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Research Article
Bacoside a Attenuates Nephrotoxicity and Acute Kidney Injury in Male Albino Rats Induced by Cisplatin

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Abstract

Background and Objective: Bacoside A (B-A) is the major component of *Bacopa monniera* which is a popular folk medicine used to treat ulcer, rheumatism and neurological disorders. The present study was aimed to investigate the renoprotective property of B-A against cisplatin-induced nephrotoxicity. **Materials and Methods:** Thirty-two male rats were purchased and equally divided into four groups. Control rats received only saline, cisplatin (CISP) group rats were intraperitoneally (i.p.) injected with cisplatin (7 mg kg^{-1}) on the 5th day. Whereas, rats received 10 or 20 mg kg^{-1} of B-A orally for 10 days after CISP induction and served as treatment group (B-A 10 or 20). **Results:** Rats treated with B-A (10 or 20) for 10 days resulted in a significant decrease in the levels of renal markers [creatinine (Cr), blood urea nitrogen (BUN)], lipid peroxidation product, inflammatory markers [Interleukin 1beta (IL-1β), Interleukin six (IL-6), tumour necrosis factor (TNF-α) and nuclear factor kappa B (NF-κB) p65 subunit) and apoptotic markers (Caspase-3/9) on comparison with CISP group. Whereas, supplementation with B-A substantially improved ($p<0.01$) the antioxidant activities [catalase (CAT), superoxide dismutase (SOD), reduced glutathione (GSH)]. Moreover, the histopathological changes in renal tissue were reverted to normal upon treatment with B-A. **Conclusion:** Both B-A 10 and 20 showed potent renoprotective activity against cisplatin-induced nephrotoxicity. Never the less, B-A 20 displayed superior renoprotective activity than B-A 10.

Key words: Bacoside A, cisplatin, nephrotoxicity, renal markers, renoprotective activity, apoptosis

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Cisplatin (CISP) or cis-diamminedichloroplatinum (II) is a frontline chemotherapeutic agent prescribed for treating many types of solid tumors such as the esophagus, head and neck, testis and lung tumors[1,2]. Nevertheless, its clinical use is much limited owing to drug resistance and various adverse effects (nephrotoxicity, hepatotoxicity) as most of the patients experience renal dysfunction/injury after a single dose of cisplatin[3,4]. The CISP can act as an intercalating agent, due to increased platinum content which forms DNA adducts and thereby interfering in DNA transcription/replication (DNA damage) and subsequently results in renal injury (as kidneys try to excrete platinum) by eliciting sudden tubular cell cycle arrest (tubular injury), mitochondrial dysfunction and necrosis[5,6]. Moreover, many scientists have demonstrated that oxidative stress (excessive free radical generation), inflammation and apoptosis provoked after DNA damage are the primary reason for the cisplatin-induced nephrotoxicity[7,8]. Therefore, recently researchers have focused on developing a natural adjuvants drug with antioxidant, anti-inflammatory and renoprotective properties which might overcome that adverse effect (nephrotoxicity) induce by CISP during chemotherapy without modulating the therapeutic property[2,9].

Bacoside A (B-A) is a 3-(a-L-arabinopyranosyl)-O-b-D-glucopyranoside-10 dammarane-type triterpenoid saponin, isolated from *Bacopa monniera* plant (syn. *Herpestis monniera*). *Bacopa monniera* or *Bacopa monnieri* is a popular folk medicine (Chinese and Indian traditional medicine) used to treat ulcer, rheumatism and neurological disorders[10,11]. *Bacopa monniera* is a famous functional food and hence it has been used in the various food system to enhance the brain function[12]. B-A co-occurs with Bacoside B (B-B), which differ only in the optical rotation (spatial configuration) and thus act as an isomer[13] for B-A. Numerous experiments have indicated that B-A is the major chemical entity for contributing various beneficial properties[14]. B-A exert many pharmacological properties including anti-oxidant, anti-inflammatory[15], anti-tumour[16] as well as neuroprotective[17], hepatoprotective[13]. Recently, Kishore *et al.*[18] hypothesized that renoprotective activity of *Bacopa monniera* is mainly due to presence of Bacoside A (Saponins). However to prove his hypothesis, the present study was framed to explore the renoprotective action by screening antioxidants, renal, inflammatory and apoptotic markers and histological changes in cisplatin-induced nephrotoxicity rat model.

MATERIALS AND METHODS

This animal study was conducted at Xiangya Hospital Central South University, Hunan, China during March, 2016- April, 2016.

Chemical and reagents: Sodium pentobarbitone, phosphate buffered saline (PBS), Tween-20, isopropanol, glycerol. Formalin was purchased from Beijing Zhongshan Golden Bridge Biotechnology Co. Ltd., (Beijing, China). Bacoside A (BA), cisplatin, sodium dodecyl sulfate (SDS), β-mercaptoethanol, hematoxylin and eosin (H and E) stain, bromophenol blue, xylene were bought from Sigma-Aldrich (St. Louis, MO, USA). All the other chemicals used in this study were of analytical grade.

Experimental animals: A total of 32 male adult (2 months old) rats weighing 190±10 g of Wistar strain were maintained at Xiangya Hospital Central South University animal research center (China). Rats were housed in a sturdy steel cage and exposed to 12 h dark/light cycle and maintained at constant temperature (22±1°C) and humidity (55±5%) with free access to standard rat chow and water (*ad libitum*). All the animal experimentation protocols employed in this experiment were approved by the ethical committee members of Xiangya Hospital Central South University and abide by the NIH guidelines (revised 1978) for the care and use of experimental animals.

Animal grouping: After 2 weeks of acclimatization period, 32 healthy males were randomly divided into four groups with 8 rats in each (n = 8). Control group rats received only saline (0.9%) for 10 days without any treatment. Cisplatin (CISP) group rats were induced nephrotoxicity by single intraperitoneal (i.p.) injection of cisplatin (dissolved in 0.9% saline) at the dose[19] of 7 mg kg^{-1} on the 5th day. Whereas, B-A 10 or 20 group rats received B-A either 10 or 20 mg kg^{-1} (oral gavage, o.p) for 10 days with cisplatin induction on the 5th day (1 h after B-A treatment).

Sample preparation: After 10 days of treatment with B-A (on the 11th day), the overnight fasted rats were weighed and sacrificed by cervical decapitation procedure under mild anesthesia (50 mg kg^{-1} of sodium pentobarbitone). Blood samples were collected in a non-anticoagulant tube and the serum sample was separated by centrifugation at 1000 rpm for 10 min at 4°C and stored at -80°C until used for

biochemical analysis. Immediately after sacrifice the kidney (renal) was harvested and washed in ice-cold saline to remove the fats and other connective tissues (decapsulated) and weighed. The relative kidney weight (kidney weight/body weight (final)×1000) was calculated as described by Potocnjak *et al.*[20]. A portion of each renal tissue (cortex) was fixed in 10% formalin (formaldehyde) for histopathological analysis and the remaining portion is homogenized using phosphate buffer (pH 7.4) in a potter-Elvehjem type homogenizer to prepare 10% renal tissue homogenate. Finally, the homogenate was centrifuged at 10000 rpm for 10 min at 4°C, the supernatant portion is separated and used for various biochemical analyses. The total protein content of the renal tissue homogenate was determined by Barford reagent kit from Sigma-Aldrich (St. Louis, MO, USA) using bovine serum albumin (BSA) as a standard. Moreover, the nuclear fraction was separated from the renal tissue homogenate (supernatant) using Nuclear/Cytosolic Fractionation Kit (Cat No: AKR171) from Cell Biolabs Inc., (San Diego, CA, USA) based on supplier procedure.

Biochemical analysis: Assessment of renal function (renal markers): Renal markers such as blood urea nitrogen (BUN, Cat No:C013-1) and serum creatinine (Cr, Cat No:A032-2) levels were assessed using the commercial assay kit bought from Nanjing Jiancheng Bioengineering Institute (Nanjing, China) by following suppliers protocol.

Assay of renal antioxidant: The activities of antioxidants like catalase (CAT, Cat No:A007-2), superoxide dismutase (SOD, Cat No:A001-1), reduced glutathione (GSH, Cat No:A006-2) as well as lipid peroxidation products like Malondialdehyde (MDA, Cat No:A003-1) levels in renal tissue homogenate were determined by the commercial kits provided by Nanjing Jiancheng Bioengineering Institute (Nanjing, China) in accordance to the supplier instructions.

Evaluation of renal inflammatory markers: The concentration of nuclear factor kappa b p65 subunit (NF-κB p65) in the nuclear fraction of renal tissue homogenate were evaluated by NF-κB p65 (Total) multispecies Instant One ELISA kit (Cat No: 85-86081-11) from Invitrogen (Thermo Fisher Scientific Inc., MA, USA). Similarly, the levels of pro-inflammatory cytokines like tumour necrosis factor (TNF-α), Interleukins 1 beta (IL-1β) and Interleukins 6 (IL-6) in renal tissue homogenate were measured using rat-specific Quantikine ELISA kit (TNF-α, Cat No: RTA00, IL-1β, Cat No: RLB00 and IL-6, Cat No: R6000B) purchased from the R and D system (Minneapolis, MN, USA) based on manufacturer's instructions.

Quantification of renal apoptosis markers: The activities of rat-specific caspase-3 (cat no: CSB-E08857r) and 9 (cat no: CSB-E08863r) from renal tissue homogenate were quantified using commercial ELISA kits from CUSABIO and CusAb (Wuhan, China) in according to manufacturer's instructions.

Histopathological examination: Renal tissue fixed in 10% formalin was sequentially dehydrated using xylene and isopropanol and embedded in liquid paraffin wax to form a block. A tissue slice (from the block) of 4-5 µm diameter was made using microtome (Leica RM 2125, Wetzler, Germany) and washed with distilled water (de-waxed using ethanol) and bound to microscopic slide and finally stained with H and E stain for overnight as described by Domitrovic *et al.*[8]. The stained renal tissue slides were then examined using alight microscope (Nikon, Eclipse 50i, Tokyo, Japan) for any histological changes. The tubular injury score was scored by an independent pathologist on 5-point grading scale: 0 = no damage, 1 = 10% medullary junction injury, 2 = 10-25% medullary junction injury, 3 = 25-50% medullary junction injury, 4 = 50-75% medullary junction injury and 5 = 75-100% medullary junction injury as described previously by Domitrovic *et al.*[8].

Data analysis: Data were expressed as a Mean±Standard Deviation for 8 rats in each group. The difference between the experimental groups was assessed by One-Way Analysis of variance (ANOVA) followed by the Dunnett's multi-comparison test using software called statistical package for the social science (SPSS, Ver 21) from IBM Inc., (NY, USA). Values of p less than 0.05 were recognized as statistically significant.

RESULTS

Effect of B-A on the body weight, changes in body weight and kidney to body weight ratio: Results showed a significant decrease ($p<0.01$) in the final body weight (reflected in changes in body weight) with substantial increased ($p<0.01$) the relative kidney weight (kidney to body weight ratio) were noted in the CISP group. While the treatment with B-A (10 or 20 mg) considerably improved ($p<0.05$) the body weight and thereby markedly decreased the relative kidney weight as compared with CISP induced rats (Table 1).

Table 1: Efficacy of Bacoside A (B-A) on the body weight, changes in body weight and kidney to body weight ratio

Groups	Initial body weight (g)	Final body weight (g)	Changes in body weight (g)	Relative kidney weight
Control	190.35±6.10	196.50±7.17	(+) 6.15±1.00	6.10±0.70
Cisplatin (CISP)	194.40±7.35	184.90±6.10	(-) 9.50±2.05^{a**}	8.65±1.10^{a**}
B-A 10+CISP	193.70±7.84	188.60±8.33	(-) 5.10±0.80^{b*}	7.42±0.90^{b*}
B-A 20+CISP	194.75±7.50	191.50±7.50	(-) 3.25±0.07^{b*}	6.70±0.80^{b*}

Data were expressed as mean±standard deviation for 8 rats in each group. *p<0.05, **p<0.01, ***p<0.001, where a represents the comparison between control vs. Cisplatin group, b represents the comparison between B-A 10 or 20 group vs. Cisplatin group. Relative kidney weight are expressed as kidney weight/b.wt.×1000

Table 2: Efficacy of Bacoside A (B-A) on the activities of renal antioxidants and lipid peroxidation products

Groups	CAT (U mg^{-1} prot)	SOD (U mg^{-1} prot)	GSH (μg mg^{-1} prot)	MDA (nmols mg^{-1} prot)
Control	59.49±9.14	5.11±0.77	9.89±0.88	0.68±0.08
Cisplatin (CISP)	42.56±5.35^{a**}	2.33±0.24^{a***}	7.01±0.92^{a**}	1.58±0.21^{a***}
B-A 10+CISP	52.83±7.61^{b*}	3.49±0.45^{b*}	8.12±1.03^{b*}	1.05±0.09^{b**}
B-A 20+CISP	55.13±6.45^{b**}	4.08±0.87^{b**}	9.04±1.20^{b**}	0.77±0.07^{b***}

Data are expressed as mean±standard deviation for 8 rats in each group. *p<0.05, **p<0.01, ***p<0.001, where a represents the comparison between control vs. Cisplatin group, b represents the comparison between B-A 10 or 20 group vs. Cisplatin group. CAT: Catalase, SOD: Superoxide dismutase, GSH: Glutathione, MDA: Malondialdehyde, U: Units, Prot: protein

Table 3: Efficacy of Bacoside A (B-A) on the levels of various renal inflammatory markers

Groups	IL-1β (ng mg^{-1} protein)	IL-6 (pg mg^{-1} protein)	NF-κB p65 (pg mg^{-1} protein)	TNF-α (ng mg^{-1} protein)
Control	32.84±4.92	41.56±9.10	28.24±4.73	52.56±12.93
Cisplatin (CISP)	103.73±12.02^{a***}	124.63±17.91^{a**}	109.56±14.67^{a***}	155.15±21.38^{a***}
B-A 10+CISP	68.64±7.92^{b*}	82.98±10.49^{b**}	55.10±7.01^{b**}	88.81±9.02^{b**}
B-A 20+CISP	46.43±8.45^{b**}	67.88±5.14^{b**}	41.83±6.42^{b***}	65.32±7.39^{b***}

Data are expressed as mean±standard deviation for 8 rats in each group. *p<0.05, **p<0.01, ***p<0.001, where a represents the comparison between control vs. Cisplatin group, b represents the comparison between B-A 10 or 20 group vs. Cisplatin group. IL-1β/6: Interleukins beta or 6, TNF-α: Tumour necrosis factor alpha, NF-κb p65: Nuclear factor kappa b p65 subunit

Effect of B-A on the renal markers: The data in Fig. 1 showed the effect of B-A on the levels of renal markers like serum creatinine and BUN in experimental rats. In comparison with the control group, the levels of creatinine and BUN were significantly increased in CISP administered group. Treatment with bacoside A (10, p<0.05 or 20, p<0.01) considerably abolished the levels of those elevated renal markers (creatinine and BUN) compared with nephrotoxicity (CISP) group.

Effect of B-A on the renal antioxidant: Efficacy of B-A on the activities of various renal antioxidants and lipid peroxidation products was epitomized in Table 2. The activities of a renal CAT, SOD and GSH were significantly decreased (p<0.01) with elevated lipid peroxidation product like MDA (p<0.001) in rats injected with Cisplatin on equivalence with control rats. However, oral supplementation with B-A (10, p<0.05 or 20, p<0.01) for 10 days could substantially improve the renal activities of CAT, SOD and GSH with concomitant reduction (p<0.001) in the levels of MDA than CISP group.

Effect of B-A on the renal inflammatory markers: The data in Table 3 typified the changes in the levels of various renal inflammatory markers before and after treatment with B-A. The CISP induction resulted in a highly significant increase (p<0.001) in the concentration of different inflammatory markers like TNF-α, IL-1β/6 and NF-κb p65 subunit than that the control group. While, the levels of these inflammatory markers (TNF-α, IL-1β/6 and NF-κb p65 subunit) were remarkably declined (p<0.01 or p<0.001) in B-A administered rats when compared with CISP group.

Effect of B-A on the renal apoptotic markers: As shown in Fig. 2 the levels of renal apoptotic markers like caspase 3 and 9 were notably escalated (p<0.001) in CISP induced rats than in those of control rats. Apoptotic markers levels were significantly reverted (p<0.01) to near normal level upon treatment with two doses of B-A (10 or 20). Nevertheless, B-A 20 showed better anti-apoptotic activity than B-A 10 by considerably lowering the levels of both caspases.

Effect of B-A on the renal histological changes in experimental and control rats: The Fig. 3 portraited the efficacy of B-A on histological changes in renal tissue with H and E stain in experimental rats and visualized using a light microscope at a magnification of 400×. The slides of control rats (3A) depicted the normal architecture of nephron with proper glomerulus/tubular and Bowman's capsule (no tubular injury). Whereas, the slides of CISP induced rats (3B) showed the abnormal glomerulus (indicated by red arrow) inferred by

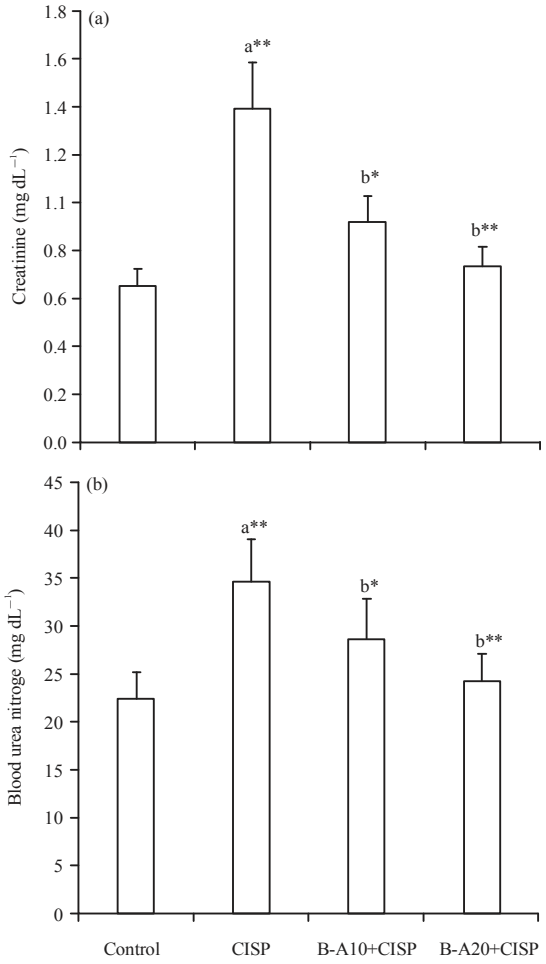

Fig. 1(a-b): Efficacy of Bacoside A (B-A) on the levels of renal markers like serum creatinine (Cr, 1A) and Blood Urea Nitrogen (BUN, 1B). Data are expressed as Mean±Standard deviation for 8 rats in each group

*p<0.05, **p<0.01, ***p<0.001, where a represents the comparison between control vs. Cisplatin group, b represents the comparison between B-A 10 or 20 group vs. Cisplatin group

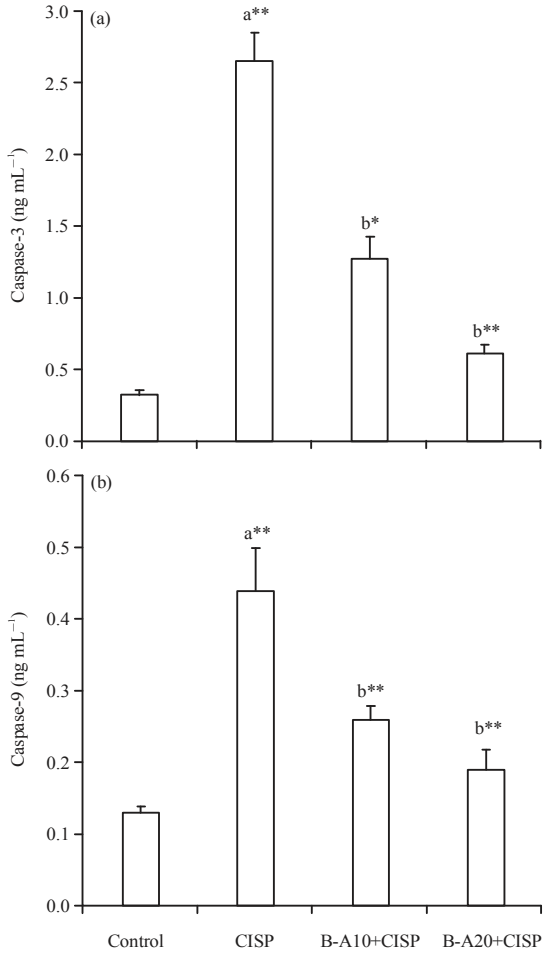

Fig. 2(a-b): Efficacy of Bacoside A (B-A) on the levels of apoptotic markers like Caspase 3 (2A) and Caspase 9 (2B) in the renal tissue. Data are expressed as Mean±Standard deviation for 8 rats in each group

*p<0.05, **p<0.01, ***p<0.001, where a represents the comparison between control vs. Cisplatin group, b represents the comparison between B-A 10 or 20 group vs. Cisplatin group

increased tubular degeneration (necrosis with greater tubular injury-(Fig. 3c) with many hyaline/protein casts and apoptotic bodies 3D (indicated by red arrow). The rats treated with B-A 10 represented a moderate number of the abnormal glomerulus and tubular damage (moderate tubular injury-bar 3 of Fig. 3e) with lesser hyaline/protein casts and apoptotic bodies. While treatment with B-A 20 treated rats showed slightly altered glomerulus (mild tubular injury-bar 4 of (Fig. 3e) with no or lesser hyaline/protein casts and apoptotic bodies. In all the biochemical, molecular and histological analysis both B-A 10 and 20 showed potent renoprotective activity by significantly improving antioxidant and normalizing the morphology of nephron as well as substantially abolishing the renal, inflammatory and apoptotic markers. However, B-A 20 displayed superior renoprotective activity than B-A 10.

DISCUSSION

The outcome of this study clearly showed that both doses of B-A (10 and 20 mg kg^{-1}) showed potent renoprotective activity by enhancing antioxidant and anti-inflammatory properties, which in turn reversed the renal injury

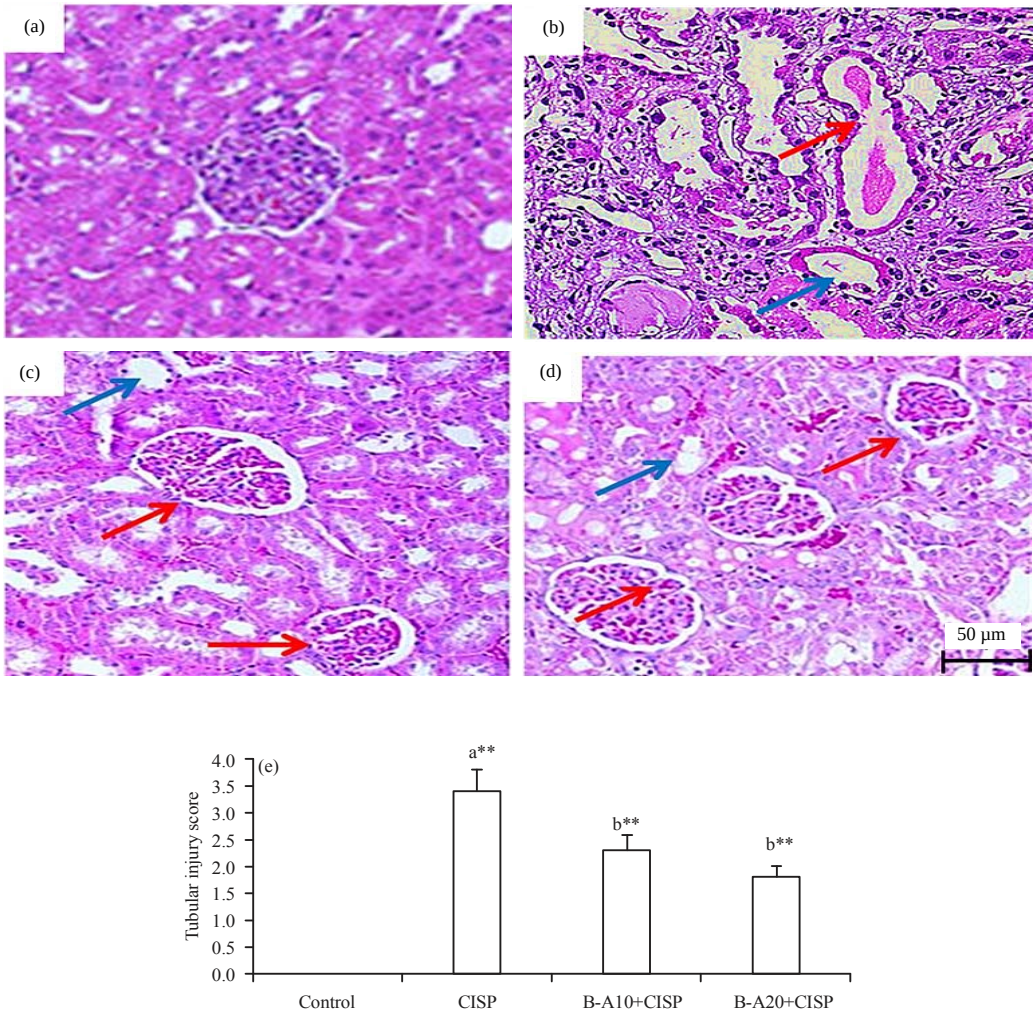

Fig. 3(a-e): Efficacy of B-A on histological changes in renal tissue with H and E stain in experimental rats and visualized using a light microscope at a magnification of 400×

(morphology of nephron) in cisplatin-induced nephrotoxicity rat model. The renal body weight changed as well as relative kidney weight was determined to check the incidence of renal hypertrophy or injury[21]. Cisplatin intoxication resulted in a significant decrease in final body weight and substantially increased the relative kidney weight due to increased kidney weight owing to increased renal hypertrophy. Treatment with B-A (10 or 20 mg) notably improved the body weight with decreased relative kidney weight by lowering kidney weight owing to antioxidant activity. Renal function was assessed by evaluating various renal markers like creatinine and BUN in experimental rats. The levels of Cr and BUN were significantly elevated in CISP induced rats as CISP was reported to trigger oxidative stress by excessive production of free radicals (ROS/RNS) in renal tubules. But, supplementation with bacoside A (10 or 20) significantly attenuated the levels of creatinine and BUN due to its free radical scavenging and antioxidant activity[13]. Previously, Anand *et al.*[11] demonstrated that bacoside extract supplementation could significantly lower the levels of BUN.

A significant reduction in the activities of renal antioxidants like CAT, SOD and GSH as well as pronounced increased in lipid peroxidation products like MDA were observed in Cisplatin administered rats. As mentioned previously, that cisplatin (platinum) is excreted by the kidney, which resulted in an overproduction of free radicals and subsequently increased lipid per oxidation with decreased antioxidant enzymes[7,22]. Cisplatin-induced rats treated with B-A remarkably enhanced the activities of various renal antioxidant enzyme activities (CAT, SOD and GSH) with decreased levels of MDA. Likewise, bacoside A treatment significantly improved the antioxidant enzymes like SOD,

CAT and GSH with reduced levels of lipid peroxidation products in cigarette smoke-exposed rats[17]. Previous studies had demonstrated that induction of cisplatin could stimulate the expression of various pro-inflammatory cytokines by activating NF-κb signaling pathway[9,23]. The concentration of various inflammatory markers like TNF-α, IL-1β/6 and NF-κb p65 subunit was significantly increased than the control group owing to interplay between oxidative stress and inflammatory cascade[8]. In the case of rats treated with B-A, the concentration of various inflammatory markers like TNF-α, IL-1β/6 and NF-κb p65 subunit was concomitantly suppressed. Viji and Helan[15], highlighted that bacoside rich fraction could significantly suppress the production of various inflammatory markers like TNF- α, IL-6, LOX and COX-2, *in vitro* and *ex vivo* conditions.

The apoptotic markers like caspase-3 and 9 were quantified as they play a crucial role in renal apoptosis (injury) after CISP induction[5,24]. The levels of both caspase-3 and 9 were significantly increased in CISP induced rats due to increased ROS production in the mitochondria of the renal cell, which in turn release cytochrome c and eventually activate caspase-9 and caspase-3 to execute apoptosis[5]. Treatment with saponin B-A (10 or 20 mg kg^{-1}) considerably lowered the levels of both caspase 3 and 9 due to the anti-apoptotic effect of bacoside[25]. Similarly, arjunolic acid a saponin from *Terminalia arjunais* reported to reduce the levels of caspase-3 and 9 in cisplatin-induced nephrotoxicity in a rat model[7].

The histological changes in the renal tissue were examined using H and E stain. The transection of control rats showed the normal architecture of nephron. But, the transection of CISP induced rats displayed abnormal glomerulus inferred by increased tubular degeneration (greater tubular injury score) with many hyaline/protein casts and apoptotic bodies, due to the cytotoxic effect of cisplatin. As mentioned earlier cisplatin induce renal injury by evoking various events like oxidative stress (lipid peroxidation), inflammation, apoptosis, necrosis and mitochondrial dysfunction[6,26]. Transection of B-A 10 and 20 treated rats represent moderate or less number of the abnormal glomerulus (moderate or mild tubular injury score) with no or few hyaline/protein casts and apoptotic bodies. This study has a few limitations such as lack of evaluation of pro and anti-apoptotic proteins and TUNEL assay (apoptosis/DNA damage). Also, other cytoprotective signaling pathways like Akt/PI3K, MAPK and GSK pathway and its correlations were not elucidated.

CONCLUSION

Taking together, both the doses of B-A (10 and 20) showed potent renoprotective activity against cisplatin-induced nephrotoxicity by improving antioxidant, normalizing the morphology of nephron as well as substantially abolishing the renal, inflammatory and apoptotic markers. However, B-A 20 displayed superior renoprotectivity than B-A 10 and can be recommended as chemo protectant (adjuvant therapy) when treated with cisplatin as a chemotherapeutic agent.

SIGNIFICANCE STATEMENT

The outcome of this animal study portrait that B-A can act as a potent renoprotective activity against cisplatin-induced nephrotoxicity by improving antioxidant, normalizing the morphology of nephron as well as substantially abolishing the renal, inflammatory and apoptotic markers. Therefore, B-A (novel pharmacotherapeutic agent) can be recommended as chemo protectant (adjuvant therapy) when treated with cisplatin as a chemotherapeutic agent to resolve the undesirable effect of cisplatin. In future, a novel compound can be synthesized by combining B-A with cisplatin for effective treatment of various cancer patients.

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