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AMELIORATION OF CISPLATIN-INDUCED TOXICITY IN EXPERIMENTAL ANIMALS BY BAICALIN

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ABSTRACT

Introduction: Cisplatin is associated with serious adverse events which overshadowed its efficacy. Baicalin found to reduce the cisplatin-induced cytotoxicity and renal damage in animal models. The aim of the current study is to demonstrate protective effect of baicalin in cisplatin-induced toxicity models in mice. **Methods:** Healthy Swiss Albino mice (weight range of 20-30 g), after acclimatization divided into 8 groups (n=8): normal control, vehicle control, baicalin (50 mg/kg), cisplatin (7 mg/kg), quercetin (50 mg/kg) + cisplatin, baicalin (40, 80, and 120 mg/kg) + cisplatin. For induction of cisplatin toxicity model, cisplatin (7 mg/kg) was administered from day 11 to 15 of study period. Baicalin was administered at 40, 80, and 120 mg/kg for 15 days. On 16th day, blood samples were collected and mice were sacrificed to excise kidneys and livers. **Results:** In cisplatin treated group, blood urea nitrogen, creatinine, serum glutamic pyruvic transaminase, and serum glutamic-oxaloacetic transaminase levels were significantly ($P<0.001$) elevated compared to control group, while, baicalin showed significant ($P<0.01$, $P<0.001$, $P<0.05$, $P<0.001$ respectively) dose dependent amelioration. On histopathology, cisplatin induced pathological changes in both liver and kindney were ameliorated by baicalin cisplatin. Similarly, Tumor necrosis factor alpha, interleukin 6, and nuclear factor erythroid 2–related factor 2 levels were attenuated significantly ($P<0.001$) by baicalin. **Conclusion:** The present cisplatin-induced toxicity model indicates that baicalin may establish as a promising approach for the prevention of cisplatin-induced toxicity.

KEYWORDS: Baicalin; cisplatin; cisplatin-induced toxicity; nuclear factor erythroid 2–related factor 2; tumor necrosis factor alpha.

INTRODUCTION

Platinum-based chemotherapy is considered as of crucial interest, instead of significant toxicity and inherent resistance and broadly accepted in late stages of cancer treatment.[1] Cisplatin, a widely used chemotherapeutic agent, is also associated with serious adverse events which overshadowed its efficacy.[2-4] The cytotoxicity of cisplatin is attributed to the formation of reactive oxygen species (ROS) which oxidatively damage mitochondrial, inhibit antioxidant enzymes and non-enzymatic molecules, and release free radicals.[5] Moreover, cisplatin administration causes lipid peroxidation and DNA damage,[6, 7] which may lead to secondary malignancies in the normal cells.[8] Hence, the antioxidant agents can be used to attenuate the adverse effects associated with cisplatin.[8-10] Efforts are also made to use natural substances to use in combination with chemotherapy to reduce the chemotherapy-associated toxicity if successful it could be the accessible approach for cancer management and treatment. Despite focused research, an effective therapy to attenuate cisplatin-induced toxicity remained a great challenge.

Flavonoids have drawn considerable attention due to its considerable health benefits.[11, 12] Flavonoids are a class of phytochemicals that include natural phenolic compounds.[13] Amongst class of flavonoids, Baicalin (5,6-dihydroxy-4-oxo-2-phenyl-4H-chromen-7-yl *β*-D-glucopyranosiduronic acid), derived from the roots of *Scutellaria baicalensis* Georgi, found protective in many liver injury animal models.[14] It is reported to have demonstrated antioxidant and anti-inflammatory properties,[15,16] and hence found to have antiviral, anti-tumour, neuroprotective and nephroprotective activity in various animal models.[17-20] Besides, baicalin found to reduce the cisplatin-induced cytotoxicity and prevent cisplatin-induced renal damage in animal models.[21, 22] Therefore, the aim of the current study is to demonstrate the protective effect baicalin in cisplatin-induced toxicity animal models. The study will promote the use of cisplatin chemotherapy in anti-cancer treatment by co-administering baicalin as a chemoprotective agent.

MATERIALS AND METHODS

Drugs and reagents

Cisplatin was obtained from NEON LABORATORIES LTD. as a gift sample. Baicalin and Quercetin were purchased from TCI CHEMICALS PVT. LTD. Blood urea nitrogen (BUN), creatinine, serum glutamic pyruvic transaminase (SGPT), and serum glutamic-oxaloacetic transaminase (SGOT) kits were purchased from BIOASSAY TECHNOLOGY

LABORATORY. Tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), and nuclear factor erythroid 2–related factor 2 (Nrf2) enzyme-linked immunosorbent assay (ELISA) kits were purchased from BIOASSAY TECHNOLOGY LABORATORY.

Animals and study design

Healthy Swiss Albino mice (weight range of 20-30 g) were procured from the National Institute of Biosciences. The animals were housed in Perspex cages and maintained under standard laboratory conditions of 14h: 10 h dark: light cycle, a temperature of (22±2 ℃), and 50-70 % humidity and fed on standard food pellets and drinking water ad libitum. The entire experimental protocol was reviewed and approved by an Institutional Animal Ethics Committee (Approval Number: CPCSEA/IAEC/P-37/2017) registered under the ‘‘Committee for the Purpose of Control and Supervision of Experiments on Laboratory Animals’’ (CPCSEA), Ministry of Environment and Forests, Government of India.

After acclimatization for one week, mice were divided into 8 groups with 8 animals in each group: Group I served as a normal control, group II was the vehicle control which received PEG 400 for 15 days and 0.9% saline from day 11 to day 15, group III was treated with cisplatin (7 mg/kg intraperitoneal injection) from day 11 to day 15, Group IV was treated with baicalin (50 mg/kg oral administration) for 15 days, group V was treated with quercetin (50 mg/kg oral administration) for 15 days and cisplatin (7 mg/kg intraperitoneal injection) from day 11 to day 15 acted as a standard control, group VI was treated with baicalin (40 mg/kg oral administration) for 15 days and cisplatin (7 mg/kg intraperitoneal injection) from day 11 to day 15, group VII was treated with baicalin (80 mg/kg oral administration) for 15 days and cisplatin (7 mg/kg intraperitoneal injection) from day 11 to day 15 by, group VII was treated with baicalin (120 mg/kg oral administration) for 15 days and cisplatin (7 mg/kg intraperitoneal injection) from day 11 to day 15.

On the16th day, blood samples were collected through the retro-orbital route and were stored at -80℃ temperature. The mice were then sacrificed, kidney and liver were excised, and stored in 10% neutral formalin for further histopathological evaluations. For biochemical examination, collected blood was centrifuged at 6000rpm for 10 minutes to separate plasma. The supernatant plasma was collected and used for the estimation of BUN, creatinine, SGOT, and SGPT levels.

For estimation of IL-6 excised kidneys were rinsed in phosphate buffer saline (PBS) (pH-7.4) and weighed. Tissues were minced and homogenize with PBS (pH-7.4) with ice-cold tissue homogenizer (Polytron, India). Homogenate was then centrifuged in a refrigerated centrifuge (Eltrec, India) and the supernatant was used for the assay of TNF-α, IL-6, and Nrf2.

Determination of TNF-α level

TNF-α levels were assayed using enzyme-linked immunosorbent assay kit (BIOASSAY TECHNOLOGY LABORATORY, INDIA) performed by Elisa microplate reader (Epoch, India) as per the instructions mentioned in the kit insert.

Determination of IL-6 levels

The IL-6 levels were determined using an enzyme-linked immunosorbent assay kit based on the Biotin double antibody sandwich technology (BIOASSAY TECHNOLOGY LABORATORY, INDIA) performed by Elisa microplate reader (Epoch, India) as per the instructions mentioned in the kit insert.

Estimation of Nrf2 levels

The Nrf2 levels were assayed using an enzyme-linked immunosorbent assay kit based on the Biotin double antibody sandwich technology (BIOASSAY TECHNOLOGY LABORATORY, INDIA) by Elisa microplate reader (EPOCH, INDIA) as per the kit instructions.

Histopathological examination

The excised kidneys and livers were washed and cleaned with 0.9% saline and kept in 10% neutral Formalin. These tissues were trimmed and routinely processed to dehydrate in ascending grades of alcohol, clear in xylene, and embedded in paraffin wax. Paraffin wax embedded tissue blocks were sectioned at 3-4 µm thickness with the rotary microtome. All the slides were stained with haematoxylin and eosin (H & E) stain.

Statistical Analysis

The statistical analysis was performed with GraphPad Prism 32bit Windows version. All the experimental groups were compared by one-way Analysis Of Variance (ANOVA) with posthoc Tukey Honestly Significant Difference (HSD). The data is represented as mean ± SEM and $p<0.05$ considered clinically significant.

RESULTS

Bodyweight and reno-somatic index (RSI)

The body weight was considerably reduced (-21.05%) in cisplatin only administration group with the highest (0.016754) RSI compared to the control group. **Table 1** indicates a change in body weight and their respective RSI across various groups.

Biochemical parameters

BUN, creatinine, SGOT, and SGPT levels were significantly ($P<0.001$) elevated in the cisplatin-treated group compared to the control group, indicates significant oxidative stress and toxicity. While, baicalin showed significant ($P<0.01$, $P<0.001$, $P<0.05$, $P<0.001$ respectively) dose-dependent amelioration in BUN, creatinine, SGOT, and SGPT levels compared to cisplatin only administered group. (**Figure 1**)

Histopathological examination

In cisplatin only administered mice, mild to moderate degenerative lesions with multifocal, severely increased hypercellularity of glomeruli, multifocal, moderate proteinaceous deposition at tubule, and focal, moderate cytoplasmic vacuolation of tubules were observed in the kidneys compared to control group. Treatment of quercetin and baicalin reduced the severity and distribution of lesions in the kidney after induction of cisplatin-toxicity. After baicalin treatment at 40 mg/kg, multifocal, mildly increased hypercellularity of glomeruli, and focal, moderate proteinaceous deposition at tubules of kidneys was observed. While 80 and 120 mg/kg baicalin treatment showed no abnormalities in the kidneys and effectively mitigates the adverse effect of cisplatin compared to cisplatin only administered group. (**Figure 2**)

The liver histopathology analysis of cisplatin only administered group showed multifocal severe lymphocytic infiltration with severe inflammatory lesions compared to the livers of the control group. Treatment of quercetin and baicalin reduced the severity and distribution of lesions in the liver after induction of cisplatin-toxicity. After baicalin treatment at 40 mg/kg showed focal moderate perivascular lymphocytic infiltration while baicalin at 80 and 120 mg/kg showed no liver abnormalities compared to cisplatin only administered group. (**Figure 3**)

Effect on IL6, TNF-α, and Nrf2 levels

In the cisplatin only group, the IL6 level was 211.4 ± 6.206 ng/ml which was significantly ($p<0.0001$) higher than the control group. Baicalin at all three doses was found associated with significantly ($P<0.001$, $P<0.0001$, $P<0.0001$ respectively) reduced levels of IL6 in the cisplatin-toxicity model. (**Figure 4**) Similarly, TNF-α levels were significantly ($P<0.0001$) elevated in cisplatin only administered group (314.6 ± 6.873 ng/ml), while, in the baicalin treated groups TNF-α level was significantly ($P<0.0001$) reduced compared to the cisplatin only administered mice. (**Figure 4**) Conversely, Nrf2 level was 6.548 ± 0.8342 ng/ml in the cisplatin only administered mice which were significantly ($P<0.0001$) reduced compared to the control group, while, in the baicalin treated group dose-dependent increase was found in the Nrf2 levels with significant ($p<0.001$) increase was found at 80 and 120 mg/kg dose compared to the cisplatin only administered group. (**Figure 4**)

DISCUSSION

Various animal studies widely reported that cisplatin induces reactive oxygen species (ROS) and imbalances antioxidant mechanisms.[23] These excessively produced ROS targets endogenous intracellular DNA, lipids, and proteins to undergo pathogenic modifications via MAPKs, NF-κB, and p53 signaling pathway to cause cellular dysfunction and apoptosis.[24] In the cisplatin-induced renal toxicity, the interaction of ROS with nitric oxide to form peroxynitrite, a potent cytotoxic, plays an important role.[25]

In the present study, in the cisplatin only administered mice, the markers of renal toxicity (BUN and creatinine) were found increased significantly compared to control. It suggests that the toxicity model selected in the study successfully induced renal-toxicity. Similarly, treatment with baicalin at all the doses significantly ($P<0.01$) reduced the markers of renal injury, suggesting baicalin could protect renal-toxicity produced after cisplatin treatment. The histopathological analysis of the kidneys in the current study also supports the finding. In the cisplatin administered mice, mild to moderate degenerative lesions with multifocal, severely increased hypercellularity of glomeruli, multifocal, moderate proteinaceous deposition at tubule, and focal, moderate cytoplasmic vacuolation of tubules was observed. Along with the histopathological analysis, decreased body weight and the highest RSI indicated increased kidney weight due to inflammatory and fibrotic changes due to cisplatin toxicity. In contrast, in baicalin treated (80 and 120 mg/kg) mice no abnormalities due to toxicity were observed, it

suggests that baicalin at 80 and 120 mg/kg dose strongly able to reverse the inflammatory and fibrotic changes induced by cisplatin.

The major pathology behind the drug-induced liver injury in hepatic oxidative stress, which raises ROS and cause liver peroxidation.[26] The elevated liver enzyme activities (SGOT, SGPT, and alkaline phosphatase (ALP)) are the diagnostic markers of liver injury as the elevated liver enzyme levels and chemicals such as bilirubin and creatinine indicate inflammation or damage to the liver.[27] In the present study, in the cisplatin only administered group, the levels of SGOT and SGPT were significantly elevated compared to control mice. Also, the histopathology of the mice in this group showed multifocal severe lymphocytic infiltration with severe inflammatory lesions along with decreased body weight and increased RSI, indicates pathological changes in the liver due to cisplatin-toxicity. Among the treatment group mice, baicalin at 80 and 120 mg/kg showed no liver abnormalities. It indicates that baicalin strongly inhibits the pathological changes in the liver induced by cisplatin. Previous studies also proved the protective effect of baicalin in cisplatin-induced liver-toxicity animal models.[28, 29]

The proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 found elevated after cisplatin administration, which, causes infiltration of leukocytes and macrophages within the damaged areas of kidney and liver.[30, 31] The deleterious effect of TNF-α is also demonstrated by the models involving pharmacological inhibition or genetic deletion of TNF-α, where, reduction in cisplatin-induced necrosis and apoptosis of epithelial cells, and infiltration of leukocytes and macrophages were observed.[14, 32] In the present study, histopathological analysis of kidneys and livers from the baicalin treatment (80 and 120 mg/kg) group showed no lymphocytic infiltration, inflammatory lesions, or hypercellularity. Additionally, in the current study the elevated levels of TNF- α and IL-6 were significantly attenuated by all three doses of baicalin (40, 80, and 120 mg/kg). It suggests that the protective effect of baicalin against cisplatin-induced inflammatory injury is attributed to the mitigation of inflammation. Additionally, as per the emerging evidence, cisplatin-induced inflammation and injury involve the MAPK pathway. The variety of biological stimuli activates the MAPK pathway, however, activation of JNK and p38 MAPK through the production of ROS and TNFα in response to cisplatin plays an important role.[6, 33-35] In the current study, the elevated markers of inflammation and proinflammatory cytokines, suggest the involvement of the MAPK pathway in the cisplatin-induced injury.

The elevated levels of Nrf2 are a main defense mechanism of cells against oxidative stress.[36] The elevated expression and transnuclear movement of Nrf2 depend on the induction of antioxidant defense and phase II detoxifying enzymes.[37] In the current study, baicalin intensified the accumulation of Nrf2 compared to the mice in the cisplatin only administered group. Heme oxygenase 1 (HO-1) is one of the downstream genes of Nrf2, is a cytoprotective enzyme involved in the regulation of intracellular redox-balancing.[38] The study by Sahu et al., in the cisplatin-induced acute kidney injury mice model found that the renal HO-1 expression is significantly elevated in the baicalin pretreated mice compared to the cisplatin alone treated mice.[22] Hence, it can be believed that the antioxidative effect of baicalin is partly attributed to the upregulation of Nrf2 and HO-1 enzyme.

Table 1: Change in body weight and renosomatic index.

	Initial weight (gm)	Final weight (gm)	Change in weight (%)	RSI
Vehicle control	26.75 ± 4	29.5 ± 2	9.32	0.013768
Cisplatin 7 mg/kg	28.75 ± 1	23.75 ± 2	-21.05	0.016754
Baicalin (50 mg/kg)	26.5 ± 4	28.33 ± 1	6.47	0.014036
Cisplatin (7 mg/kg) + Quercetin (50 mg/kg)	27.75 ± 4	23.38 ± 7	-18.72	0.015578
Cisplatin (7 mg/kg) + Baicalin (40 mg/kg)	27 ± 3	23.86 ± 2	-13.17	0.016719
Cisplatin (7 mg/kg) + Baicalin (80 mg/kg)	27.63 ± 4	25.13 ± 4	-9.95	0.014038
Cisplatin (7 mg/kg) + Baicalin (120 mg/kg)	27 ± 3	22.75 ± 3	-18.68	0.015576

RSI: Reno-somatic index

FIGURES

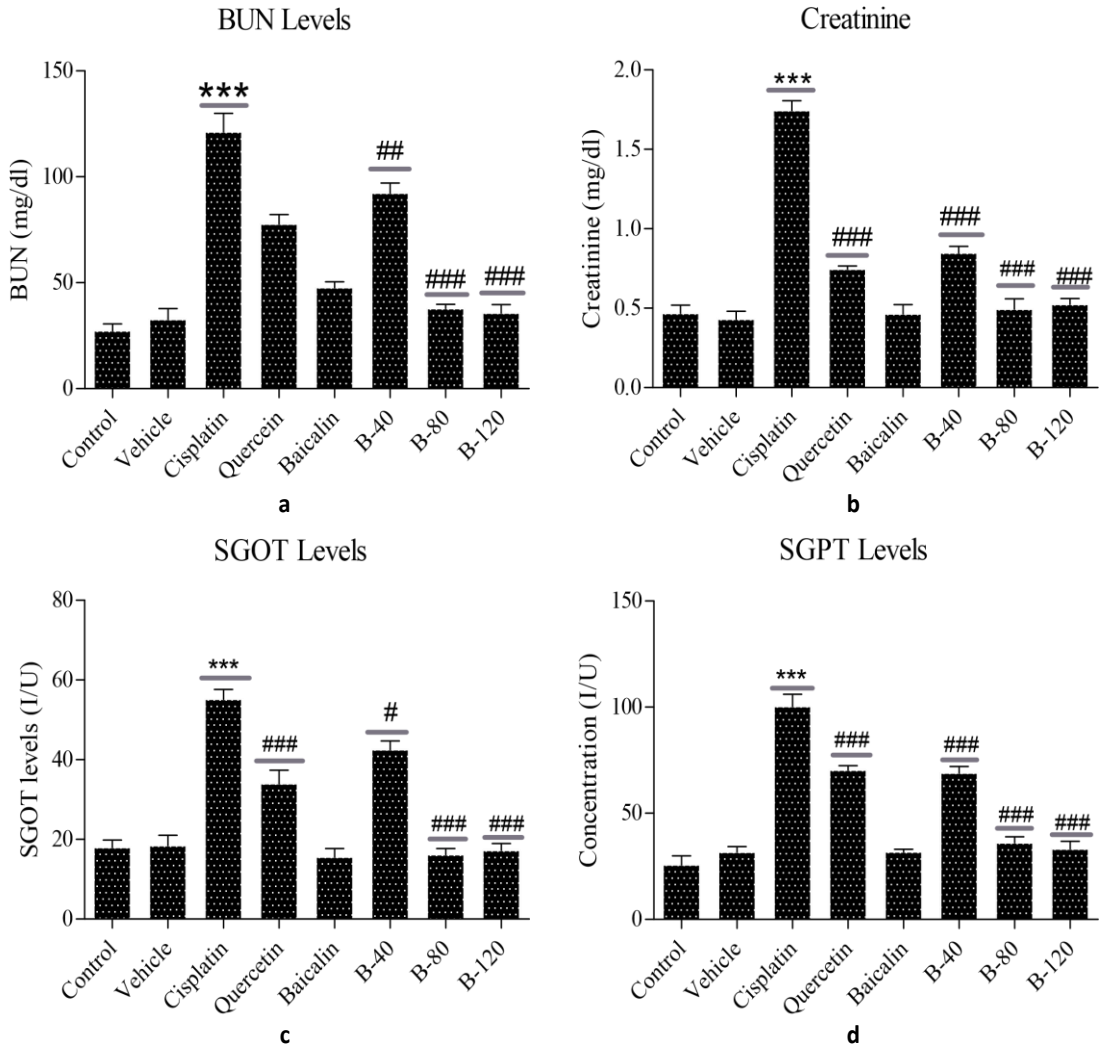

Figure 1: a: Plasma blood urea nitrogen (BUN) levels, b: Plasma creatinine levels, c: Plasma serum glutamic-oxaloacetic transaminase (SGOT) levels, d: Plasma serum glutamic pyruvic transaminase (SGPT) levels. The values are expressed as Mean ± SEM (n=6). Data was analysed by one way analysis of variance (ANOVA) followed by Tukey's test. *p<0.05, **p<0.01, ***p<0.001 when compared with control group. #p<0.05, ##p<0.01, ###p<0.001 when compared with cisplatin group.

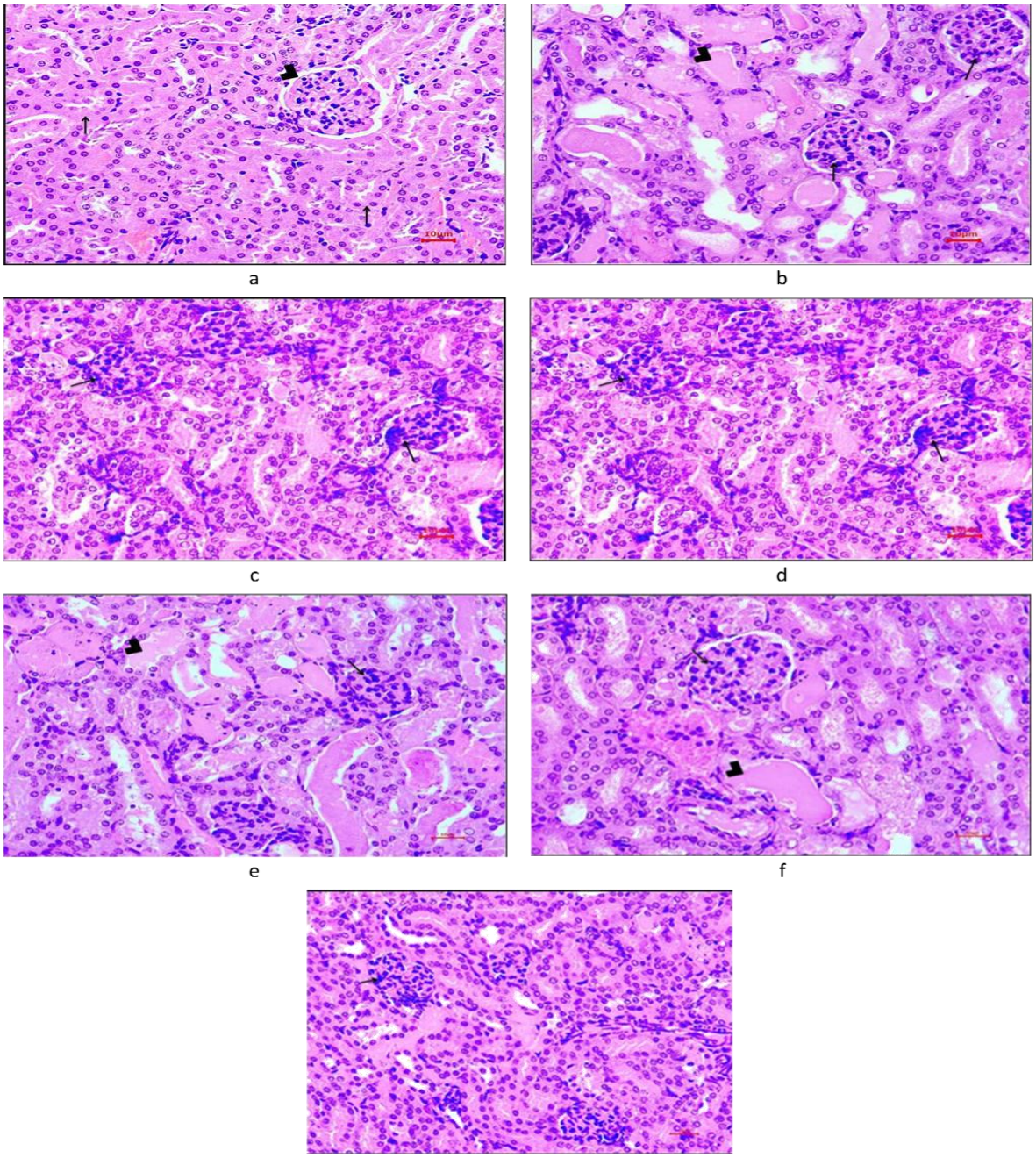

Figure 2: Histopathological examination of Kidneys: a: Vehicle control group, b: Cisplatin (7 mg/kg) treated group, c: Baicalin (50 mg/kg) treated group, d: Cisplatin (7 mg/kg) + Quercetin (50 mg/kg) treated group, e: Cisplatin (7 mg/kg) + Baicalin (40 mg/kg) treated group, f: Cisplatin (7 mg/kg) + Baicalin (80 mg/kg) treated group, g: Cisplatin (7 mg/kg) + Baicalin (120 mg/kg) treated group.

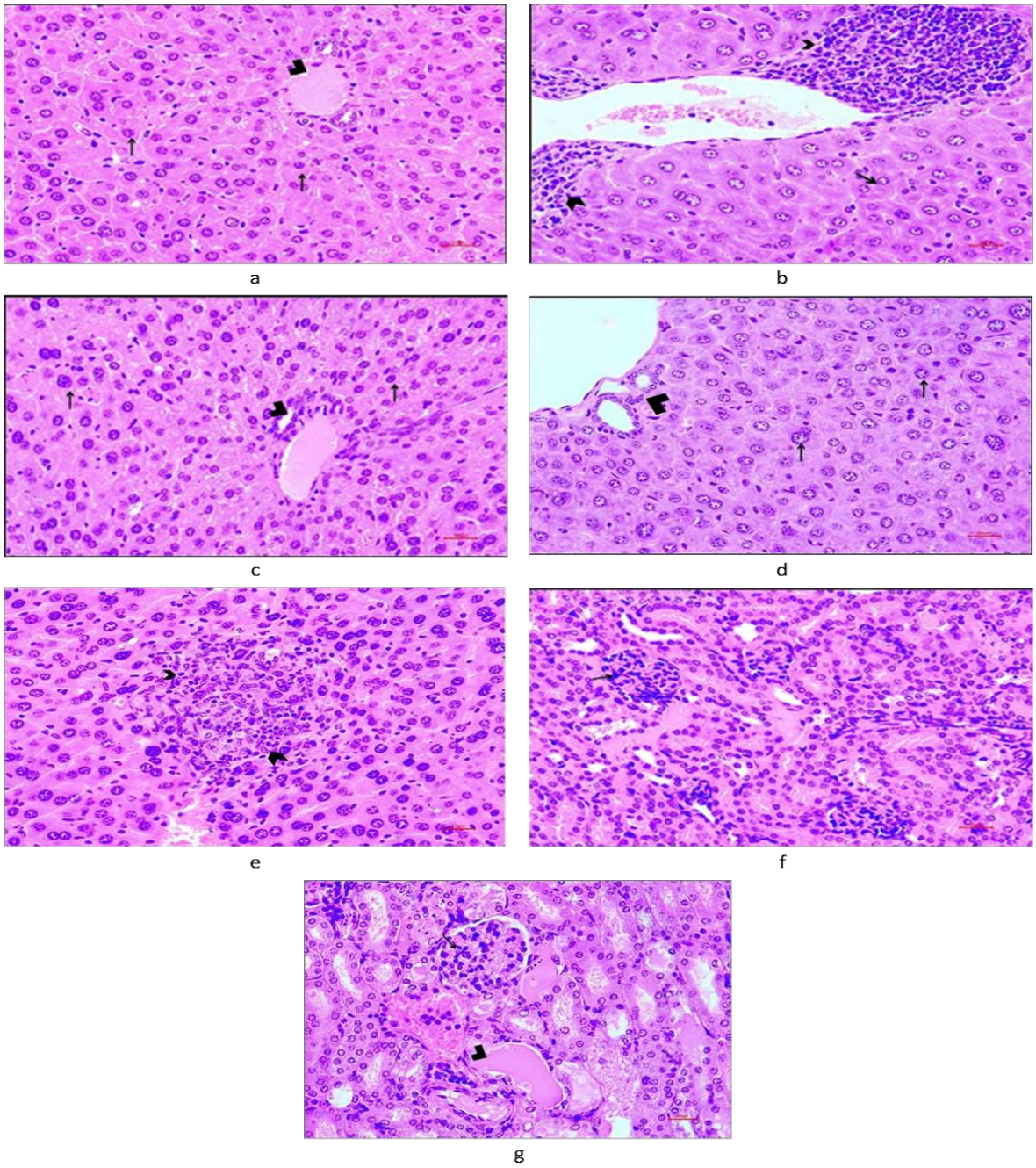

Figure 3: Histopathological examination of Livers a: Vehicle control group, b: Cisplatin (7 mg/kg) treated group, c: Cisplatin (7 mg/kg) + Quercetin (50 mg/kg) treated group, d: Baicalin (50 mg/kg) treated group, e: Cisplatin (7 mg/kg) + Baicalin (40 mg/kg) treated group, f: Cisplatin (7 mg/kg) + Baicalin (80 mg/kg) treated group, g: Cisplatin (7 mg/kg) + Baicalin (120 mg/kg) treated group

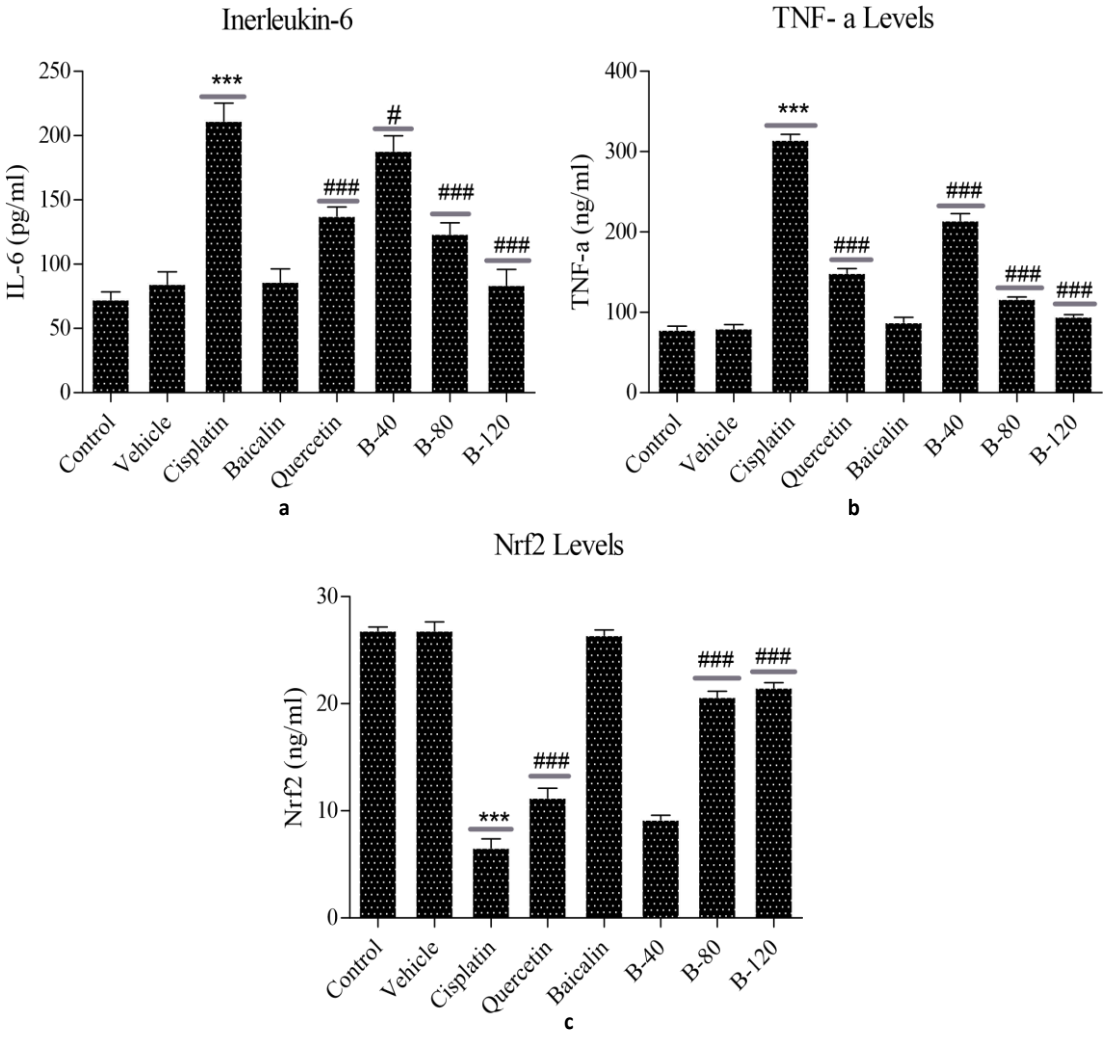

Figure 4: a: Plasma IL-6 levels, b: Plasma TNF-α levels, c: Plasma Nrf2 levels. The values are expressed as Mean ± SEM (n=6). Data was analysed by one way analysis of variance (ANOVA) followed by Tukey's test. *p<0.05, **p<0.01, ***p<0.001 when compared with control group. #p<0.05, ##p<0.01, ###p<0.001 when compared with cisplatin group.

FIGURES LEGENDS

Figure 1: A: Plasma blood urea nitrogen (BUN) levels B: Plasma creatinine levels C: Plasma serum glutamic-oxaloacetic transaminase (SGOT) levels D: Plasma serum glutamic pyruvic transaminase (SGPT) levels. The values are expressed as Mean ± SEM (n=6). Data was analysed by one way analysis of variance (ANOVA) followed by Tukey's test. *p<0.05, **p<0.01, ***p<0.001 when compared with control group. #p<0.05, ##p<0.01, ###p<0.001 when compared with cisplatin group.

Figure 2: Histopathological examination of Kidneys.

Figure 3: Histopathological examination of Livers.

Figure 4: A: Plasma IL-6 levels B: Plasma TNF-α levels C: Plasma Nrf2 levels. The values are expressed as Mean ± SEM (n=6). Data was analysed by one way analysis of variance (ANOVA) followed by Tukey's test. *p<0.05, **p<0.01, ***p<0.001 when compared with control group. #p<0.05, ##p<0.01, ###p<0.001 when compared with cisplatin group.

CONCLUSION

The present cisplatin-induced toxicity model in mice indicate that baicalin may establish as a promising approach for the prevention of cisplatin-induced toxicity. The protective effect of baicalin may be attributed to the down-regulation of oxidative stress, apoptosis, and inflammation via the up-regulation of Nrf2/HO-1 proteins and inhibition of the MAPK activation pathway.

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