Full Length Research Paper

Protective effect of *Haloxylon salicornicum* on hepatic and renal functions of Wistar rats exposed to aluminium

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Aluminium is present in some manufactured medicines and foods. It is known that aluminium causes oxidative stress. Therefore, the present study was undertaken to determine the effectiveness of *Haloxylon salicornicum* extract in modulating aluminium chloride ($AlCl_3$) induced oxidative stress in rats. Male rats (40 to 50 g) were divided into four groups of six animals each. The experimental protocol was based on the administration of $AlCl_3$ (30 mg/kg/body weight) intraperitoneally (ip) every 5 days for 15 days. The groups treated with the plant receive daily dose of 0.05 g/kg/body weight. Increased level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), urea, and creatinine in serum indicated hepatic and renal dysfunction. The variation of catalase (CAT), superoxide dismutase (SOD), reduced glutathione (GSH), and lipid peroxidation (thiobarbituric acid reactive substances, TBARS) were assessed. These parameters indicated the extent of oxidative damage in liver and kidney, thus confirming the histology results in liver and kidney. It was found that the consumption of *H. salicornicum* extract protects the liver and kidney against aluminium chloride toxicity. The aim of the present study was to evaluate the protective effect of the *H. salicornicum* extract on the damages caused by administration of aluminium chloride ($AlCl_3$) in young rats.

Key words: Aluminum chloride, Wistar rats, *Haloxylon salicornicum*, lipid peroxidation, superoxide dismutase (SOD), reduced glutathione, catalase.

INTRODUCTION

Aluminium is an abundant metallic element on the earth; it is used highly because of its excellent properties (Bai et al., 2012). Biological function of aluminium is not understood very well (Farina et al., 2002; Joshi et al., 2013). Aluminum presents 8% of all mineral components of earth. There is not a maximum level fixed for aluminium in food (AFSSAPS, 2011).

It can be used as a food additive and in materials in

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contact with foodstuffs (AFSSAPS, 2011), used as water clarifying agent (coagulation, flocculation, etc.). It is found in water intended for human consumption with a maximum concentration of 0.2 mg/L (AFSSAPS, 2011). This metal is also used in the preparation of some drugs (Ochmanski and Barabasz, 2000; Turkez et al., 2010). In mammals, aluminum is accumulated in kidney, liver, heart, blood, bones, and brain (Sanchez-Iglesias et al., 2007; Gonzalez et al., 2009; Al-Kahtani, 2010). The accumulation of aluminum in liver generates significant lesions (Nikolov et al., 2010; Shati and Alamri, 2010). Kidney prevents the accumulation of aluminium in different organs, this by urinary excretion (Shirley et al., 2004; Stoehr et al., 2006). However, kidney can be very vulnerable to the nephrotoxic effects of aluminium (Mahieu et al., 2003; Stoehr et al., 2006).

Aluminium can produce free radicals in the body. It induces a toxic effect due to its ability to transfer electrons (Taus et al., 2013). These free radicals resulting from aluminum can affect cell integrity, producing the peroxidation of the lipids in the intracellular membranes, and the cross-linking with the macromolecules in the membranes (Taus et al., 2013). Aluminium is known to affect the permeability of cellular membranes, of sub-cellular organelles, the structure and functions of proteins and the structure of nucleic acids (Taus et al., 2013).

Plants have always play a major role in treatment of human and animal diseases. Medical plants are a therapeutic resource much used in the traditional population of the world specifically for health care (Kadham, 2008).

Haloxylon salicornicum is a desert plant which belongs to the family of Chenopodiaceae which includes 100 genus and 1200 species (Ferheen et al., 2005). Most of the species of this family are weedy and grow in unfertile areas of soil (Ferheen et al., 2005). *H. salicornicum* is a diffuse shrub with a lot of branches, woody stem, 25 to 60 cm tall. It is widely distributed in Northern Africa and Asia, in both temperate and tropical regions (Ashraf et al., 2012). This plant contains, among other chemical constituent such as sodium (28.48%), potassium (9.49%), carbonate (61.06%), alkaloid, saponin and phenol (Al-Saeed, 2002). This plant was used effectively in folk medicine as diuretic (Al-Saeed, 2002), anti-ulcer (Shahana et al., 1990), hypoglycemic and anti-microbial (Abbas et al., 2006). Ahmad and Eram (2011) have shown that this plant has a hepatoprotective effect.

The aim of the present study was to evaluate the protective effect of the *H. salicornicum* extract on the damages caused by administration of aluminium chloride (AlCl$_3$) in young rats.

MATERIALS AND METHODS

Plant

The plant was collected from May to April in El-bayadh region of Southern Algeria. Aerial parts of *H. salicornicum* were air-dried at room temperature for 30 min. The dried plants were collected and ground to fine powder.

Preparation of aqueous extract

The powdered aerial parts of *H. salicornicum* (10 g) were extracted with boiled water (100 ml) for 20 min. After this step, the decoction was filtered and was freeze dried. The yield of this extraction is 13.01%.

Animals

Wistar rats were used as an experimental model to evaluate the effect of aluminium on liver and kidney. Aluminium chloride (AlCl$_3$) was administered intraperitoneally to rats at a dose of 30 mg/kg/body weight, every five days for 15 days. The lyophilized extract of *H. salicornicum* is dissolved in distilled water. The plant is administered daily to the rats using a feeding tube at a dose of 0.05 g/kg/body weight. Wistar rats (40 to 50 g) were randomly distributed in four groups containing 6 rats each: group (control): control rats were given nothing; group (Al): animals were given three injections of AlCl$_3$ (30 mg/kg/body weight); group (Al+P): rats received three injections of AlCl$_3$ (30 mg/kg/body weight) in addition to the plant (0.05 g/kg/body weight); group (P): animals were given only the plant (0.05 g/kg/body weight).

Rats were sacrificed after 5 days of the last dose and blood was collected in hemolysis tube. Liver and kidney were rinsed with saline solution (0.9% NaCl). For evaluation of oxidative status, liver and kidney were homogenized in suitable buffers: in 0.1 M phosphate buffer (pH 7.1) for superoxide dismutase (SOD), CAT, and reduced glutathione (GSH) in 1.15% KCl for thiobarbituric acid reactive substances (TBARS). Some portions of liver and kidney were fixed in formalin for histological study.

Biochemical parameters

Aspartate aminotransferase (AST), alanine aminotransferase (ALP), lactate dehydrogenase (LDH), creatinine, and urea were measured using Chronolab kits (Spain). Biochemical parameters were estimated in serum.

Catalase activity (CAT)

CAT was assayed colorimetrically at 620 nm, expressed as µmoles of H$_2$O$_2$ consumed/min/mg/protein (Sinha, 1972). The reaction mixture of 1.5 ml contained 1.0 ml of 0.01 M pH 7.0 phosphate buffer, 0.1 ml of homogenate, and 0.4 ml of 2 M H$_2$O$_2$. The reaction was stopped by the addition of 2.0 ml of dichromate-acetic acid reagent, 5% potassium dichromate, and glacial acetic acid was mixed in 1:3 ratios.

Lipid peroxidation (TBARS)

Lipid peroxidation was assessed by measuring substances which react with TBARS (Yagi, 1976). 125 µl of sample, 50 µl of TBA, and 125 µl of trichloroacetic acid-butylated hydroxytoluene (TCA-BHT) were mixed. After stirring, incubation was done at 80°C (10 min) and centrifugation was done (100 *g* for 10 min). The supernatant was removed. 200 µl of the supernatant were mixed with 40 µl of HCl (0.6 M) and 160 µl of Tris-TBA (26 mM Tris, 120 mM thiobarbituric acid). After stirring, and incubation at 80°C (10 min), the optical density was measured at 530 nm. The quantity of

Table 1. Levels of ALT, AST, and LDH in serum.

Group	ALT (U/L)	AST (U/L)	LDH (U/L)
Control	5.32±1.02	21.25±3.71	200.92±20.00
Al	21.17±1.11***	101.57±71.02***	548.92±7.15***
Al +P	12.53±0.26*§§§	41.22±2.36**§§§	267.33±21.39*§§
P	5.12±0.17§§§	18.66±0.82*§§§	173.26±67.17§

*Comparison with the control group. §Comparison with Al group.

TBARS (nM/g)
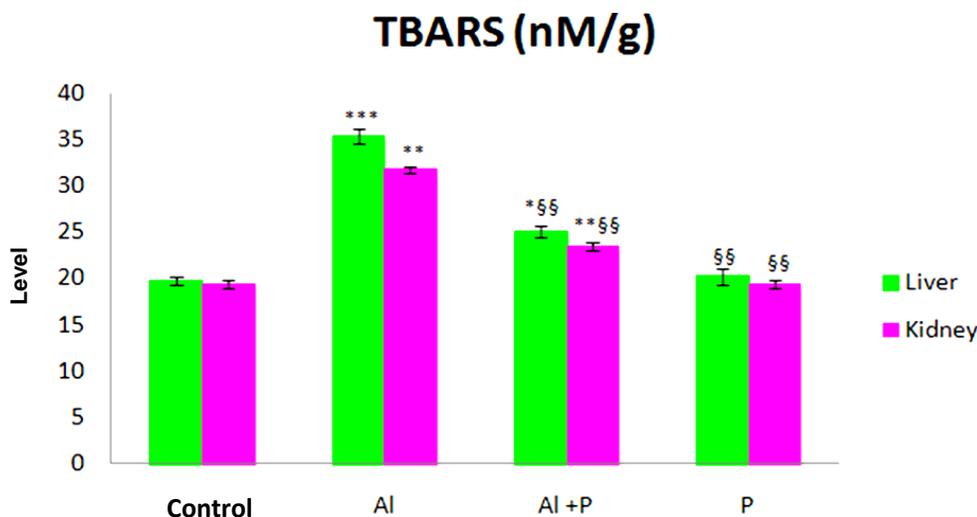
Figure 1. Levels of TBARS in liver and kidney. *Comparison with the control group. §Comparison with Al group.

TBARS was calculated using an extinction coefficient of 156 mM^{-1} cm^{-1}.

Reduced glutathione (GSH)

GSH was measured by the method of Ellman (1959). Samples were deproteinized with 5-5 'dithiobes (2-nitrobenzioc acid), and the optical density was measured at 412 nm.

Superoxide dismutase (SOD)

SOD was assessed using assay kit provided by Cayman (Chemical, USA).

Histological study

The sections were taken from liver and kidney and they were fixed in a formalin solution 1:10 to pH 7, dehydrated in acetone, clarified in xylene, and finally embedded in paraffin. Histological sections were cut at 3 µm using a microtome. The samples were stained with hematoxylin-eosin, and observed with an optical microscope.

Statistical analysis

The data were analyzed using Student's t-test. At $p < 0.05$, the results were considered significant. Values are expressed as the mean ± standard error.

RESULTS

Liver

The liver function is assessed by measuring of transaminases and LDH activities. AST, alanine aminotransferase (ALT), and LDH activities in the group (Al) were increased highly significantly ($p<0.001$) as compared to the group (control) (Table 1). A significant decrease of these activities is recorded in the group (Al+P) as compared to group (Al). The comparison between groups (control) and (P) shows that there was no significant difference except for AST (Table 1). Activities decreased highly significantly for ALT and AST ($p<0.001$), and significantly for LDH ($p<0.05$) in group (Al+P) in relation to the group (Al) (Table 1).

TBARS (Figure 1) and GSH (Figure 2) are higher in group (Al). The difference between groups (control) and (Al) is highly significant ($p<0.001$) for TBARS and very significant ($p<0.01$) for GSH. On the other hand, the comparison between groups (Al) and (Al+P) is very significant

GSH (nmol/mg)
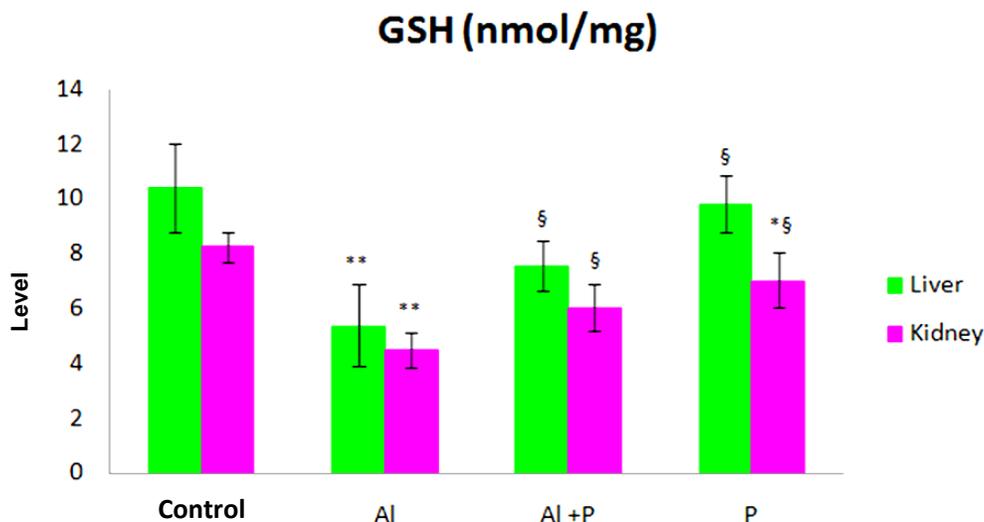
Figure 2. Levels of GSH in liver and kidney. *Comparison with the control group. §Comparison with Al group.

CAT mM/g
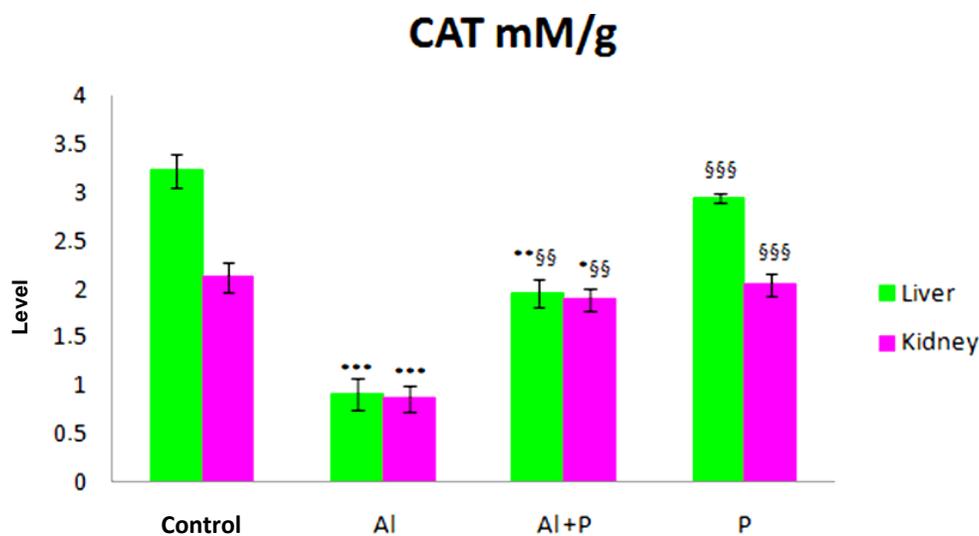
Figure 3. Levels of CAT in liver and kidney. *Comparison with the control group. §Comparison with Al group.

significant ($p<0.01$) for TBARS (Figure 1) and significant ($p<0.05$) for GSH. In group (P), TBARS and GSH (Figure 2) decreased.

The CAT (Figure 3) and SOD (Figure 4) activities are decreased in group (Al). The difference between groups (control) and (Al) is highly significant ($p<0.001$) for CAT and very significant ($p<0.01$) for SOD. The comparison between groups (Al) and (Al+P) is very significant ($p<0.01$) for CAT (Figure 3) and significant ($p<0.05$) for SOD (Figure 4).

Figure 5a and d presents regular histological structure of the liver tissue of control rats with a granular cytoplasm,

central core, and the open sinusoidal spaces of hepatocytes. Exposure to aluminium (Figure 5b) causes a loss of the arrangement of the hepatocytes with a degeneration of membrane, nucleus, and cytoplasm. Histological observations of liver of rats treated with *H. salicornicum* illustrate an improvement in some areas and a normal sinusoidal space (Figure 5c).

Kidney

Creatinine and urea were examined to verify the renal
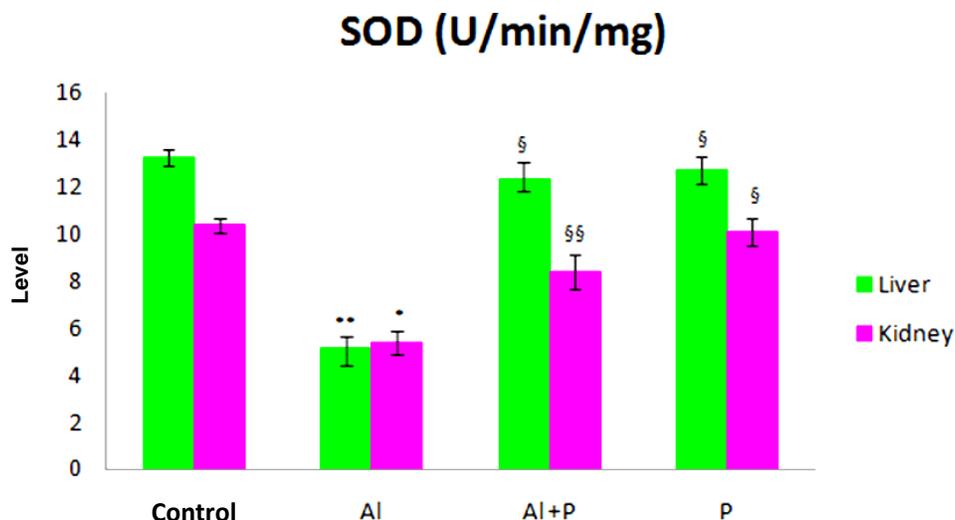
Figure 4. Levels of SOD in liver and kidney. *Comparison with the control group. §Comparison with Al group.
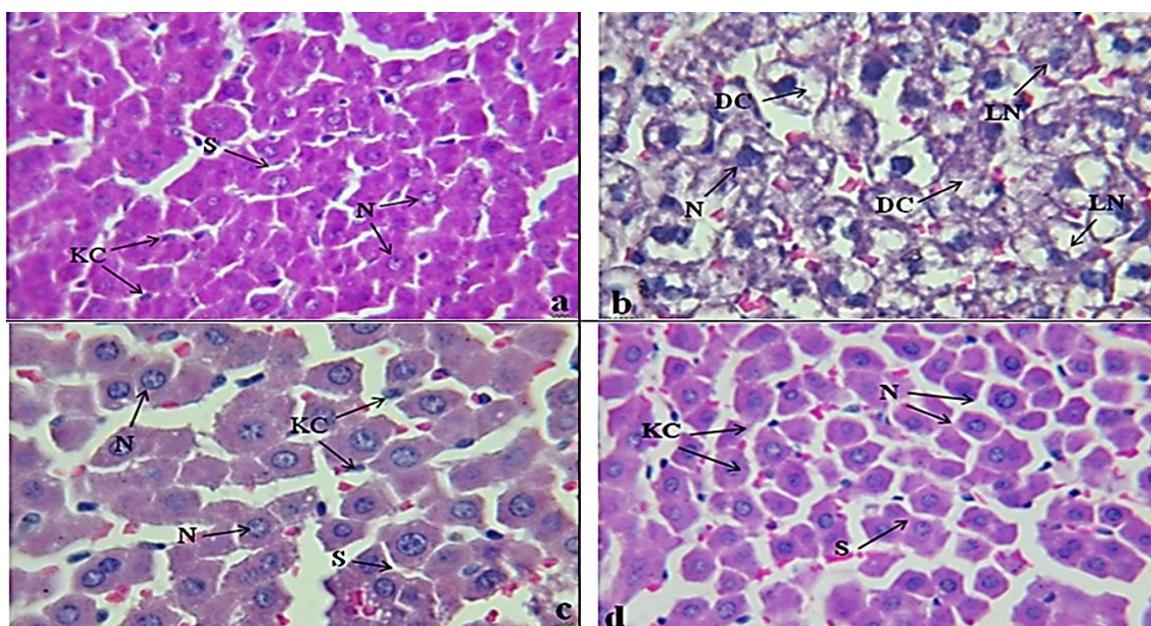
Figure 5. Optic microscopy sections of liver of Wistar rats stained using the haematoxylin-eosin method (400×). **(a)** Control. **(b)** Al. **(c)** Al+P. **(d)** P. DC, Degeneration in cytoplasm; KC, kupffer cells; LN, loss of nucleus; N, nuclei; S, sinusoidal spaces.

Table 2. Levels of creatinine and urea in serum.

Group	Creatinine (mg/L)	Urea (g/L)
Control	2.90±0.53	0.21±0.01
Al	6.30±0.26***	0.61±0.01***
Al +P	5.27±0.21*§§	0.51±0.02**§§§
P	3.17±0.06§§	0.26±0.03§§

*Comparison with the control group. §Comparison with Al group.

function. These parameters increased highly significantly ($p<0.001$) in rats treated with aluminum (Al) relative to control) (Table 2). The consumption of plant leads a remarkable improvement (Table 2). The comparison between groups (Al) and (Al+P) shows that creatinine decreased very significantly ($p<0.01$) and urea decreased highly significantly ($p<0.001$).

The difference between groups (control) and (P) is not
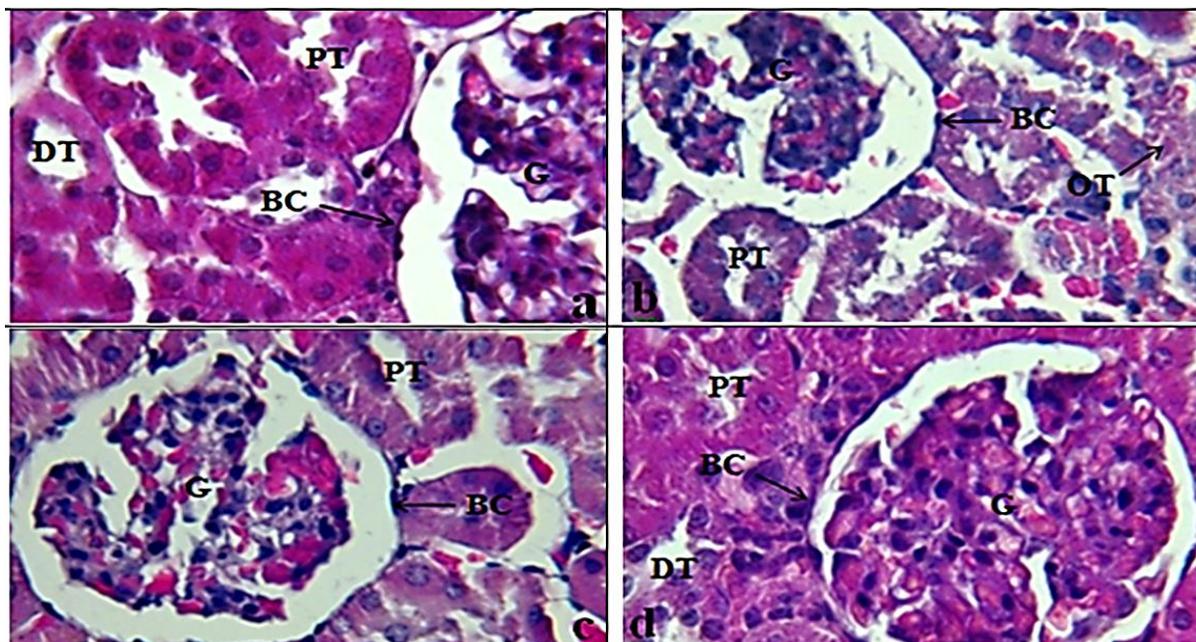
Figure 6. Optic microscopy sections of kidney (cortex) of Wistar rats stained using the haematoxylin-eosin method (400×). ×). **(a)** Control. **(b)** Al. **(c)** Al+P. **(d)** P. G, Glomerulus; DC, degeneration in cytoplasm; DT, distal tubules; PT, proximal tubules; OT, obstruction in renal tubules; LN, loss of nucleus; N, nuclei.

significant; however, the comparison between groups (Al) and (P) parameters decreased very significantly ($p<0.01$). The difference between groups (control) and (Al) is very significant ($p<0.01$) for TBARS (Figure 1) and significant ($p<0.05$) for GSH (Figure 2). The comparison between groups (Al) and (Al+P) is very significant ($p<0.01$) for TBARS (Figure 1) and significant ($p<0.05$) for GSH (Figure 2).

The comparison between groups (control) and (Al) is highly significant ($p<0.001$) for CAT (Figure 3) and significant ($p<0.05$) for SOD (Figure 4). The difference between groups (Al) and (Al+P) is very significant ($p<0.01$) for CAT and significant ($p<0.05$) for SOD. The consumption of plant only did not cause changes.

Figure 6a shows a normal histological structure of kidney cortex of control rats, Bowman capsules with an appropriate form, containing regular glomeruli and normal proximal and distal tubules with basal prominent nuclei (Figure 6a). Exposure to aluminium shows a kidney cortex with Bowman's capsule dilated, atrophic and destroyed glomerulus, tubular obstruction, and degeneration of tubular cells with pyknotic nuclei (Figure 6b). In group (Al+P), glomerulus adorned the greatest and not atrophied tubules are partially damaged. Despite these changes, the architecture of the renal cortex remained intact than that observed in the group treated with aluminum (Figure 6c). Kidney of the group treated with plant showed a normal histological structure (Figure 6d).

Kidney medulla of control rats shows that collecting tubules had a regular shape. The tubular cells are distinct and well defined (Figure 7a). Treatment with aluminium caused degeneration of tubular cells and loss of nuclei (Figure 7b). The group (Al+P) presents a degeneration of cytoplasm and tubular cells, however, the administration of the plant had induced a remarkable improvement in this tissue (Figure 7c). Kidney medulla of group treated with the plant shows a normal histological structure (Figure 7d).

DISCUSSION

The liver is a vital organ that is responsible for many of the processes that keep us alive. It drives a variety of metabolic substance and synthesizes a large number of enzyme (Bai et al., 2012). Hepatocytes are easily disintegrated by a variety of factors and harmful products (Bai et al., 2012). Exposure to high doses of aluminium may give an accumulation of this metal in the liver and cause alterations of the hepatic function (Nikolov et al., 2010). Degeneration, inflammation, and necrosis caused by hepatocyte damage can lead to an increase in the permeability of cell membranes. While AST and ALT are released into the blood through the cell membrane and their concentrations in the blood increases, ALT and AST are indicators of liver damage (Chinoy and Memon, 2001; El-Demerdash, 2004; Yeh et al., 2009; Shati and Alamri, 2010; Bai et al., 2012). In our study, the activities of AST and ALT in serum significantly increased in rats intoxicated with aluminium compared to controls. It was a
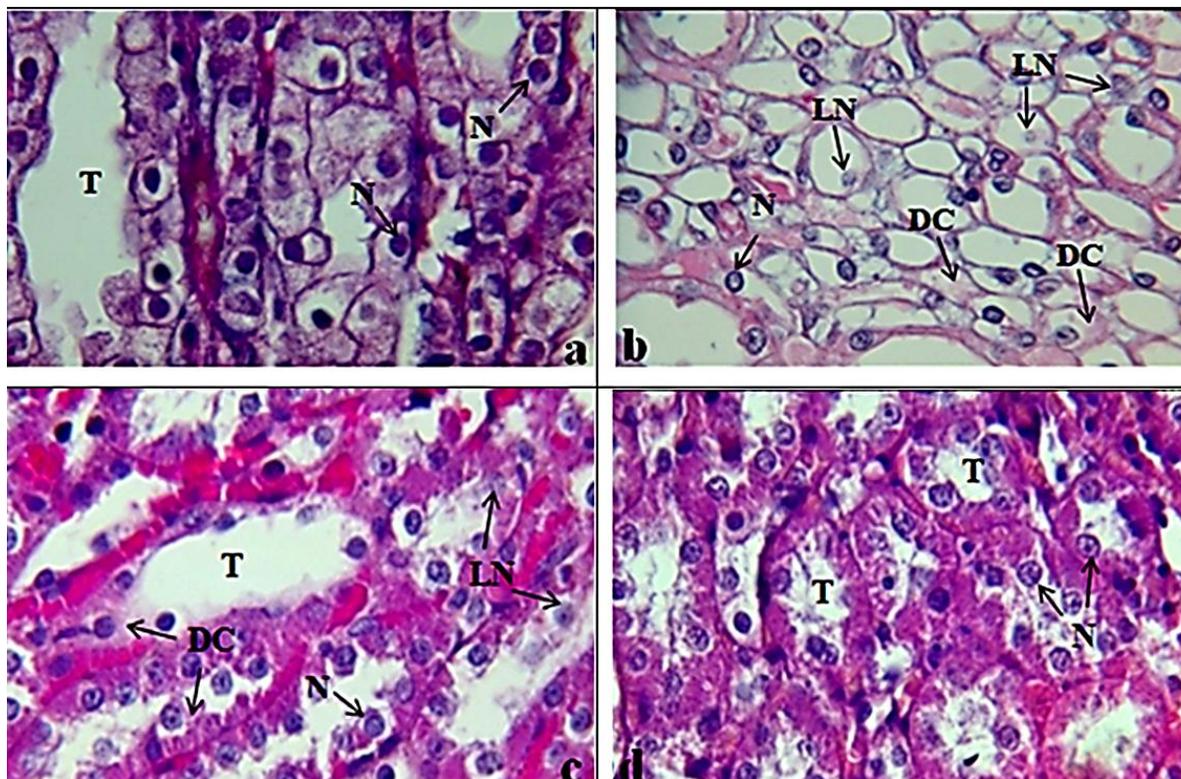
Figure 7. Optic microscopy sections of kidney (medulla) of Wistar rats stained using the haematoxylin-eosin method (400×). **(a)** Control. **(b)** Al. **(c)** Al+P; **(d)** P. DC, Degeneration in cytoplasm; T, tubules; LN, loss of nucleus; N, nuclei.

sign of deterioration of liver function, these results were compatible with results of Zhuo et al. (2007), Ma et al. (2008), Yeh et al. (2009), Bai et al. (2012), Bhadauria (2012), Denen et al. (2015), and Kalaiselvi et al. (2015).

In group (Al+P), enzyme activities of AST and ALT in serum significantly decreased; therefore, the liver damage induced by aluminium can be improved by the plant.

LDH is an enzyme that is used to evaluate tissue damage of the affected organ (Anane and Creppy, 2001; Bhatti et al., 2014). Serum LDH is a biomarker of liver tissue lesions (Suzuki et al., 1995) and kidney (Karadeniz Cerit et al., 2013). Cell necrosis leads to increase LDH in tissue and serum (Türkez et al., 2011). LDH release in the blood is an indicator of cell death and disintegration of the cell membrane (Lindell et al., 1996). LDH is a marker of aluminium toxicity (Anan and Creppy, 2001). In this study, serum LDH was very high in rats treated with aluminium; it increased significantly in rats intoxicated with aluminium as compared to controls. The results of this study are consistent with results of Chinoy and Memon (2001), El-Demerdash (2004), and Türkez et al. (2011).

Exposure to aluminium causes changes in renal function (El-Demerdash, 2004; Şener et al., 2007; Renugadevi and Prabu, 2010; Vijayaprakash et al., 2013). The assessment of harmful effects of aluminium is realized by measuring of biochemical parameters

(Kowalczyk et al., 2004). Creatinine and urea are significant indicators of renal function (Al-Attar and Al-Taisan, 2010; Yakubu and Musa, 2012). According to the results of this study, the comparison between rats intoxicated with aluminium and control indicate a significant increase in both parameters. Yeh et al. (2009) reported that the plasma creatinine level is elevated in rats that received diets containing aluminium as compared to controls. According to Soudani et al. (2010), the increases of creatinine and urea concentrations indicate that the glomeruli and tubules are damaged.

Histology of organs is realized in order to verify the proper functioning of these organs. Microscopic observations in the control group (Figures 3a, 4a, and 5a) are similar to that of group (P) (Figures 3d, 4d, and 5d), respectively. These groups showed a normal structure of the liver and kidney, against group (Al) having abnormalities in the liver and kidney (Figure 3b, 4b, and 5b). Treatment with *H. salicornicum* induced an improvement in histology of liver and kidney (Figure 3c, 4c, and 5c). Therefore, *H. salicornicum* was found to reshuffle the damage led by aluminium.

Bhadauria (2012) cited that aluminium exposure caused loss of cord arrangement of hepatocytes and sinusoidal spaces with degenerated plasma membranes and nuclei; for central vein filled with debris, severe necrosis was also seen. Buraimoh et al. (2012) mentioned that in their

study, there were distorted sinusoids and congested central vein of the liver of the aluminium treated rats. Tehrani et al. (2013) reported that exposed animals showed cell damage in the liver. Al-Qayim and Mashi (2014) reported that light microscopic examination of kidney tissues sections revealed the negative and deleterious effects of aluminium chloride. Rats that received aluminium chloride showed infiltration of inflammatory cells and congestion of blood vessels. In spite of the material deposed in the lumen of tubules, there was enlargement of epithelial cells lining urinary tubules leading to occlusion of some urinary tubules and stenosis in others. Joshi et al. (2015) reported that aluminium induced kidney damage was illustrated not only by a significant alteration in serum metabolites, but also an altered histological feature in the kidney tissue reminiscent of some known diseases.

Accumulation of aluminum in organism can cause lesion directly or indirectly (Bai et al., 2012). It has been reported that aluminium exposure can increase lipid peroxidation rates (Anand et al., 2012). Lipid peroxidation is a chemical mechanism capable of disrupting the structure and the function of the biological membranes that occurs as a result of free radical attack on lipids (Yeh et al., 2009).

In this study, the rate of TBARS in liver and kidney of rats intoxicated is significantly increased as compared to the control rats. It was found out that the consumption of *H. salicornicum* induces a decrease in TBARS. From these results, it was shown that *H. salicornicum* has a potential protective effect against oxidative stress induced by aluminium. El-Demerdash (2004) reported that administration of 34 mg $AlCl_3$/kg body weight induced free radicals and increased TBARS level in liver. Yeh et al. (2009) reported that the level of TBARS of the plasma and liver was increased with the increasing dose of aluminium. Mahieu et al. (2009) administered to male rats 0.57 mg aluminium per 100 g of body weight; they mentioned that their results indicated a significant increase of TBARS level of kidney in Al-treated rats when compared with the control animals. Joshi et al. (2013) administered 100 mg/kg of aluminium by gavage to young and adult rats; they reported a significant increase the lipid peroxidation in rats intoxicated versus control in liver and kidney.

The oxidant (reactive oxygen species [ROS] and nitrogen species [RNS]) and antioxidants are balanced in healthy individuals (Joshi et al., 2013). If the balance is disrupted due to over production of ROS, oxidative stress may occur, which influences oxidative damage to organs (Joshi et al., 2013). GSH is an important non-protein thiol present in the animal cells (Özkaya et al., 2010). It is a key component of the cellular defense cascade against injury caused by ROS (Hsu et al., 2000). The level of GSH in tissues serves as an indicator of oxidative stress (Hsu et al., 2000). Some antioxidant enzymes, such as SOD and CAT, play a principal role in antioxidation and elimination of ROS (Jihen et al., 2009). SOD catalyzes

the dismutation of O_2^- to H_2O_2 which is decomposed by CAT. However, H_2O_2 may react with O_2 to generate OH∘, which is the initiator of the lipoperoxidation. The hydroxyl radical is highly toxic, because there is no specific enzyme system able to degrade it (Vamecq et al., 2004). According to our results, the comparison between groups (control) and (Al) demonstrate that the levels of GSH, SOD, and CAT decreased after exposure to aluminium. However, *H. salicornicum* consumption causes an increase in GSH levels, SOD, and CAT when compared with intoxicated rats. Based on the results of this study, it was concluded that *H. salicornicum* reshuffles oxidative stress caused by aluminium in liver and kidney.

These results are in good accordance with those obtained by Özkaya et al. (2010), Bai et al. (2012), and Joshi et al. (2013). Newairy et al. (2009) revealed that the level of TBARS was increased and the activities of GST, SOD, and CAT were decreased in liver, kidney, and brain of rat treated with 34 mg/kg body weight $AlCl_3$ daily for 70 days. Yeh et al. (2009) mentioned that aluminium depleted GSH stores and reduced CAT activities.

Conclusion

Oxidative stress results from an imbalance between prooxidants and antioxidants. Biochemical indicators were measured and the redox status in liver and kidney was evaluated to check aluminium effect in both organs. From our results, exposure to aluminum release oxidative stress and a dysfunction in liver and kidney. Histological study confirmed the results. The administration of plant *H. salicornicum* induced improvement in all parameters studied. It was concluded that the plant reshuffle the harmful effects of aluminium.

Conflict of Interests

The authors have not declared any conflicts of interest.

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