The role of *Allium cepa* on aluminum-induced reproductive dysfunction in experimental male rat models

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ABSTRACT

AIM: Reproductive toxicity is a major challenge associated with aluminum (Al) exposure. Studies that associated Al with reproductive dysfunction did not account for the possible influence of *Allium cepa* extract. This study, therefore, investigates the influence of *A. cepa* on aluminum-induced reproductive dysfunction. **MATERIALS AND METHODS:** Six male rats per group were assigned to one of the following four treatment groups: The control animals were on control diet. *A. cepa*-treated rats received 1 ml of the extract/100 g body weight (BW), Al-treated rats received 100 mg $AlCl_3$/kg BW, and *A.cepa*+Al received 1 ml of the extract/100 g BW plus 100 mg $AlCl_3$/kg BW. Rats were orally administered their respective doses. *A. cepa* treatment was for 8 weeks, while Al treatment was for the last 3 days of the experimental period. **RESULTS:** Results obtained showed that Al significantly decreased ($P < 0.05$) plasma testosterone, follicular stimulating hormone (FSH), luteinizing hormone (LH), sperm count, motility, morphology and viability, superoxide dismutase (SOD) and catalase (CAT) activities, while lipid peroxidation index [malondialdehyde (MDA)] was significantly ($P < 0.05$) increased. Reproductive hormones (except testosterone), sperm qualities, and enzymatic antioxidants were significantly ($P < 0.05$) increased in *A. cepa*-treated rats and *A. cepa* plus Al-treated rats, while MDA was significantly ($P < 0.05$) improved. Weights of testes were comparable in all groups. **CONCLUSION:** It is thus suggested that Al exerts reproductive dysfunction by oxidative damage. *A. cepa* antagonizes the toxic effects of $AlCl_3$ and improves the antioxidant status and sperm quality of male rat. However, testosterone level did not increase with *A. cepa* treatment.

KEY WORDS: *Allium cepa*, aluminum toxicity, fertility, lipid peroxidation, reproductive hormones, sperm

INTRODUCTION

Aluminum (Al) has been reported to be an environmental factor that may contribute to some diseases, affect several enzymes and other biomolecules, and induce free radical-mediated cytotoxicity. Studies on laboratory animals have shown that Al induces reproductive toxicity and exerts a significant adverse effect on the steroidogenesis.[1-3] Al accumulation has been associated with necrosis of the sperm cells and infertility.[4,5] Alessio *et al.*[6] reported that high serum level of Al in mine workers caused a decrease in their thyroid stimulating hormone and prolactin. Renal failure patients on dialysis with high serum Al also showed low reproductive potentials.[7]

Mechanisms associated with Al-induced infertility have been reported. Studies have reported Al to block voltage-gated calcium channels,[8-10] thereby impairing gonadotrophin secretion in the hypophysis[11,12] with resultant low sperm counts.[13,14] Al has also been reported to cause testicular toxicity by increasing testicular nitric oxide.[5,15] Some studies have shown that Al reduces antioxidants[3] and increases lipid peroxidation,[16-18] though none has reported its effect on testicular lipid peroxidation.

Allium cepa has been reported to have medicinal potentials.[19-21] Studies have also documented the antioxidant value of *A. cepa*.[22-25] The antioxidant effect of *A. cepa* has been associated with reduced

lipid peroxidation index [malondialdehyde (MDA)] and increased superoxide dismutase (SOD).[25] The present study was therefore designed to investigate the effect of Al on reproductive hormones, sperm quality, and lipid peroxidation profile, and the possible role of *A. cepa* against Al-induced changes on reproduction profile.

MATERIALS AND METHODS

Animals

Male white rats of Wistar strain weighing between 150 and 200 g were used for the experiment. They were housed in standard rat cages under laboratory conditions with 12:12 h light/dark cycle at 25 ± 2°C. The animals were allowed to acclimatize for 2 weeks.[26] The experiment was conducted in accordance with the guidelines of the US National Institute of Health (NIH) on the care and use of laboratory animals.

Treatment

Six rats per group were assigned to one of the following four treatment groups:

Control: 0 ml *A. cepa*/100 g and 0 mg $AlCl_3$/kg body weight (BW)

AcE-treated rats: 1 ml *A. cepa*/100 g BW

Al-treated rats: 100 mg $AlCl_3$/kg BW

AcE + Al-treated rats: 1 ml *A. cepa*/100 g BW plus 100 mg $AlCl_3$/kg BW

The doses were similar to those used in previous studies.[24,25,27] Rats were orally administered their respective doses once daily. *A. cepa* treatment was for 8 weeks, while Al treatment was for the last 3 days of the experimental period. All rats, both control and test groups, were fed on standard rat chow and water *ad libitum*. Blood samples were collected 24 h after the treatment period.

Preparation of aluminum chloride ($AlCl_3$)

Four grams of aluminum chloride was dissolved in 100 ml distilled water to prepare a stock solution (40 mg/ml). The solution was prepared weekly and kept in a plane bottle at 4ºC.

$AlCl_3$ was daily administrated to rats orally at a sub-lethal dose level of 100 mg/kg BW.

Extraction of *A. cepa*

AcE was prepared following the procedures from previous studies.[21,25] Fresh *A. cepa* (common onion) bulbs were rinsed thoroughly in distilled water, air-dried, and 200 g was then blended. Juice was then filtered and squeezed out of it using a tight sieve. The juice was prepared on weekly basis following the same procedure and kept at 4ºC to prevent it from losing its potency.[24,25]

Collection of blood samples and animal sacrifice

Each rat was sacrificed by cervical dislocation and blood samples were obtained by cardiac puncture. Serum was obtained by centrifugation at 300 rpm for 10 mins. Testes were excised, rinsed in potassium chloride (KCl), homogenized, and preserved in buffer solution for biochemical investigation.

Testes weight and reproductive hormones

Testes were excised and weighed. Testosterone, follicular stimulating hormone (FSH), and luteinizing hormone (LH) were analyzed using standard enzyme immunosorbent assay (EIA) test kit.

Sperm characteristics analysis

Epididymis sperm was obtained by mincing the epididymis in normal saline and filtering through a nylon mesh (80-μm pore size). The sperms were counted using a hemocytometer. The numbers of sperm in five squares (four corners and the center) in the center grid of both sides were counted based on the dilution factor and averaged following previous methods.[28,29]

The caudal epididymis was dissected and minced in pre-warmed normal saline (37°C). One drop of sperm suspension was placed on a glass slide to analyze 200 motile sperms in four different fields. The motility of the epididymal sperms was evaluated microscopically within 2–4 mins of their isolation from the epididymis and data were expressed as percent motility.[29,30]

Sperm morphology was done by staining the sperm smears on the microscope slides with two drops of Walls and Ewas stain and air-dried. The slides were examined under the microscope using ×100 objectives under oil immersion. The normal sperm cells were counted and the percentage was calculated.[29]

A viability study (percentage of live spermatozoa) was done using eosin/nigrosin stain. Semen was squeezed onto a microscope slide and two drops of the stain were added. The motile (live) sperm cells were unstained, while the non-motile (dead) sperm absorbed the stain. The stained and the unstained sperm cells were counted using ×40 objectives of the microscope and an average for each was taken from which percentage viability was calculated.[29]

Lipid peroxidation profile

Estimation of lipid peroxidation based on the reaction of MDA with thiobarbituric acid (TBA) forming MDA–TBA_2 that absorbs strongly at 532 nm was followed according to the method of Varshney and Kale.[31] The level of SOD activity in the supernatant was determined by the method of Fridovich and Misra.[32] Catalase activity was determined

by following the consumption of exogenous H_2O_2, measured according to the previous study, at 560 nm.[33]

Histological study

Testicular tissues were fixed in Bouin's fluid for 6 h and transferred into 10% formalin. They were dehydrated with varying percentage of ethanol. Sections were cleared in xylene and embedded in molten wax. Thin sections were cut (5 μm), stained with hematoxylin and eosin, and microscopically analyzed.

Statistical analysis

All results are expressed as mean ± SEM. The differences between the mean values were evaluated by analysis of variance (ANOVA) followed by unpaired Student's *t*-test (two-tailed *P* value). Values of $P < 0.05$ were considered statistically significant.[34]

RESULTS

Effect of *A. cepa* and aluminum on reproductive hormones

Table 1 shows that the weights of testes were similar in all groups ($P > 0.05$). Testosterone was significantly ($P < 0.05$) reduced in all treated rats. FSH and LH were significantly ($P < 0.05$) increased in *A. cepa*-treated group, but significantly ($P < 0.05$) reduced in Al-treated rats when compared with all groups. FSH and LH in AcE + Al rats were significantly ($P < 0.05$) higher than in the Al-treated rats, but significantly ($P < 0.05$) lower than in the control and *A. cepa*-treated rats.

Effect of *A. cepa* and aluminum on sperm characteristics

In comparison with all groups, sperm quality was significantly ($P < 0.05$) improved in *A. cepa*-treated rats. Al treatment caused significant ($P < 0.05$) impairment of sperm quality when compared with all groups. Sperm quality was significantly ($P < 0.05$) enhanced in *A. cepa* + Al rats when compared with Al-treated rats [Table 2].

Effect of *A. cepa* and aluminum on lipid peroxidation status

A. cepa treatment led to significant ($P < 0.05$) enhancement of lipid peroxidation status when compared with all groups. In comparison with other groups, rats treated with Al showed significantly ($P < 0.05$) increased lipid peroxidation and reduced antioxidant levels. *A. cepa* + Al treatment showed significant ($P < 0.05$) improvement of lipid peroxidation status when compared with Al-treated rats [Table 3].

Effect of *A. cepa* and luminum on testicular cytoarchitecture

Al treatment led to degenerative necrosis with degeneration of spermatogenic cells. This effect was milder in *A. cepa* + Al treatment. *A. cepa* treatment showed testicular cytoarchitecture similar to that of control [Figure 1].

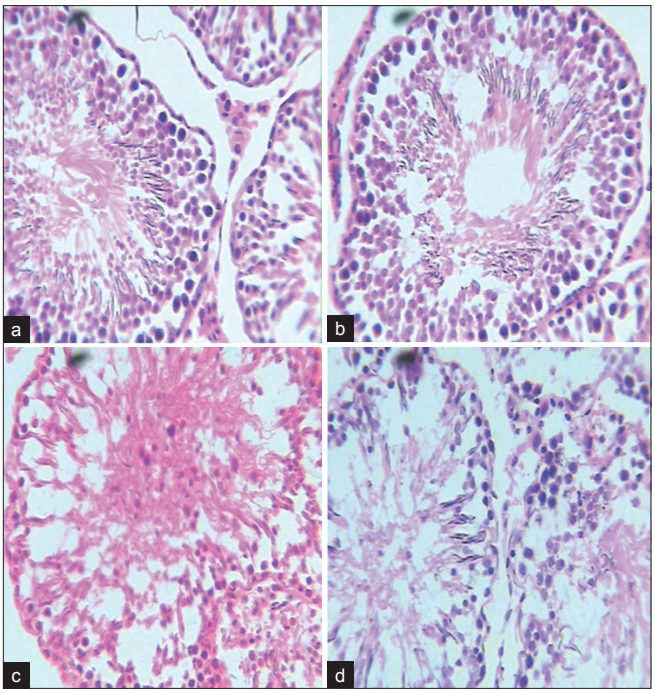

Figure 1: Histograph of the testes showing the seminiferous tubules. Al treatment led to degenerative necrosis with degeneration of spermatogenic cells. This effect was milder in AcE+Al treatment. AcE treatment showed similar testicular cytoarchitecture to the control

DISCUSSION

The result of this study shows that Al did not affect the weight of the testes. This is inconsistent with previous studies[1,35] that reported reduced body weight gain and testes weight on Al treatment. Dissimilarity observed in this study might be due to the duration of Al treatment. This implies that short-term Al treatment is unlikely to affect the weight of testes, while its long-term treatment would cause reduced testicular weight. Similarly, *A. cepa* treatment in both *A. cepa* rats and *A. cepa* + Al rats showed comparable weight of the testes with the control and Al-treated rats. This is in consonance with a previous study.[25] This confirms the low caloric and protein content of *A. cepa*.[36,37]

The study results show that testosterone, FSH, and LH were significantly reduced in Al-treated rats. This is in agreement with previous studies.[3,15,38] This might be associated with calcium channel blocking effect of Al,[8,9] which led to impaired secretion of gonadotrophins in the hypophysis,[11,12] and thus low testosterone level. It might also be due to high testicular nitric oxide levels and low cAMP associated with Al, which suppressed steroidogenesis.[15] On the other hand, *A. cepa* treatment improved LH and FSH levels, probably by inhibiting these mechanisms. However, *A. cepa* reduced testosterone level also.

Al treatment led to impaired sperm quality. This is in

Table 1: Effect of *Allium cepa* (AcE) on testes weight and reproductive hormones in aluminum (Al)-treated rats

Variables	Control	AcE-treated rats	Al-treated rats	AcE + Al-treated rats
Testes weight (g)	3.73 ± 0.0121[a]	3.71 ± 0.0122[a]	3.71 ± 0.0123[a]	3.72 ± 0.0122[a]
Testosterone (ng/ml)	10.24 ± 0.2395[a]	7.632 ± 0.0223[b]	5.50 ± 0.0316[c]	4.50 ± 0.9417[c]
FSH (ng/ml)	11.10 ± 0.2915[a]	12.71 ± 0.2354[b]	3.08 ± 0.1319[c]	9.34 ± 0.3326[d]
LH (ng/ml)	12.70 ± 0.255[a]	13.78 ± 0.2905[b]	3.84 ± 0.2657[c]	9.98 ± 0.3412[d]

Values are expressed as means ± SEM. Means in rows showing common superscript letters (a, b, c, d) are not significantly different; $P < 0.05$

Table 2: Effect of *Allium cepa* (AcE) on sperm quality in aluminum (Al)-treated rats

Variables	Control	AcE-treated rats	Al-treated rats	AcE + Al-treated rats
Sperm count (10^6/ml)	53.8 ± 0.8602[a]	60.6 ± 1.40000[b]	27.4 ± 0.3970[c]	31.9 ± 0.4317[d]
Sperm motility (%)	72.4 ± 3.0750[a]	91.8 ± 1.8550[b]	36.2 ± 0.5831[c]	45.8 ± 1.1580[d]
Sperm morphology (%)	67.8 ± 1.9850[a]	81.0 ± 2.0980[b]	27.4 ± 1.9650[c]	52.6 ± 2.8390[d]
Sperm viability (%)	78.2 ± 4.5210[a]	90.2 ± 1.8000[b]	30.6 ± 2.1590[c]	52.8 ± 1.8810[d]

Values are expressed as means ± SEM. Means in rows showing common superscript letters (a, b, c, d) are not significantly different; $P < 0.05$

Table 3: Effect of *Allium cepa* (AcE) on lipid peroxidation profile in aluminum (Al)-treated rats

Variables	Control	AcE-treated rats	Al-treated rats	AcE + Al-treated rats
MDA (µg/l)	1.19 ± 0.1026[a]	0.53 ± 0.0103[b]	1.48 ± 0.0001[c]	0.63 ± 0.0643[d]
SOD (U)	1.38 ± 0.0956[a]	1.71 ± 0.0416[b]	0.90 ± 0.1789[c]	1.66 ± 0.0321[d]
CAT (mmol/min)	0.0009 ± 0.000089[a]	0.0015 ± 0.000066[b]	0.0004 ± 0.000092[c]	0.0010 ± 0.000070[d]

Values are expressed as means ± SEM. Means in rows showing common superscript letters (a, b, c, d) are not significantly different; $P < 0.05$

agreement with previous studies[1,39,40] that documented reduced sperm count, motility, and viability on Al treatment. The reduced sperm count observed in Al-treated rats could be associated with reduced gonadotrophins and testosterone seen in rats, since these hormones are essential for spermatogenesis. LH stimulates the interstitial cells of the Leydig to secrete testosterone, which in association with FSH is necessary for stimulation of spermatogenesis.[41] Reduction of these hormones in Al-treated rats led to low sperm count. The reduced motility and viability with increased morphological abnormality seen in Al-treated rats could be associated with Al-induced increase in nitric oxide, which has been reported to cause reduced rate and motility, as well as increased morphological abnormalities of sperm cells.[42]

In a healthy body, reactive oxygen species (ROS) and antioxidants remain in balance. When the balance is disrupted toward an overabundance of ROS, oxidative stress occurs, which influences reproductive lifespan. Oxidative stress results from an imbalance between prooxidants (free radical species) and the body's scavenging ability (antioxidants).[43] ROS not only serve as key signal molecules in physiological processes, but also have a role in pathological processes involving reproductive fecundity. Results from this study show that Al increased the lipid peroxidation index (MDA) and reduced testicular antioxidants. This is in tandem with previous studies.[3,17,18] This observation could be responsible for the reduced reproductive hormones and poor sperm quality seen in Al-treated rats, since ROS have been proposed to have a role in steroidogenesis and gametogenesis.[43] However, *A. cepa*, which has been reported to have antioxidant potential,[25] led to improved oxidative status in experimental animals. *A. cepa*-induced impairment of lipid peroxidation and enhancement of antioxidant levels could be associated with the raised FSH and LH levels as well as the improved sperm quality seen with *A. cepa* treatment when compared to Al-treated rats.

Histopathologic study reveals altered testicular architecture with area of degenerative necrosis of germ cells lining the seminiferous tubules in Al-treated rats when compared with other groups. This agrees with previous study.[44] This observation could be linked to Al-induced oxidative damage and the ability of Al to cross the blood–testis barrier after inducing oxidative stress and lipid peroxidation that damages the biological membrane of the testes. This could also be attributed to the low sperm count, motility, viability, and morphological abnormality seen in Al-treated rats. Penetration of Al through the blood–testis barrier could cause degeneration and alteration of spermatogenic cells. Observation in this study shows that *A. cepa* treatment considerably increased the formation of antioxidant products and reduced lipid peroxidation, thus maintaining the cytoarchitecture of the testes.

Phytochemical screening of *A. cepa* showed that it contains abundant flavonoids, and weak saponins, tannins, glycosides, sterols, and triterpenoids.[45] The effects of *A. cepa* observed in this study could be attributed to the activities of the flavonoid constituent. Flavonoids are known antioxidants and enhance the oxidation status as seen in this study. However, they have been implicated as antifertility agents.[46,47] Studies have reported that

flavonoids cause antispermatogenic effects with reduced sperm qualities.[48-50] However, observations from this study showed that though *A. cepa* flavonoids reduced testosterone level, they improved the sperm quality by preventing lipid peroxidation. Furthermore, the increased LH and FSH seen with reduced testosterone could suggest that *A. cepa* inhibited testosterone synthesis at the testicular level probably by inhibiting cholesterol conversion.

CONCLUSION

The results of this study show that Al has harmful effects on male reproductive profile in experimental rat model enough to cause infertility via oxidative damage. *A. cepa* antagonizes Al-induced damage by alleviating oxidative stress, thus enhancing sperm quality. However, caution should be taken because *A. cepa* resulted in reduced testosterone.

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