

Acai-berry ameliorates Cisplatin-induced nephrotoxicity in rats; insights on oxidative stress and apoptotic machineries

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ABSTRACT

Acute kidney injury is a complicated disease with a high incidence of morbidity and mortality worldwide. Cisplatin is a chemotherapy drug commonly employed in the treatment of various types of cancer, including testicular, ovarian, and breast cancer. However, it was reported to be directly associated with renal toxicity. Acai-berry was found to possess antioxidant and anti-apoptotic activities. The main goal of this research was to examine the impact of acai-berry on cisplatin-induced nephrotoxicity in rats. Rats were randomly distributed into four experimental groups: control group, cisplatin-treated group (7 mg/kg), cisplatin and acai-berry (300 mg/kg)-treated group, and acai-berry alone-treated group. Cisplatin treatment induced histopathological changes in renal tubules, as well as enhancing the levels of creatinine and urea. Moreover, cisplatin treatment induced oxidative damage and apoptosis in renal tissues via its effect on reduced glutathione (GSH), nuclear factor-erythroid factor 2-related factor-2 (Nrf-2), Bax, Bcl-2, and caspase-3. On the other hand, acai-berry treatment protected kidney tissues from the toxic effects of cisplatin and lowered serum BUN and creatinine. Furthermore, acai berry prevented oxidative stress by enhancing GSH and Nrf-2 levels. In addition, acai-berry counteracted apoptosis induced by cisplatin via reducing Bax/Bcl2 and caspase-3 expression. Therefore, acai-berry may be a promising nephroprotective solution for many cancer patients on cisplatin treatment.

Keywords: Acai-berry; kidney injury; cisplatin; Nrf-2; oxidative stress; apoptosis.

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1. Bile acids

Cisplatin is an effective DNA antineoplastic agent used for the treatment of several malignant diseases [1]. However, its effective usage for cancer therapy has been severely limited due to multiple toxicities, with nephrotoxicity being the most prominent one [2]. Nephrotoxicity is considered the most prevalent adverse effect of cisplatin occurring in over 20-30% of patients

following chemotherapy administration [3]. Multiple protein transporters were reported to help cisplatin deposit in the kidneys [4]. Clinical signs of kidney damage induced by chemotherapeutic treatment include decreased renal perfusion and glomerular filtration rate, and hence, an increase in blood urea nitrogen (BUN) and serum creatinine [5, 6].

Moreover, cisplatin-induced nephrotoxicity may promote nephrogenic cell damage via

reactive oxygen species (ROS) generation together with depletion of antioxidant compounds, glutathione (GSH), and downregulation of the antioxidant protein nuclear factor-erythroid factor-2 (Nrf-2), eventually leading to a status of oxidative stress [7]. Besides, cisplatin can further promote mitochondrial dysfunction and, hence, kidney tubular damage [8].

And since oxidative stress triggers a cascade of signaling pathways, there is a large body of evidence that cisplatin-induced kidney toxicity is associated with apoptosis of renal tubular cells [9]. Cytochrome-c networks with proteins Bcl-2 and Bax, which facilitate the production of caspase-3, initiating the programmed apoptotic machinery [10].

Therefore, searching for a novel strategy for prophylaxis against cisplatin-induced nephrotoxicity is a challenge facing medical research nowadays. Recently, there has been a growing interest in the field of phytochemicals. The fruits of the Brazilian palm *Euterpe oleracea* Mart. of the *Arecaceae* family, popularly known as 'acai-berries', have gained considerable attention in recent years due to their diverse health benefits [11].

Acai-berry extract is known for its prominent antioxidant capacity due to the abundance of polyphenolic compounds in its composition, such as anthocyanins, catechin, and epicatechin [12]. These antioxidant effects can be mediated through scavenging free radicals, primarily superoxide and peroxy radicals [13]. Furthermore, acai-berry has been reported to possess promising nephroprotective capabilities as evidenced by ameliorating glycerol-induced acute renal failure [14].

Accordingly, acai-berry can be considered as a potential candidate to be investigated for its nephroprotective impact against nephrotoxicity

induced by cisplatin. Therefore, the main target of the present research was to illustrate the protective effect of acai-berry against cisplatin-induced nephrotoxicity in rats, and to clarify the potential underlying mechanisms involved.

2. Materials and methods

2.1. Drugs and chemicals

Acai-berry was obtained from Natrol® (US). Cisplatin was purchased from Mylan, Saint-Priest (France). Anti-rat Bax (Biorbyt, Catalogue No. orb378567), anti-rat Bcl-2 (Biorbyt, Catalogue No. orb418681), anti-rat Nrf-2 (Novus Bio. Co, Catalogue No. NBP1-32822), and anti-rat caspase-3 (AB clonal, Catalogue No. A11319) antibodies were used for immunohistochemical analysis.

2.2. Animals

Male rats (age of 8-week-old, 180-200 g, Sprague-Dawley) were purchased from El-Roaa company for animal breeding, Cairo, Egypt. The animals were placed in an air-conditioned environment at 25 °C with a 12-h light and 12-hour dark photoperiod. Suitable cages were utilized for animal housing. Rats were fed on animal chows (45% carbohydrate, 20% protein, 5% fat, and 30% calcium and fiber). The study protocol was performed in accordance with the ethical guidelines for the care and use of laboratory animals [U.K. Animals Act (1986)] and complied with the ARRIVE guidelines. The research design was approved by the research ethical committee of the Faculty of Pharmacy, Ain Shams University (Egypt) (Approval No.# REC76).

2.3. Experimental design

A total of 32 rats were distributed among four groups, with eight rats in each group, and treated for seven consecutive days. Group 1 (the control group) was administered a single intraperitoneal (i.p.) injection of saline (0.9%

sodium chloride) on day 2, along with 0.5% carboxymethylcellulose in distilled water (vehicle for acai-berry) orally for seven days. Groups 2 and 3 were administered a single dose of cisplatin (7 mg/kg in 0.9% saline) i.p. on day 2 [15]. In addition, Group 3 received acai-berry (300 mg/kg) for seven days orally [16]. Group 4 was treated with acai-berry (300 mg/kg) for seven days orally. On day 7, blood samples were collected under anesthesia (ketamine, 75 mg/kg, ip) [17] for serum urea and creatinine detection. Following blood collection, the rats were euthanized by cervical dislocation, and their kidneys were harvested. These kidney samples were then fixed in buffered formalin (10%) and embedded in paraffin for histological and immunohistochemical assessment. Additionally, the remaining kidney tissues were homogenized in saline at a ratio of 1:10 (w/v) for the determination of GSH.

2.4. Serum Urea and Creatinine

Serum urea and creatinine were determined using kits provided by Biodiagnostics, Giza, Egypt. Serum urea was assessed using the Urease-Berthelot Method. Urea in the samples was hydrolyzed using the urease enzyme, forming ammonium ions. Blue dye indophenol product can be determined at 550 nm. Results were expressed as g/dL [18]. Serum creatinine was determined according to Schirmeister et al. [19]. After deproteinization, Creatinine in the samples forms a colored complex with picrate in an alkaline medium, measured at 520 nm. Results were expressed as mg/dL.

2.5. Reduced glutathione (GSH) determination

The levels of GSH were quantified using a calorimetric method with kits obtained from Biodiagnostics, Giza, Egypt. Briefly, the measurement is based on the reaction of GSH with 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB), which leads to the formation of a yellow product.

The absorbance of this product was recorded at 405 nm. The results were expressed as micromoles of GSH per gram of tissue [20].

2.6 Immunohistochemical determination of Bax, Bcl-2, caspase-3, and Nrf-2

For immunohistochemical analysis, 5 μ m-thick paraffin-embedded tissue sections were used. After deparaffinization, 0.3% hydrogen peroxide was added to tissue sections for 20 minutes. They were then incubated overnight at 4 °C with primary antibodies targeting rat Nrf-2, Bax, Bcl-2, or caspase-3. Following a rinse with PBS, the sections were treated with a secondary antibody for 20 min, washed again, and incubated with diaminobenzidine for 15 minutes. Counterstaining was performed using hematoxylin, followed by dehydration and clearing in xylene, after which the sections were mounted for microscopic analysis. Six non-overlapping fields were randomly visualized from each tissue section to assess the optical density (OD) of positive immunohistochemical staining using ImageJ software. Imaging was performed using a full HD microscopic system controlled by the Leica Application Module (Leica Microsystems GmbH, Wetzlar, Germany) [21].

2.7. Histopathological examination

Kidney samples from different groups were fixed in 10% neutral buffered formalin. Next, they were washed and dehydrated with serial dilutions of alcohol. Subsequently, the samples were cleaned with xylene and paraffinized (56 °C -24 h). Tissue blocks were sectioned at a thickness of 4 μ m using a slide microtome, and the sections were deparaffinized on glass slides. Hematoxylin and eosin staining was done. The slides were examined using a full HD microscopic camera controlled by the Leica application module for tissue section analysis (Leica Microsystems GmbH, Wetzlar, Germany)

[22].

2.8. Statistical analysis

The data are presented as mean $\pm$ SD. One-way ANOVA was used for multiple comparisons, with the Tukey post hoc test applied afterward. A significance level of 0.05 was set. All statistical analyses and graph creation were performed using GraphPad Prism version 7 (GraphPad Software, Inc., La Jolla, CA, USA).

3. Results

3.1. Effect of acai-berry on serum urea, BUN, and creatinine in cisplatin-induced nephrotoxicity in rats

The cisplatin-treated group revealed a marked increase in serum creatinine ($F_{3,20}=43.54$, $p<0.0001$) level by 4.65-fold and serum

urea ($F_{3,16}=91.16$, $p<0.0001$) level by 5.06-fold compared to the control group. On the other hand, the acai-berry-treated group illustrated a substantial decrease in serum creatinine level by 2.8-fold and serum urea by 1.84-fold relative to the cisplatin-treated group (**Fig. 1A and 1B**).

3.2. Effect of acai-berry on GSH in cisplatin-induced nephrotoxicity in rats

Cisplatin-treated rats demonstrated a significant reduction in tissue level of the antioxidant compound, GSH, compared to the control group by 37.42%. On the other hand, treatment with acai-berry showed a significant elevation in GSH ($F_{3,20}=9.467$, $p=0.0004$) level in comparison with the cisplatin-treated rats by 28.49% (**Fig. 1C**).

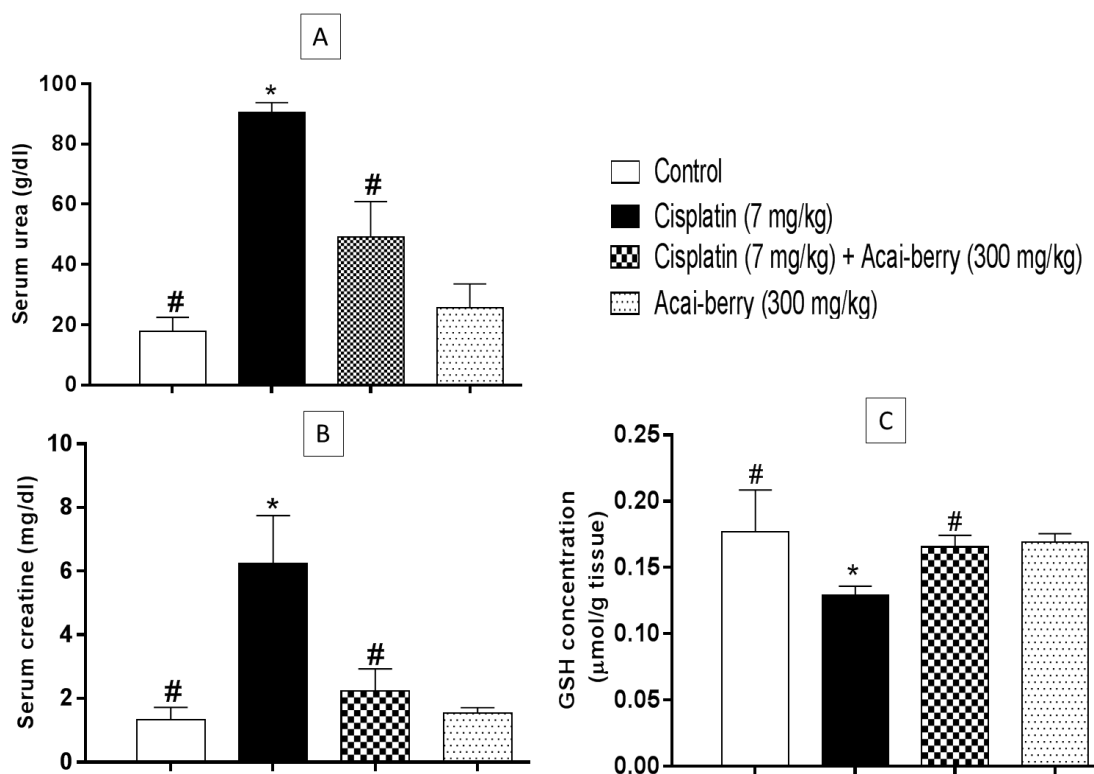


Fig. 1. Effects of acai-berry treatment on serum urea (BUN) (A), serum creatinine (B), and reduced glutathione (GSH) (C) levels in rats with cisplatin-induced nephrotoxicity. Cisplatin was administered intraperitoneally (7 mg/kg), and acai berry (300 mg/kg, orally) was given for 7 consecutive days. Data are presented as mean $\pm$ S.D. ($n = 6$). * and # indicate statistical significance compared to the control and cisplatin-treated groups, respectively, at $P < 0.05$, as determined by one-way ANOVA followed by Tukey's post-hoc test.

3.3. Effect of acai-berry on Nrf-2 in cisplatin-induced nephrotoxicity in rats

The expression of antioxidant protein, Nrf-2, in kidney tissues was assessed using immunohistochemical staining. The results were expressed as optical density (OD) (**Fig. 2E**).

Cisplatin (**Fig. 2B**) reduced Nrf-2 ($F_{3,56} = 13.8$, $p < 0.0001$) expression relative to the control group significantly (**Fig. 2A**). Conversely, the acai-berry-treated group (**Fig. 2C**) showed significant elevation in Nrf-2 expression OD relative to the cisplatin-treated group (**Fig. 2D**).

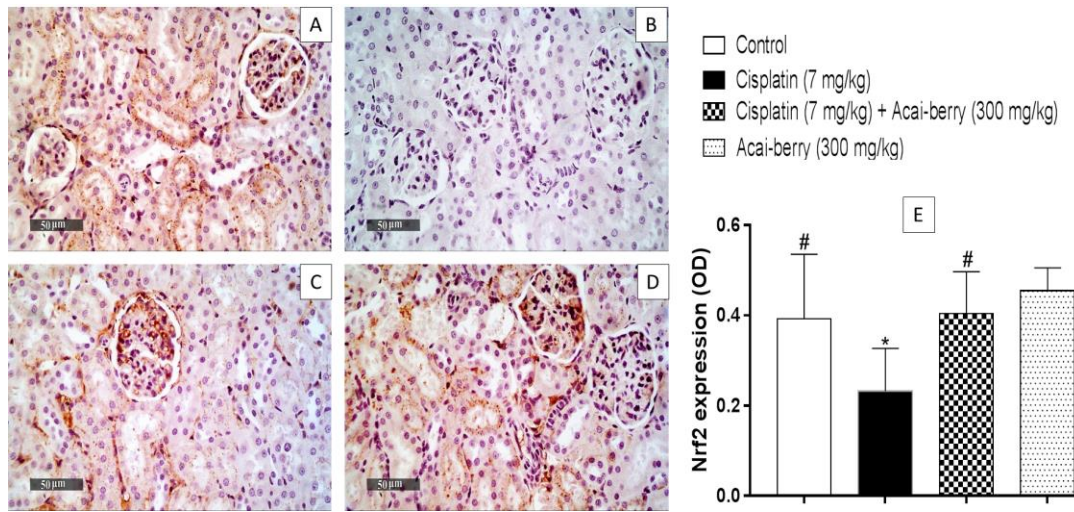


Fig. 2. Immunohistochemical staining of Nrf-2 expression in renal tissues (100x magnification). Photomicrographs of kidney histological sections from (A) control group, (B) cisplatin-treated group (7 mg/kg), (C) acai-berry-treated group (300 mg/kg), and (D) acai-berry alone-treated group. The brown color (positive) indicates specific immunostaining for Nrf-2, while the blue color (negative) represents hematoxylin staining. Scale bar = 50 μ m. (E) Quantitative image analysis ($n = 3$) of immunohistochemical staining presented as optical densities (OD) across 15 different fields for each rat section. * and # indicate statistical significance compared to the control and cisplatin-treated groups, respectively, at $P < 0.05$, as determined by one-way ANOVA followed by Tukey's post-hoc test.

3.4. Effect of acai-berry on Bax, Bcl-2, and caspase-3 in cisplatin-induced nephrotoxicity in rats

The expressions of Bax and Bcl-2 ($Bax F_{3,56} = 46.36$, $p < 0.0001$) ($Bcl-2 F_{3,56} = 19.27$, $p < 0.0001$) and caspase-3 ($F_{3,20} = 63.37$, $p < 0.0001$) were assessed and computed as optical density (OD) (**Fig. 3E and 3F**). Cisplatin treatment (**Fig. 3B**) illustrated a marked enhancement in the Bax/Bcl-2 ratio in kidney tissues relative to group 1 (**Fig. 3A**) as evidenced by a significant elevation in OD. By contrast, the treatment of animals with acai-berry (**Fig. 3C**) reduced this ratio in a significant manner relative to group 2. Moreover, rats treated with acai-berry alone (**Fig. 3D**)

revealed no significant difference relative to the corresponding control group.

Caspase-3 was further assessed in kidney tissues, where the cisplatin-treated group of rats (**Fig. 4A**) demonstrated a marked amelioration in the caspase-3 expression by 56.65% compared to the normal group (**Fig. 4B**). In contrast, acai-berry-treated rats (**Fig. 4C**) revealed an obvious reduction in the protein expression of caspase-3 in relation to the cisplatin-treated group by 48.35%. Results of OD were recorded in **Fig. 4E**.

3.5. Histological examination

Control rats displayed the typical histological features of the renal cortex with no

histopathological alterations (**Fig. 5A**). In contrast, cisplatin-treated rats illustrated nuclear pyknosis in the tubular lining epithelium of renal cortex while the corticomedullary portion and medulla showed necrosis with cystic dilatation in the tubules (**Fig. 5B**). Nevertheless, acai-berry extract administration preserved nearly the normal histological architecture of renal

glomeruli and tubules. Some sections showed mild necrosis and nuclear pyknosis (**Fig. 5C**). In addition, there were no histopathological alterations in the group treated only with acai-berry extract (**Fig. 5D**). Semi-quantitative determination of histological alterations was recorded in **Table 1**.

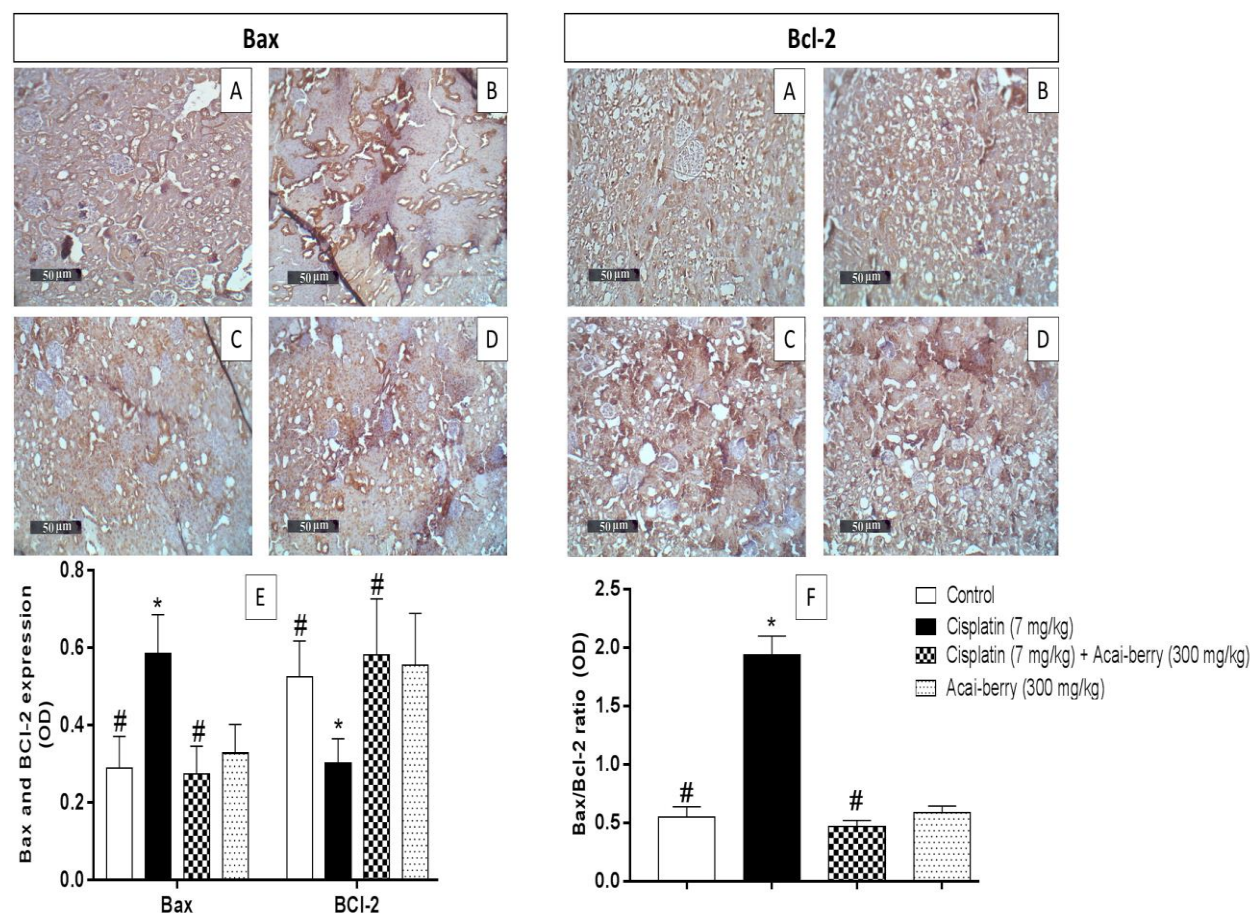


Fig. 3. Immunohistochemical staining of Bax and Bcl-2 expression in renal tissues (100x magnification). Photomicrographs of kidney histological sections from (A) control group, (B) cisplatin-treated group (7 mg/kg), (C) acai-berry-treated group (300 mg/kg), and (D) acai-berry alone-treated group. The brown color (positive) indicates specific immunostaining for Bax or Bcl-2, while the blue color (negative) represents hematoxylin staining. Scale bar = 50 μ m. (G) Quantitative image analysis (n = 3) of immunohistochemical staining presented as optical densities (OD) across 15 different fields for each rat section for Bax and Bcl-2 (E), as well as the Bax/Bcl-2 expression ratio (F). * and # indicate statistical significance compared to the control and cisplatin-treated groups, respectively, at $P < 0.05$, as determined by one-way ANOVA followed by Tukey's post-hoc test.

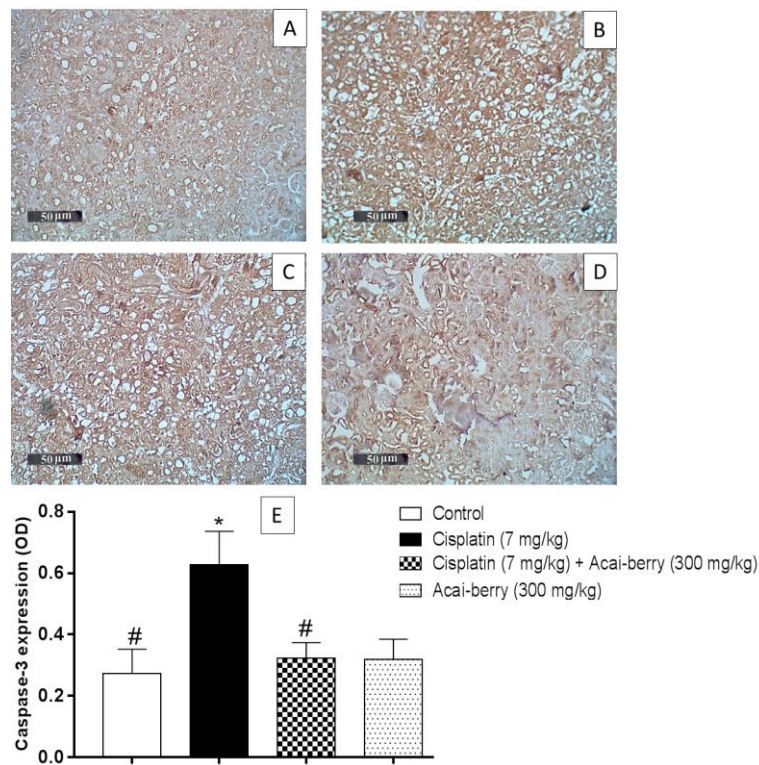


Fig. 4. Immunohistochemical staining of caspase-3 expression in renal tissues (100x magnification). Photomicrographs of kidney histological sections from (A) control group, (B) cisplatin-treated group (7 mg/kg), (C) acai-berry-treated group (300 mg/kg), and (D) acai-berry alone-treated group. The brown color (positive) indicates specific immunostaining for caspase-3, while the blue color (negative) represents hematoxylin staining. Scale bar = 50 µm. (E) Quantitative image analysis (n = 3) of immunohistochemical staining presented as optical densities (OD) across 15 different fields for each rat section (E). * and # indicate statistical significance compared to the control and cisplatin-treated groups, respectively, at $P < 0.05$, as determined by one-way ANOVA followed by Tukey's post-hoc test.

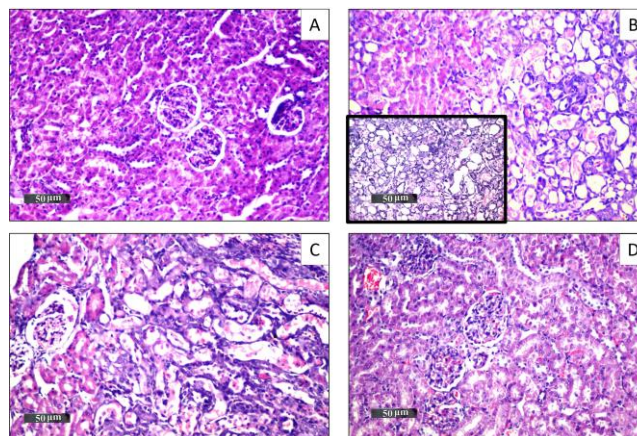


Fig. 5. Effect of treatment with acai-berry against cisplatin-induced nephrotoxicity on histological alterations of the renal tissues. Photomicrographs of haematoxylin and eosin-stained sections of kidney from the control group (A), cisplatin-treated group (7 mg/kg) (B), acai-berry-treated group (300 mg/kg) (C), and acai-berry alone-treated group (D) with 100x magnification power. The control group (A) showed normal histological structure of the glomeruli and renal tubules. The cisplatin-treated group (B) showed nuclear pyknosis and necrosis with cystic dilatation in renal tubules. Acai-berry-treated and acai-berry alone-treated groups (C and D) revealed no histopathological alterations in renal tissue.

Table 1. Semi-quantitative analysis of histopathological alterations

Group	Control	Cisplatin	Cisplatin + Acaiberry	Acaiberry
Nuclear pyknosis	-	+++	+	-
Necrosis	-	++	+	-
Cystic tubular dilations	-	++	-	-

Effect of acai-berry on histopathological alterations induced by cisplatin in rats. Cisplatin was administered once in a dose of 7 mg/kg, i.p. Acai-berry was given in a dose of 300 mg/kg orally for 7 consecutive days. Grading of histological alterations was determined as follows: (-) means normal histological structure of renal tubules. (+) Mild tubular cell necrosis and pyknosis (<25%), (++) Moderate tubular cell necrosis and pyknosis (<50%), (+++) Severe tubular cell necrosis and pyknosis (<75%).

4. Discussion

Nephrotoxicity is one of the fundamental dose-limiting factors associated with chemotherapy. Many cancer patients on chemotherapy were reported to experience nephrotoxicity at different levels [23]. Acai-berry is a Brazilian fruit from palms of the *Arecaceae* family that has recently attracted much attention due to its compelling antioxidant potential related to the ample flavonoid content of the anthocyanin compounds [24]. The main target of the present study was to elucidate the kidney protective impact of acai-berry on cisplatin-induced nephrotoxicity in rats, as well as demonstrate the potential anti-oxidative and anti-apoptotic mechanisms.

Cisplatin was reported to induce nephrotoxicity via enhancing oxidative stress and apoptosis [25]. In this study, cisplatin-induced histopathological changes in kidney tubules were revealed as interstitial hemorrhage, glomerular shrinkage, peritubular capillary congestion, tubular cell vacuolation, pyknosis, shedding, necrosis, and the infiltration of inflammatory cells, all of which indicate renal damage. These changes reflect a significant deterioration in kidney function. On the other side, acai-berry treatment corrected such changes and protected kidney tissues from the toxic effects of cisplatin.

Furthermore, nephrotoxicity induced by

cisplatin was further proven by the biochemical measurement of nephrotoxicity indices, serum urea, and creatinine. Cisplatin induced substantial increases in serum levels of both serum urea and creatinine. Increased levels of serum urea and creatinine may be an indication of renal tubular damage. Interestingly, acai-berry treatment came to correct such elevated levels of serum urea and creatinine, implying the nephroprotective properties of acai-berry against cisplatin-induced nephrotoxicity. Consistent with current findings, researchers reported that acai-berry seed extract could normalize serum urea and creatinine, as well as reduce kidney fibrosis in renal injury associated with diabetes and hypertension in rats [26].

The next step of this research was to explore the renal protective pathways of acai-berry against cisplatin-induced renal injury. The pathophysiology of cisplatin-induced nephrotoxicity is multifactorial, with oxidative stress being the major driving force for inducing renal damage [25]. This was evidenced by a marked amelioration in the level of GSH and Nrf-2 expression. Cisplatin was previously reported to induce the release of free radicals, which in turn could promote oxidative stress [1]. Satoh et al [27] reported that cisplatin may cause the production of highly reactive ROS, such as hydroxyl and superoxide radicals, which can

damage and modify cellular components (DNA, proteins, and lipids), ultimately leading to cell death. Indeed, ROS overproduction leads to the exhaustion of intracellular antioxidant defenses, hence, aggravating the imbalance in the oxidative status. In this regard, cisplatin-induced oxidative stress was found to be characterized by reduced levels of anti-oxidant enzymes, such as reduced glutathione, and anti-oxidant proteins, such as Nrf-2 [28, 29].

Nrf-2 is considered the key player in cellular transcriptional oxidation that directly controls antioxidant levels and the oxidative stress process as a whole [30]. Under oxidative conditions, Nrf-2 is sequestered in an active status in the cytoplasm by binding to its repressor protein, Keap 1, thus preventing its interaction with antioxidant-responsive elements instead of exposing it to proteasomal degradation [31].

Of interest, Nrf2 is crucial for managing the intracellular glutathione balance by regulating the genetic expression of the glutamate-cysteine ligase that greatly modulates glutathione biosynthesis [32]. Interestingly, GSH level and Nrf-2 expression were found to be enhanced with acai-berry treatment. In line with our study, several experimental studies have affirmed the potent antioxidant capabilities of Acai fruit, as shown by attenuating oxidative injury in hypercholesterolemic rats and guarding against hydrogen peroxide-mediated damage to rats' cerebral cortex, hippocampus, and cerebellum [33, 34]. This could be related to the acai berry's ability to scavenge free radicals, reduce the generation of ROS, and enhance the regeneration of both GSH and Nrf-2 expression [13, 35, 36].

Oxidative stress not only induces direct damage to cellular components but also plays a crucial role in provoking cell death by eliciting mitochondrial-dependent apoptotic cascades [37]. Apoptosis of the renal tubular epithelial cells via a mitochondrial-dependent pathway is a

distinctive attribute of cisplatin-induced nephrotoxicity [38]. The Bcl-2 family proteins primarily control the intrinsic apoptotic pathway by modulating mitochondrial membrane permeability [39].

Within this family, Bcl-2 preserves mitochondrial membrane integrity, whereas Bax induces disruption of membrane permeability [40]. The equilibrium between pro- and anti-apoptotic proteins within the Bcl-2 family is essential for the regulation of apoptosis. Therefore, the Bax/Bcl-2 ratio serves as an indicator of the cell's susceptibility to apoptosis [41].

The massive ROS generation driven by cisplatin intoxication is associated with activation of the pro-apoptotic protein Bax, which further causes permeabilization of the mitochondrial membrane, followed by cytochrome c production, followed by activation of the chief enzyme in execution of apoptotic cell death, caspase-3 [42]. In our study, cisplatin treatment enhanced the expression of Bax and caspase-3 and hindered that of Bcl-2. The Bax/Bcl-2 enhanced ratio could activate the intrinsic pathway of apoptosis, leading to a series of caspase activations ending with caspase-3, leading to programmed cell death. These findings were supported by previous studies that reported that cisplatin intoxication induced marked apoptotic cell death characterized by augmented expression of the caspase-3 enzyme, as well as elevated Bax/Bcl-2 ratio [43]. By contrast, acai-berry treatment counteracted enhanced expression levels of the Bax/Bcl-2 ratio and caspase-3, preventing apoptosis. These results are in agreement with [26]. They reported that acai-berry extract reduced caspase-3 expression in a significant manner.

While the present study demonstrates the potential nephroprotective effects of acai-berry against cisplatin-induced renal toxicity in rats,

several avenues for future research are warranted. First, further mechanistic studies are needed to elucidate the precise molecular pathways through which acai-berry exerts its antioxidant, anti-inflammatory, and cytoprotective effects in renal tissues. Second, dose-response and time-course studies should be conducted to optimize the therapeutic window and efficacy of acai-berry administration. Third, translational research, including preclinical trials in larger animal models and eventual clinical trials in human patients undergoing cisplatin chemotherapy, will be essential to evaluate the safety, pharmacokinetics, and efficacy of acai-berry-based interventions in clinical oncology settings.

This research shed light on the nephroprotective effect of acai-berry on cisplatin-induced kidney injury in rats. First of all, acai-berry treatment corrected histopathological changes induced by cisplatin. Moreover, serum urea and serum creatinine levels have been reduced following acai-berry treatment. Furthermore, acai-berry prevented oxidative stress and apoptosis, neutralizing the effect of cisplatin-induced renal toxicity. Such an effect was evidenced by the acai-berry effect on GSH level, Nrf-2 expression, Bax/Bcl2 expression ratio, and caspase-3 expression. Therefore, acai-berry may provide a promising solution for kidney injury induced by cisplatin affecting cancer patients worldwide.

Declarations

Ethics approval and consent to participate

The research design was approved by the research ethical committee of the Faculty of Pharmacy, Ain Shams University (Egypt) (Approval No.# REC76).

Consent to publish

Not applicable

Availability of data and materials

Data will be made available on reasonable request.

Competing interests

The authors declare that no competing interests exist.

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Author's Contribution

EM Mantawy and MY George contributed to the research study and design. MA Elhawary, MM Eltobgy, AS Moubarak, E Helmy, and MA Awwad performed biological experiments and biochemical analyses. MY George performed the statistical analysis and interpretation of data. MA Elhawary wrote the first draft of the manuscript. EM Mantawy revised the article critically for important intellectual content. All authors contributed to and have approved the final manuscript.

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