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RENOPROTECTIVE EFFECT OF IPOMOEA BATATAS AQUEOUS LEAF EXTRACT ON CYCLOSPORINE-INDUCED RENAL TOXICITY IN MALE RATS

Israa M. Shatwan

Food and Nutrition Dept., Faculty of Home Economics, King Abdulaziz University, Jeddah, KSA.

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ABSTRACT

Renal toxicity is a common disease worldwide. The current work was conducted to assess the possible renoprotective activity of Ipomoea batatas leaves extract (LB) in the cyclosporine (CE)-induced nephrotoxicity in rats. Forty male rats were distributed into 4 groups; Control (Cont), CE; rats intraperitoneal (IP) injected with CE (twenty-five mg/kg) for twenty-one days, LB 200 mg/ kg with +CE, LB 400 mg/ kg with +CE; rats received LB orally for twenty-one days, followed by IP injection with CE. Biochemical samples were collected after 24 h from the last dose of CE. The renal tissue samples were collected for histopathological examination. The results of the CE group showed that there were significant increases in renal lipid peroxidation (MDA), serum anti-inflammatory cytokines (TNF-α and IL-1β), serum kidney function parameters, and the serum ionic potassium (K^+) level, with significant decreases in the renal superoxide dismutase (SOD) and serum ionic sodium (Na^+) compared with the control group. In addition, the renal tissues of the same group showing congestion, focal hemorrhage, and interstitial nephritis, with coagulating necrosis of the renal tubules compared with the control group. Oral administration of LB extract significantly ameliorated CE-induced renal oxidative stress. It reduced CE-induced elevation in serum anti-inflammatory cytokines and kidney function parameters, as well as the changes in ionic Na^+ and K^+ levels compared to the CE group. It also protected against CE-induced histopathological changes. Therefore, LB extract ameliorates nephrotoxicity caused by CE through antioxidant and anti-inflammatory mechanisms.

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Introduction

Chronic illnesses are crucial health and therapy challenges of modern societies [1]. Organ transplantation is the preferred way in some cases to increase survival and improve life quality. Cyclosporine, a cyclic undecapeptide, is powerful immunosuppressive medicine, which is widely used to prevent the rejection of the transplanted organ, and in the treatment of autoimmune disorders [2, 3]. Hepatotoxicity, nephrotoxicity, cardiovascular diseases, dyslipidemia, and diabetes are the common side effects of immune-suppressive treatment [4-6]. Cyclosporine long term treatment is limited because of its intense side effects. It leads to irreversible kidney failure *via* tubulointerstitial fibrosis, renal vasoconstriction, changes in the tubular and glomerular epithelial cell [7].

Cyclosporine renal toxicity exhibited functional derangements and morphological damage based on treatment length [8]. Oxidative stress, renin-angiotensin-aldosterone activation, and vasoconstriction are the main reasons in CE renal toxicity [9-11]. Cyclosporine increases the ROS of renal, therefore the natural products with antioxidant properties could protect renal from toxicity

Ipomoea batatas leaves (LB), belonging to the *Conuvlvulaceae* family, is widely used as a medicinal plant [12]. Anthocyanins and polyphenolic are the main active biological compounds which have multifaceted effects including antioxidant, anti-carcinogenesis, anti-mutagenicity, and anti-inflammation properties [13, 14]. The LB has higher polyphenols content which has significant antioxidant activity and protects from degenerative diseases particularly cardiovascular, and cancer compared with any other vegetable [15, 16]. Its extract has hypolipidemic and antioxidant activities in hyperlipidemic subjects [17].

Corresponding Author: Israa M. Shatwan; Food and Nutrition Dept., Faculty of Home Economics, King Abdulaziz University, Jeddah, KSA; Email: safaaqusti @ yahoo.com

Recently, Rofiu and Luka [18] revealed that LB aqueous extract has a hypoglycemic effect and prevents diabetic complications through induced improvement in renal and blood hematological functions in diabetic rats. In addition, LB increase hemoglobin, platelets, and red blood cells [19, 20]. Anthocyanin, an abundant phytochemical in LB, reduceى coronary disease risk [21] and showed immunomodulatory effects in humans [22]. Moreover, the high antimicrobial activity of LB reported in several studies through inhibition of the microorganisms' growth [23-25]. Oxidative stress is the main pathway in CE renal toxicity and LB has potent antioxidant compounds. Therefore, this study assessed the potential renal protective role of LB against CE in rats.

Material and Methods

Drugs and chemicals and plant material

Cyclosporine A (CE) soft capsules were provided by Novartis Pharmaceuticals, Australia. All chemicals and kits with high grades obtained from Sigma-Aldrich (St. Louis, MO) Chemical Co. *Ipomoea batatas* Leaves were obtained from the local market, Jeddah, Saudi Arabia

Extracts of *Ipomoea batatas* leaves

Two hundred grams of air-dried leaves of LB were boiled with 1.5 liters of water for 40 minutes, after which it was rapidly filtered through a muslin cloth. The filtrate was allowed evaporating for another 45 minutes to give a brownish-black almost solid residue [26].

Experimental design

Forty male rats weighing 160-180 g were purchased from the animal house of King Fahd Medical Research Center, KAU. They adhered to Canadian ethical acceptance guidelines with free water and a regular diet from KAU's national biomedical ethical board. After one week of acclimatization, rats were distributed into 4 groups (n=10 in each group). Group I (Cont) rats received distilled water for 2 weeks then IP injected with olive oil (vehicle) for 21 days. Group II (CE) rats received distilled water for 2 weeks then were IP injected with CE at a dose of 25 mg/kg diluted in olive oil for a period of twenty-one days according to Chandramohan and Parameswar [27]. Group III received LB 200 mg/ kg +CE [28]. Group IV received LB 400 mg/ kg +CE. Rats in groups III and IV received LB orally for twenty-one days, followed by IP injected with CE.

Samples collection

Twenty four hours after the last injected dose of the CE drug, rats were anesthetized, then blood and renal samples were collected. The serum samples were separated and stored at -80 °C until used for biochemical analysis. The renal samples were either prepared for biochemical analysis or preserved in neutral buffer formaldehyde solution for histopathological studies.

Biochemical analysis

Renal oxidative stress biomarkers; MDA and the activity of SOD enzyme were estimated in homogenated renal using ELISA kits.

The anti-inflammatory cytokines*;* the serum levels of tumor necrosis interleukin-1beta (IL-1β) and -α (TNF-α) were assessed by ELISA kits.

The levels of kidney function; blood urea nitrogen (BUN), uric acid (UA), and creatinine (Cr), as well as serum levels of sodium (Na^+) and potassium (K^+) were measured using colorimetric kits.

All kits used were obtained from MyBioSource, the USA followed the steps and instructions of kits.

Histopathological studies

After the rats were slaughtered, the kidney was removed from all experiment groups. Tissue was set in 10% formalin neutral, dehydrated, coated in paraffin wax, and then stained by routine procedures with hematoxylin-eosin.

Statistical analysis

All results were analyzed by SPSS ver. 24, by using ANOVA. The values were expressed as mean± SMD, and P-value < 0.05 considered significance.

Results

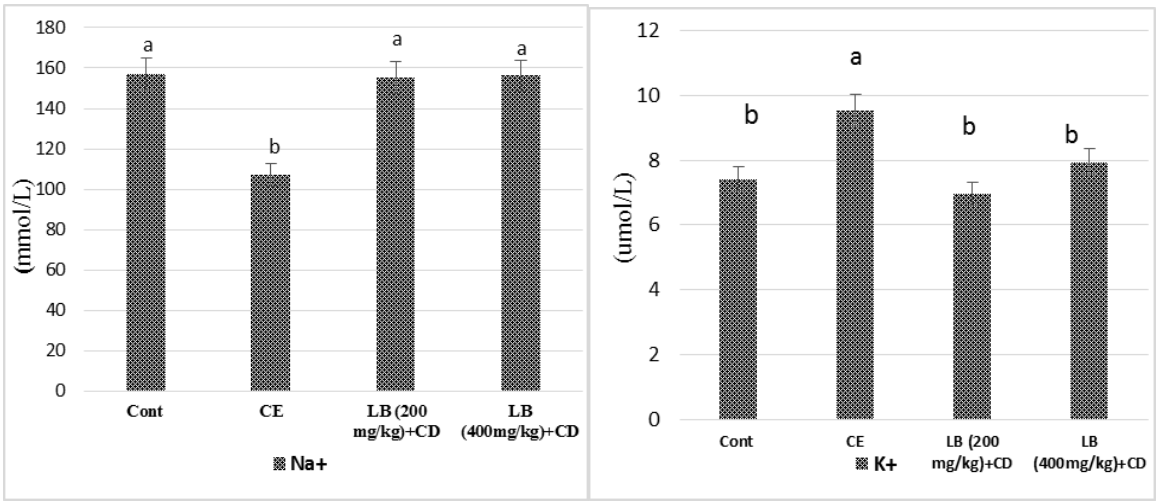
Effect of LB on renal oxidative stress in nephrotoxic rats by CE

The levels of non-enzymatic MDA and enzymatic SOD antioxidant in the renal tissue in different groups are represented in Figure (1). The level of MDA was significantly ($p<0.05$) increased along with a significant ($p< 0.05$) decrease in SOD activity in CE compared with the Cont group. Oral administration of LB induced a significant improvement in the antioxidant status of renal. The MDA level significantly decreased ($p< 0.05$) and the SOD enzyme activity significantly

increased ($p<0.05$) in the LB administration (200 mg/kg) and the (400 mg/kg) groups as compared with the CE group. Significant ($p< 0.05$) changes were observed in LB (200 mg/kg) + CE and LB (400 mg/kg) + CE, which indicated the protective effect of LB is dose-dependent.

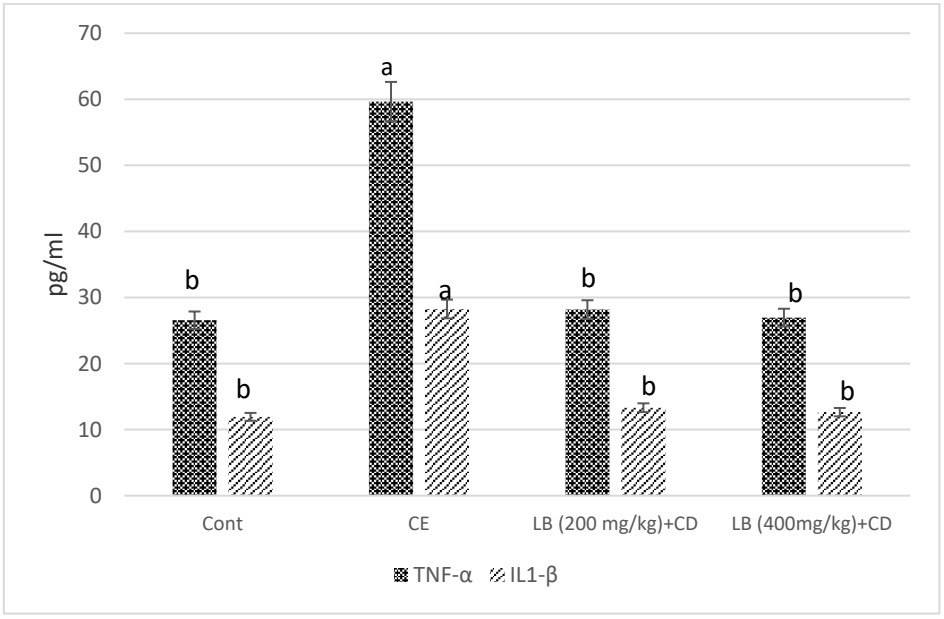
Effect of LB on serum anti-inflammatory cytokines in nephrotoxic rats by CE

The serum levels of IL1-β and TNF-α in different groups are shown in Figure (2). The levels of TNF-α and IL1-β were significantly ($p< 0.05$) increased in CE compared with the Cont group. Oral administration of LB induced significant decreases in the serum anti-inflammatory cytokines status. There were significant ($p< 0.05$) decreases in TNF-α and IL1-β levels in both LB groups as compared with the CE intoxicated group. Significant ($p< 0.05$) changes were observed in LB (200 mg/kg) + CE, and LB (400 mg/kg) + CE.



In each group N = 10, values are expressed as mean ± SMD.
Values with different superscript letters within a column are significantly different at P<0.05

Figure 1: Effect of LB extract on renal non-enzymatic (MDA) and enzymatic (SOD) levels against CE-induced nephrotoxicity in rats.



In each group N = 10, values are expressed as mean ± SMD.
Values with different superscript letters within a column are significantly different at P<0.05

Figure 2: Effect of LB extract on serum inflammatory TNF-α and IL1-β levels aginst CE-induced nephrotoxicity in rats.

Effect of LB on renal functions in nephrotoxic rats by CE

Table (1) represents the levels of serum renal functions (Cr, BUN, and UA) in different groups. The serum of kidney function level in the CE group was significantly ($p< 0.05$) increased compared to the Cont group. The LB administration (200 and 400 mg/kg) reduced the serum kidney function levels significantly ($p< 0.05$) as compared with the CE group,

which may be an indicator of renal toxicity induced by CE. Significant ($p< 0.05$) changes were observed in LB (200 mg/kg)+ CE and LB (400 mg/kg)+ CE, which indicated the protective effect of LB is dose-dependent.

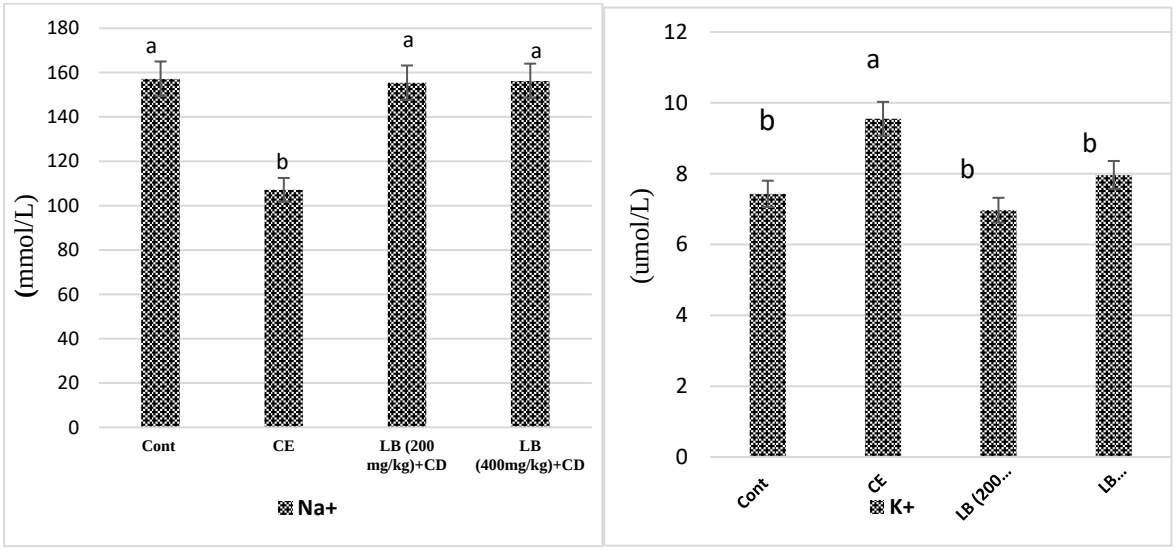
Table 1: Effect of LB extract on renal function against CE-induced nephrotoxicity in rats.

Groups	Creatinine (µmol/L)	Urea nitrogen (mmol/L)	Uric acid (umol/L)
Cont	28.15 ± 1.09 b	9.23 ± 0.22 b	71.54 ±.53 b
CE	57.22± 1.13 a	19.71 ± 0.13a	129. 31 ± 0.12 a
LB (200 mg/kg)+CE	29. 79 ± 1.29 b	10. 06 ± 0.04 b	73.09 ± 0.42 b
LB (400mg/kg)+CE	29.05 ±1.45 b	9.85 ± 0.06 b	72.01 ±0.23 b

In each group N = 10, values are expressed as mean ± SMD.
Values with different superscript letters within a column are significantly different at P<0.05.

Effect of LB on ionic sodium and potassium in nephrotoxic rats by CE

Figure (3) shows the levels of serum ionic Na^+ and K^+ in different experimental groups. The serum level of ionic Na^+ was significantly ($p< 0.05$) decreased along with significant ($p< 0.05$) increase in the serum ionic K^+ in the CE group compared with the Cont group. The oral LB administration significantly ($p< 0.05$) increased the ionic Na^+ level with a significant ($p< 0.05$) increase in the ionic K^+ level in the LB administration groups as compared with the CE intoxicated group. Significant ($p< 0.05$) changes were observed in LB (200 mg/kg) + CE and LB (400 mg/kg) + CE.



In each group N = 10, values are expressed as mean ± SMD.
Values with different superscript letters within a column are significantly different at P<0.05

Figure 3: Effect of LB extract on serum ionic Na^+ and K^+ levels against CE-induced nephrotoxicity in rats

Histopathological results

The Cont of the kidneys displayed normal glomerular and tubular histology. In the CE group, the kidney tissue showed peritubular and blood vessel obstruction, resulting in the presence of inflammatory cells. In the LB (200 mg/kg) +CE group, renal tissue showing mild tubular necrosis and inflammatory changes were reversed. The LB (400 mg/kg) +CE group present the normal appearance of renal tissue.

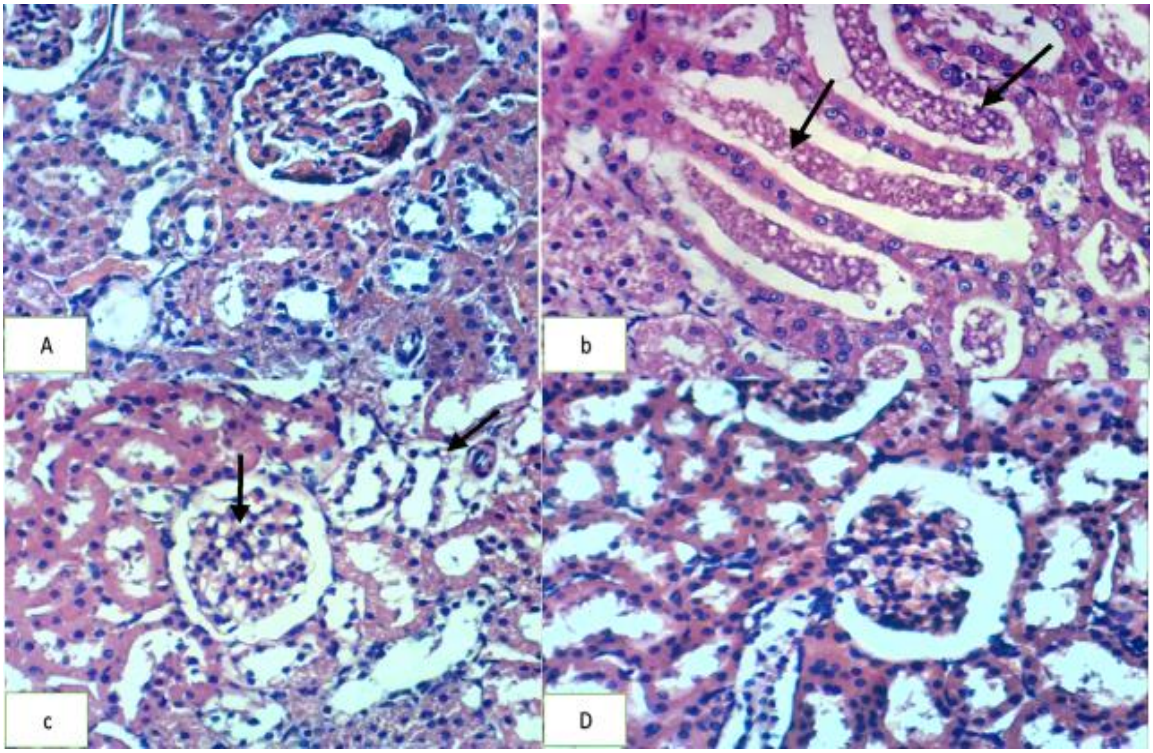


Figure 4: Photomicrography illustrating H&E-stained sections of kidneys in different groups. The Cont group revealed normal glomerular and tubular histology (Photo A). Photo B represents the CE group, demonstrated peritubular and blood vessel obstruction, resulting in the presence of inflammatory cells. Extract therapy LB (200 mg/kg) +CE group shows mild tubular necrosis and inflammatory changes were reversed (Photo C). Photo D presents the normal appearance of renal tissue in the LB (400 mg/kg) +CE group.

Discussion

Cyclosporine is an efficacy immunosuppressive therapy for allograft rejection. Nephrotoxicity has emerged as a serious side effect for usage clinically, despite CE is still widely used drugs [29]. Currently, the research approaches are to improve outcomes through retarding or preventing CE-nephropathy and other side effects, besides reduction of the dose or duration of treatment. The LB extract has potent active compounds which have multifaceted effects including antioxidant, and anti-inflammation properties [13, 14]. To this point, the protective effective role of LB against renal toxicity of CE has not been studied. Therefore, this study assessed the nephroprotective role of LB against CE in rats, with highlighting the remedy role of LB as antioxidant and anti-inflammatory.

Administration of CE induced significant renal function damage (increase Cr, BUN, and UA), disturbed the ionic electrolyte levels, increased renal oxidative stress (increase MDA and decrease SOD levels), and cytokines inflammation (TNF-α and IL-1β) relative to Cont group. Examined tissue confirmed the results of biochemical analysis, CE induced noticeable inflammation in glomerular cells and obstruction of blood vessels. Several studies confirmed the same obtained results [30, 31].

Chronic administration of CE for 21 days resulted in marked renal impairment, pronounced oxidative stress, a significant increase in kidney functions and lipid profile testes, with disturbances in electrolyte concentrations relative to untreated CE rats [32]. Thus, the oxidative stress mediated by CE through activating the variety of the vasoactive mediators' formation, affect directly on renal function, decreasing glomerular filtration rate (GFR), and inducing renal vasoconstriction [33]. Whereas creatinine and uric acid were used as an index for GFR, their elevation levels are indicators of the renal injury [34].

Yoon and Yang [6] illustrated that rats given CE caused renal toxicity damage, increase Cr and BUN, exhibited degeneration of tubular cells, inflammatory cells infiltration, and necrosis. Several pathways have been proposed to explain CE nephrotoxicity, namely, vasoactive substances imbalance-induced renal vasoconstriction [6], inductions of enzymes cytochrome P450 [35], activation of renin-angiotensin system [36], and immunoglobulin A nephrotoxicity, with development of interstitial fibrosis in renal [37]. Oxidative stress has a pivotal role in the functional and structural renal impairment [38], thus attributed to elevating the oxidants' production and activated xanthine oxidase [39]. Moreover, CE therapy increases the production of free radicals and lipid peroxides formation, explaining the involvement of oxygen free radicals in renal injury pathogenesis [40].

Furthermore, the CE-renal damage could be explained via CE induced imbalance between vasoconstrictors and vasodilators, and loss of proximal tubular cell brush border [41]. Moreover, Shalby *et al*. [42] found that CE caused elevated serum inflammatory cytokines. This could be explained through increased expression [43], cell death apoptotic in kidney tissue [44,

45], and decreasing the extracellular matrix proteins degradation [10]. The inflammation induced by CE could be a potent pathogenic agent of renal toxicity [46].

Oral administration of LB induced significant protection of the deterioration of renal function and ionic electrolyte, also improve the renal antioxidants content, along with the decline in the levels of the inflammatory cytokine, with preventing from the histopathological alteration induced by CE in a dose-dependent manner. These results could be explained by LB's significant antioxidant activity [47]. Moreover, the LB compared with butylated hydroxyanisole (BHA), a synthetic antioxidant, displayed notable antioxidant activities, which elevated linearly in a dose-dependent manner, as assessed by scavenging effect on the free radical DPPH and normalized intracellular levels of GSH in cells with glucose-induced oxidative stress [48].

The antioxidant properties of LB were explained *via* its high content of flavonoids and total phenols compound [49]. In addition, LB is rich in anthocyanins [50]. Seow-Mun *et al*. [51] demonstrated that LB extract relative to ascorbic acid showed high radical scavenging activity, and the increment in its reducing power positively correlated with increasing concentrations.

Furthermore, Margaret *et al*. [52] evaluated the potential anti-inflammatory effects of LB aqueous extract by a membrane-stabilizing method. The LB extract showed high anti-inflammatory activity. Also, the phytochemical analyses of LB showed its high content of flavonoids, phenols, anthraquinones, tannins, reducing sugars, polyphenolics, anthocyanins, and at least 15 biologically active anthocyanins, which have therapeutic value [53, 54].

In conclusion, the LB has significant renal protective effects. Antioxidant and anti-inflammatory could be the possible pathway by the extract, that prevent renal against CE-induced nephrotoxicity in rats.

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