 1, Fig. 2 and 3).

Table 1 Effect of aqueous extract of leaves and bark of *Croton bonplandianus* on different kidney functions

Samples	Uric acid mg/dl	Sodium mEq/l	Potassium mEq/l	Chloride mEq/l	Bicarbonate mEq/l
Control	1.6 ± 0.02	143 ± 1.27	4.2 ± 0.15	97 ± 0.24	28 ± 0.18
GM	1 ± 0.0	141 ± 0.16	4.6 ± 0.32	104 ± 0.45	20 ± 0.03
GM-PC	1 ± 0.0	143 ± 0.42	3.9 ± 0.47	103 ± 0.17	22 ± 0.4
GM (81 mg/kg)	1.41 ± 0.36	143 ± 0.77	4.85 ± 0.01	101 ± 0.24	27 ± 0.15
GM (54mg/kg)	1.84 ± 0.27	141 ± 1.58	6 ± 0.23	101.5 ± 0.98	23.5 ± 1.26
GM (27 mg/kg)	1.12 ± 0.06	142 ± 0.10	4.4 ± 0.17	104.5 ± 0.35	25 ± 0.77

Notes: Control - control group treated with distilled water (10 ml/Kg), GM - group treated with gentamicin, GM-PC - group treated with paracalcitriol (100 mg/kg) with gentamicin, GM-CB - groups treated with Aqueous extract of leaves of *C. bonplandianus* (81, 54 and 27 mg/kg). Not significant result obtained compared with control $P > 0.05$. Data expressed as mean ± SEM (n = 6) (ANOVA). *P* values < 0.05 were considered significant.

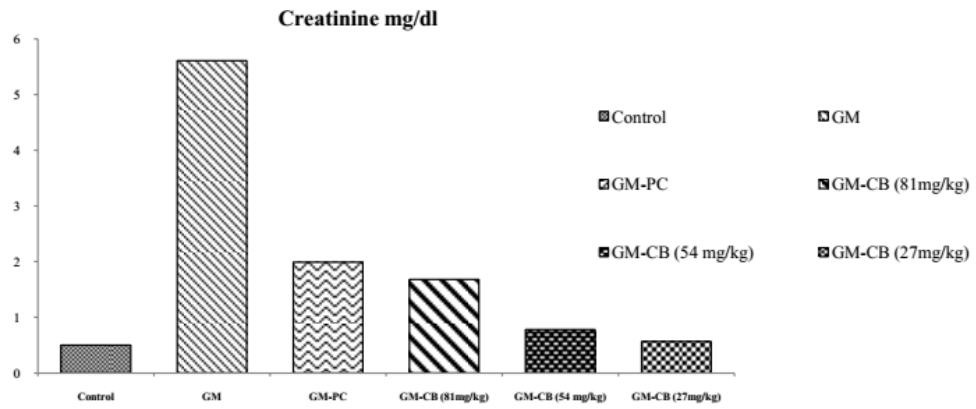


Fig. 2 Effects of different groups on creatinine levels for kidney function

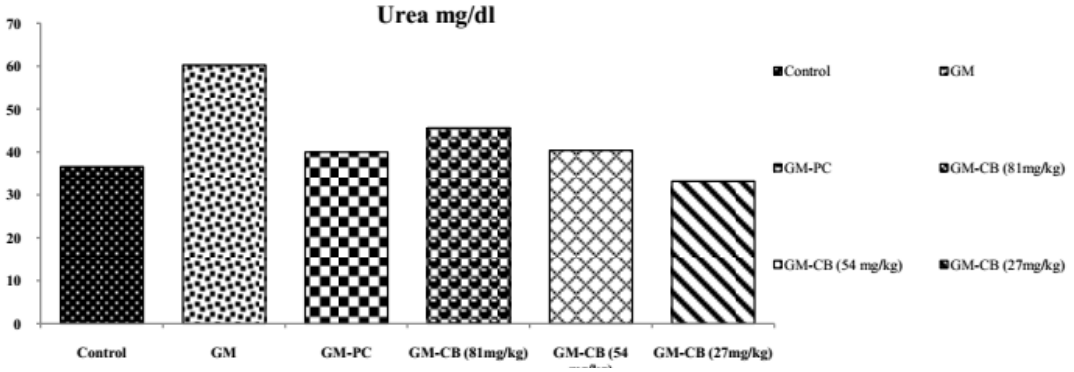


Fig. 3 Effects of different groups on urea levels for kidney function

2.1.2. Hepatic Functional Biomarkers

In the present studies, gentamicin induced liver damage indicated by elevated levels of transaminases (ALT, AST) in serum and minute increase in gamma GT (Fig. 4). The group treated with GM also showed an increased in plasma bilirubin concentration, which is characteristic marker that indicates liver injury and inhibition of detoxifying functions of the liver (fig. 5). Concomitant administration of CB extracts in different Doses along with GM showed a protective effect on the liver as all hepatic biomarkers were significantly reduced. All the doses of CB produce almost similar protective effects on GM-induced hepatotoxicity. These hepatic damage markers were also recently reported to be decreased by another species of croton called *Croton hypoleucus* [27]. In another investigation, the presence of α-amyrin in the leaf extract of *C. bonplandianus* has been documented against hepatocellular damage [28].

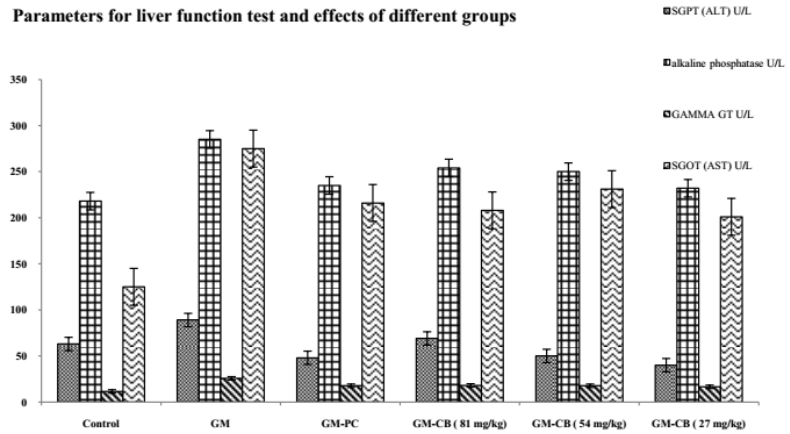


Fig. 4 Effects of different groups on liver function evaluation

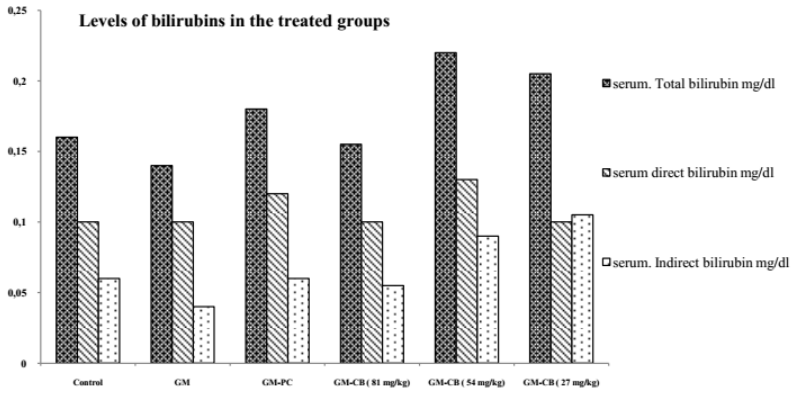


Fig. 5 Effects of different groups on different bilirubin on liver function evaluation

2.2. Histopathological Studies

2.2.1. Kidney

The kidney sections of the control group rats only exhibited a normal histological structure of renal tubules and glomeruli. Prominent macula densa and distal convoluted tubules were also noticed (Fig. 6a). The kidney section of the GM-treated group rats expressed variable and severe histological alteration. Lymphocyte infiltration, degeneration in the epithelial cell wall, dilated and edematous interstitium, and tubular epithelial necrosis were clearly observed.

Overall architecture showed marked inflammation, periarteriolar hemorrhages, and damaged renal glomeruli. Congested and dilated capillaries with degenerated and damaged glomerular were seen (Fig. 6b). The kidney section of the group of rats treated with GM-PC exhibited moderate lymphocyte infiltration in proximal convoluted tubules (PCT), mild dilation, and congestion in capillaries. The epithelial lining is slightly ruptured with inflammation (Fig. 6c).

These pathological alterations were observed in groups that received aqueous extract of leaves of *C. bonplandianus* with concurrent administration of GM in different doses (81, 54 and 27 mg/kg). The alleviated changes were indicated in low doses of aqueous leave extract. Renal glomeruli showed normal architecture with intact bowman capsules and minimal inflammation in GM-CB (27 mg/Kg) group (fig. 7c). The kidney section of rats of group GM-CB (54 mg/Kg) indicated mild damaged in epithelial cells and moderate inflammation, normal renal architecture, and intact bownans capsules (Fig. 7b). The kidney section of rats that were treated with high doses i.e., GM-CB (81 mg/Kg) showed moderate inflammatory cell infiltration, minor hemorrhages, and mild thickness in the epithelial lining (fig. 7a).

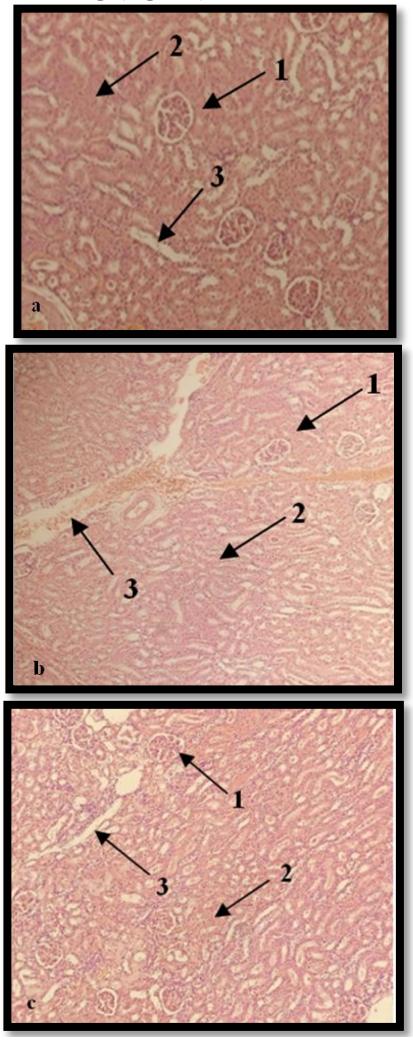


Fig. 6 Photomicrograph of 5-micron thick H & E-stained paraffin section from kidney rats: 1 - Bowman's capsule, 2 - Renal tubules, 3 - Interstitium (a: Control; b: GM; c: PC-GM)

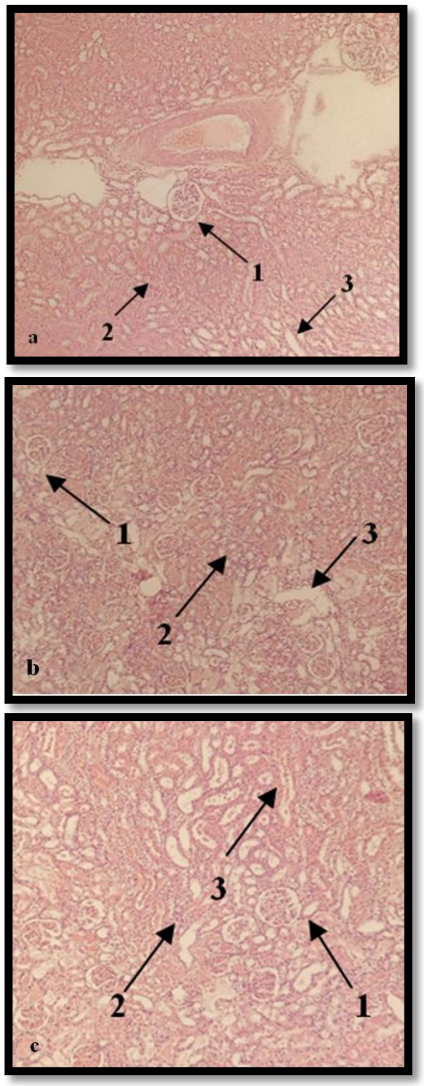


Fig. 7 Photomicrograph of 5 micron thick H & E-stained paraffin section from kidney rats: 1 - Bowman's capsule, 2 - Renal tubules, 3 - Interstitium (a: GM-CBn (81 mg/kg); b: GM-CB (54 mg/kg); c: GM-CB (27 mg/kg))

2.2.2. Liver

Histopathological analysis of the liver of albino rats was carried out to determine the changes in the normal architecture of the liver with a treated sample along the standard drug, to evaluate the degree of damaged cells compared with untreated rat's liver. In the control groups, overall architecture seems intact and normal with normal diameter of the central vein and sinusoids (fig. 8a). In the GM-treated group, dilated, congested and distorted central and portal veins were seen. Moderate inflammatory cell infiltration, sinusoidal dilation and hemorrhages and ruptured hepatic architecture were observed (fig. 8b). 3 portal veins were observed in GM-PC group (fig. 8c).

The series of groups treated with aqueous extracts of *C. bonplandianus* with different doses and concurrent administration of GM showed the following results:

In GM-CB (81 mg/Kg) normal diameter of the central vein with severe congestion has been indicated.

Disturbed portal triad, dilation, and inflammation in the portal vein with moderate hemorrhages were observed. Sinusoidal dilation, distorted, and necrotized hepatocytes were also present (fig. 9a). Group GM-CB (54mg/Kg) showed moderate dilation in the central and portal veins and inflammation in the portal triad (fig. 9b). GM-CB (27mg/Kg) group displayed intact hepatic architecture and moderate sinusoidal dilation with no hemorrhages. A normal portal triad with mild central vein dilation was noted (fig. 9c).

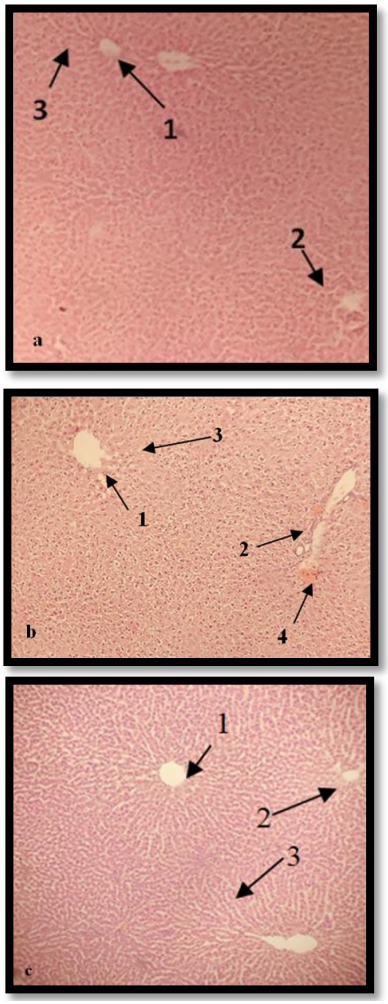
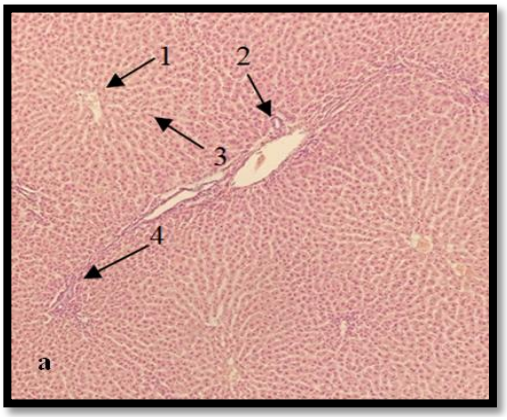


Fig. 8 Photomicrograph of 5-micron thick H & E-stained paraffin section from the liver of rats (a: Control: 1 - Central vein, 2 - Portal vein, 3 - Hepatic architecture; b: GM: 1 - Central vein, 2 - Portal triad, 3 - Necrosis, 4 - Hemorrhages; c: GM-PC: 1 - Central vein, 2 - Portal triad, 3 - Hepatic architecture)



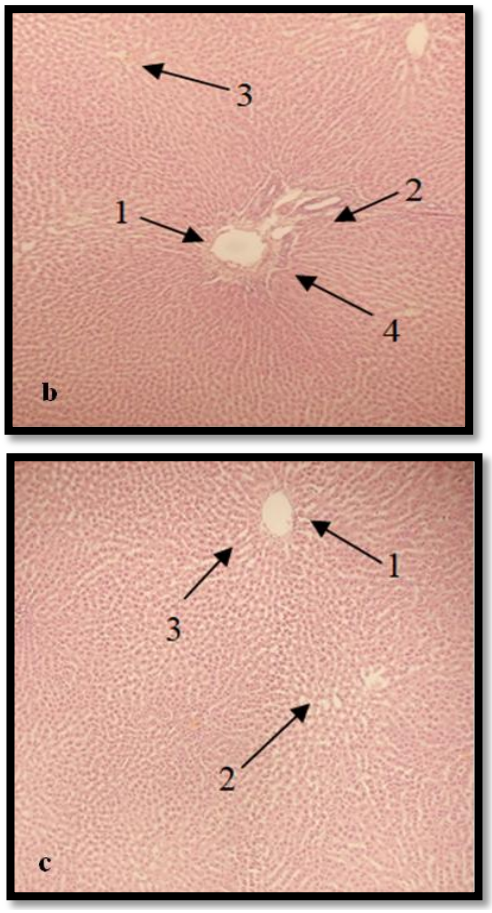


Fig. 9 Photomicrograph of 5-micron thick H & E-stained paraffin section from the liver of rats. a: GM-CB (81 mg/kg): 1 - Central vein, 2 - Portal triad, 3 - Sinusoid, 4 – Necrosis; b: GM-CB (54 mg/kg): 1 - Central vein, 2 - Portal triad, 3 - Sinusoid, 4 – Inflammation; c: GM-CB (27 mg/kg): 1 - Central vein, 2 - Portal triad, 3 - Hepatic architecture

3. Discussion

Gentamicin is the most widely used antibiotic as an effective aminoglycoside for various pathogens. Recent research shown that it may cause hepatorenal injuries [29]. In this study gentamicin-induces liver and kidney damage was selected for estimating the hepatoprotective and nephroprotective effects of aqueous extract of leaves of *C. bonplandianus*. Paracalciteriol was used as a reference or standard drug [23, 29]. Routine analysis of the above-mentioned parameters consolidates and confirms the kidney function [30, 31]. No significant changes were observed in all groups that indicated that administration of gentamicin alone and in combination may not alter levels of sodium, potassium, chloride, and uric acid (Table 1). However, significant reductions in creatinine and urea were exhibited in the treated groups compared with the group that received gentamicin alone, which showed that improvement in kidney function in the treated groups (Fig. 2, 3, 6 and 7). Similarly, most of the liver diseases are associated with the used of antibiotics such as gentamicin, carbon tetrachloride, or intake of alcohol etc. [32]. In the present study, the hepatoprotective and nephroprotective effects of leaves extracts are may be due to the abundance of flavonoids

and polyphenolic compounds in the aerial parts of plants [33, 34]. These compounds possess antioxidant and free radical scavenging properties.

4. Conclusion

The hepatoprotective and nephroprotective effects based on histopathological screening were observed in the underlying study. Limited literature is available on the renal and hepatic protection of leaves extract of *Croton bonplandianus.* The aforementioned findings led to undertake that the promising hepatoprotective and nephroprotective therapeutic potential to reduce GM-induced renal and hepatic functional and structural abnormalities. Hepatotoxicity and nephrotoxicity induced by GM are reduced by antioxidant action. The production of free radicles due to metabolic reactions lead toward the oxidative stresses. The leaf extract holds the free radical scavenging activities consequently, exhibiting anti-oxidant role. The study provides a scientific justification for the usage of the leaves extracts of *C. bonplandianus*. However, in the future, detailed molecular studies with isolation of active compounds will be deemed to prove the mentioned activities. Furthermore, extensive preclinical and clinical investigation in different ways must be complemented toward the diversity of a new drug molecule that may be used as an active moiety in the pharmaceutical industries.

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