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Research Article

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Experimental evaluation of protective action of resveratrol against aluminum- induced toxicity in male rats.

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Abstract

Polyphenolic compounds are known to have vast pharmacological activities. Resveratrol (RSV), a polyphenol was evaluated to attenuate oxidative stress induced by aluminum (Al, a well-known, ubiquitous and toxic element for human and animals) in rats. The oral administration of Al in form of aluminum chloride ($AlCl_3$) for 6 weeks at the dose of 100 mg/kg body weight (b.w) resulted in significant increase of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), creatinine, urea, triglycerides, total cholesterol and glucose and plasma lipid peroxidation product (malondialdehyde, MDA) whereas serum albumin and total protein (TP), plasma reduced glutathione (GSH) and superoxide dismutase (SOD) were significantly decreased. On the other hand, histopathologicl examination of liver, kidney, testis and brain showed sever alterations as a result of Al toxicity. Oral treatment of rats with RSV for 6 weeks at the dose of 20 mg/kg b.w didn't induce any negative effects on both tested parameters and organs. Meanwhile, simultaneous administration of Al and RSV resulted in significant attenuation of deleterious effects of Al on biochemical parameters, tested organs through reduction of oxidative stress induced by Al. We concluded that RSV was a peerless polyphenol which possesses substantial remedial properties.

Keywords: Aluminum chloride, oxidative stress, rats, resveratrol, toxicity.

Introduction

Aluminum (Al) is one of the most pervasive metals and represents 8% of mineral content of earth's crust (Verstraeten and Aimo, 2008). Furthermore, Al widely used in many industries and products including medicine, cosmetics, cans, cooking utensils, signs, construction materials, aircraft industry, water purification and metal alloys production process (ATSDR, 1990). Many sources contribute to human and animal exposure to Al through environmental pollution or food and water intake (Yokel and McNamara, 2001). Most of food and feed crops and products scarcely contain Al which cultivated on contaminated soil and water or packaged in aluminum (Ochmanski and Barabasz, 2000). Al exposure was linked to many neurological disorders, as factor in Alzheimer's disease (Ferreyra-Moyano and Barragan, 1994) and dialysis encephalopathy in renal failure patients due to hem dialysis for long term (Alfrey *et al*., 1976). Experimental studies on Al toxicity on various animal models proposed that Al accumulates in target organs and induce damage of liver, kidney (Shrivastava, 2013), testes (Pandey and Jain, 2017), heart (Ghorbel *et al*., 2017), brain (Al-Otaibi *et al*., 2018), bone, lung and blood cells (ATSDR, 1990). Al induces biochemical, physiological and morphological abnormalities through generation of reactive oxygen species (ROS) and depleting of antioxidant defense (Ghorbel *et al*., 2016).

Recently polyphenol from natural sources became subject of interest as a possible safe remedy of several injurious oxidative conditions.

Resveratrol (RSV, 3,4,5-trihydroxystilbene) a small natural polyphenolic compound found in nutritious plants such as grapes in seeds and skin, berries and nuts (Diaz-Gerevini *et al*., 2016). Kim *et al*. (2017) and Wahab *et al*. (2017) present a review of recent studies on health benefits of RSV. RSV has countless myriads of pharmaceutical actions like neuroprotective, hepatoprotective, nephroprotective, antiaging and against several chronic conditions such as metabolic disorders, cardiovascular disease, cancer and diabetes due to its antioxidative and anti-inflammatory properties (Manna *et al*., 2000).

We aimed to assess the possible antioxidant power of RSV against Al toxicity via evaluation of biochemical, histopathological changes associated with oxidative stress in male albino rats.

Materials and Methods

Chemicals: Aluminum chloride was purchased from Sigma-Aldrich chemical Co. (St. Louis, USA). *Trans*-Resveratrol (≥98%) was purchased from Carl Roth GmbH + Co. KG. Dimethyl sulfoxide (DMSO) was purchased from Merck (Darmstadt, Germany). Analytical kits of GSH, SOD and MDA were purchased from Biodiagnostic, France.

Animals and treatment: Forty male albino rats weighing about 160±10g supplied and housed by Food Technology Research Institute (FTRI), Agricultural Research Center, Giza, Egypt, in cages under controlled light and temperature conditions (12-h light/dark cycle, 22±2^{O}C). Rats have free access to water and basal diet throughout adaptation period (2 week) and experimental period (6 weeks). Basal diet was formulated according to guidelines of National Research Council (1995). Meanwhile experimental protocol conforms to the recommendations of the European Union regarding animal experimentation (Directive of the European Counsel 86/609/EC). Rats were randomly divided into four groups (*n* =10) and treated for 6 weeks as follow:

G I (control, vehicle treated): received 3 ml DMSO: water (1:3) and 3 ml distilled water/kg b.w daily by gavage.

G II (RSV): received RSV daily by gavage at dose level 20 mg/kg b.w (Zhang *et al*., 2017) dissolved in 3 ml DMSO: water (1:3) and 3 ml distilled water/kg b.w.

G III (Al): received $AlCl_3$ daily by gavage at dose level 100 mg/kg b.w (Kalaiselvi *et al*., 2015) dissolved in 3 ml water and vehicle (3 ml DMSO: water (1:3)/ kg b.w).

G IV (RSV+ Al): received RSV and $AlCl_3$ at the same previous dose level.

Blood sampling: Blood samples were collected from rat's eye (from retro-orbital venous plexus) under carbon dioxide anesthesia at the end of 6th weeks of the treatment period on hepranized tube to obtain plasma and non hepranized to obtain serum. Serum and plasma stored at -20ºC.

Biochemical analysis: Biochemical Blood Analyzer (Alfa Wassermann Dignostic Technologyies, LLC, ACE, Alera, USA) employed in purpose of estimation of ALT, AST, ALP, TP, albumin, creatinine, urea, uric acid, total cholesterol, triglycerides and glucose in serum.

Estimation of MDA, GSH and SOD: Lipid peroxidation (thiobarbituric acid reactive substances (TBARS)) react with malondialdehyde (MDA) and estimated spectrophotometrically in plasma at 534 nm based on methods of Onkawa *et al.* (1979). Plasma GSH and SOD were estimated spectrophotometrically at 405 nm and 560 nm according to methods of Beutler *et al*. (1963) and Nishikimi *et al*. (1972), respectively.

Tissue specimen and processing: Rats were sacrificed by cervical decapitation at the end of 6th week of experiment and dissected. Livers, kidneys, brains and testes were removed then fixed in 10% buffered formalin. Tissues were processed and stained with haematoxylin and eosin (H&E) according to Banchroft *et al*. (1996) then subjected for pathological examination by the light microscope.

Statistical analysis: Results of biochemical analysis introduced in form of mean±SE. Data statistically analyzed utilizing computer Duncan institute program and the least significant difference test (LSD) at the 5% level of probability as outlined by Snedecor and Cochran (1980).

Results

Obtained data of biochemical analysis (table 1-4) revealed that, the RSV administration (G II) didn't have any negative impact on any examined parameters (corresponding to control (GI) (*P<0.05*)) as well as histology of tested organs.

Liver function parameters: Analysis of variance illustrated in Table (1) indicated that there was a significant increase in ALT, AST and ALP activities, and a significant decrease in TP and albumin concentrations in rats treated with Al for 6 weeks (corresponding to control (*P<0.05*)). However, simultaneous administration of RSV and Al resulted in significance amelioration of adverse effect of Al on liver function parameters, moreover the activity of ALP and concentrations of TP and albumin in serum of rats was restored to normal (compared with control (*P<0.05*)).

Table (1): Liver function parameters in serum of control and treated rats (means ± SE).

Parameters / Groups	ALT (U/L)	AST (U/L)	ALP (U/L)	TP (g/dL)	Albumin (g/dL)
G I (Control)	43.80±1.77^{c}	83.80±3.48^{c}	167.00±2.68^{bc}	6.84±0.17^{ab}	4.30±0.04^{a}
G II (RSV)	44.40±1.86^{c}	80.60±3.57^{c}	162.40±2.38^{c}	6.96±0.19^{a}	4.34±0.05^{a}
G III (Al)	80.20±2.06^{a}	156.60±3.17^{a}	210.40±3.23^{a}	4.88±0.17^{c}	3.62±0.05^{b}
G IV (RSV+ Al)	53.40±1.91^{b}	94.80±2.78^{b}	175.20±3.01^{b}	6.32±0.19^{b}	4.26±0.05^{a}
$LSD_{0.05}$	5.71	9.79	8.53	0.54	0.15

Within the same column, various superscript letters indicate significant differences (Duncan, *P <0.05*).

Kidney function parameters: Results presented in Table (2) demonstrated that Al administration for 6 weeks resulted in significant elevation *(P<0.05*) of serum creatinine and urea. However, supplementation of Al-intoxicated rats with RSV (G IV) ameliorated the adverse effect of Al on creatinine and restore urea concentration to normalcy level (comparing with control (*P<0.05*)).

Table (2): Kidney function parameters in serum of control and treated rats (means ± SE).

Parameters / Groups	Creatinine (mg/dL)	Urea (mg/dL)
G I (Control)	0.55±0.03^{c}	47.40±1.72^{b}
G II (RSV)	0.52±0.03^{c}	46.60±1.91^{b}
G III (Al)	0.97±0.04^{a}	71.60±2.52^{a}
G IV (RSV+ Al)	0.79±0.03^{b}	50.40±1.72^{b}
$LSD_{0.05}$	0.09	5.98

Within the same column, various superscript letters indicate significant differences (Duncan, *P <0.05*).

Lipid profile parameters: The data in Table (3) showed that Al induced significant increase in serum total cholesterol and triglycerides concentrations comparing with control (*P<0.05*). Simultaneous administrations of RSV and Al in G IV rats resulted in significant reduction of triglycerides concentrations and normalized cholesterol level at 6th week of treatment comparing with control (*P<0.05*).

Table (3): Total cholesterol, triglycerides and glucose concentrations in serum of control and treated rats (means ± SE).

Parameters / Groups	Cholesterol (mg/dL)	Triglycerides (mg/dL)	Glucose (mg/dL)
G I (Control)	82.00±2.85^{bc}	61.60±1.47^{c}	111.68±3.37^{c}
G II (RSV)	76.00±2.53^{c}	58.40±1.89^{c}	106.95±3.16^{c}
G III (Al)	116.00±2.39^{a}	106.00±1.92^{a}	150.45±3.40^{a}
G IV (RSV+ Al)	85.80±2.31^{b}	68.80±1.69^{b}	123.09±2.34^{b}
$LSD_{0.05}$	7.58	5.25	9.29

Within the same column, various superscript letters indicate significant differences (Duncan, *P <0.05*).

Glucose concentration: Glucose concentration was significantly elevated (corresponding to control group (*P<0.05*)) in serum of Al-treated rats (Table 3). Meanwhile, co-administration of RSV and Al resulted in attenuation of that increase (in respect to corresponding control (*P<0.05*)).

Antioxidant profile: Data in Table (4) illustrated that Al treatment significantly reduce *(P<0.05)* plasma GSH and SOD levels and significantly elevate *(P<0.05)* plasma MDA level (lipid peroxidation product). RSV administration produced significant elevation of GSH and SOD and reduction of MDA levels in plasma of Al-intoxicated rats comparing with corresponding control *(P<0.05)*.

Table (4): GSH, SOD and MDA levels in plasma of control and treated rats (means ± SE).

Parameters / Groups	GSH (mg/dL)	SOD (U/ml)	MDA nmol/ml
G I (Control)	0.69±0.01^{a}	518.30±11.60^{a}	5.06±0.24^{c}
G II (RSV)	0.70±0.01^{a}	520.09±15.84^{a}	4.82±0.19^{c}
G III (Al)	0.49±0.01^{c}	330.86±13.59^{c}	9.02±0.18^{a}
G IV (RSV+ Al)	0.62±0.01^{b}	467.07±18.05^{b}	6.07±0.17^{b}
$LSD_{0.05}$	0.04	44.88	0.59

Within the same column, various superscript letters indicate significant differences (Duncan, *P <0.05*).

Histopathological Results:

Liver: Liver of rats from G I (control) revealed the normal histological structure of hepatic lobule. Moreover, liver of rats from G II which treated with RSV (20 mg/Kg b.w) daily showed no histopathological changes (Figure 1). Meanwhile, liver of rats from G III that treated with $AlCl_3$ (100 mg/Kg b.w) daily showed hydropic degeneration of hepatocytes (Figure 2), congestion of central vein (Figure 3), focal hepatic necrosis associated with inflammatory cells infiltration (Figure 4) and fibroplasia in the portal triad (Figure 5). Examined sections from G IV that co treated with RSV and Al revealed no changes except hydropic degeneration of hepatocytes (Figure 6).

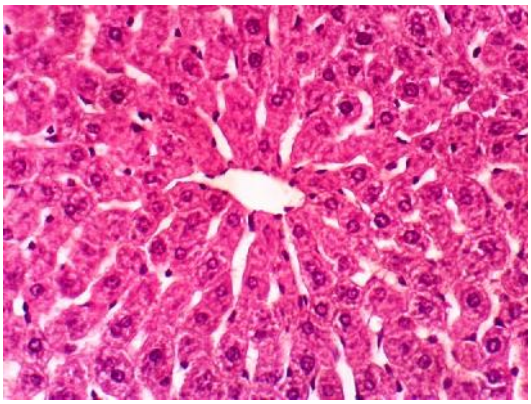

Figure 1: Liver of rat from G II showing the normal histological structure of hepatic lobule (H & E X 400).

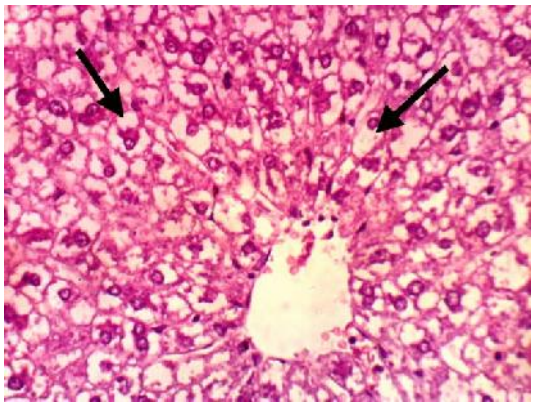

Figure 2: Liver of rat from G III showing hydropic degeneration of hepatocytes (H & E X 400).

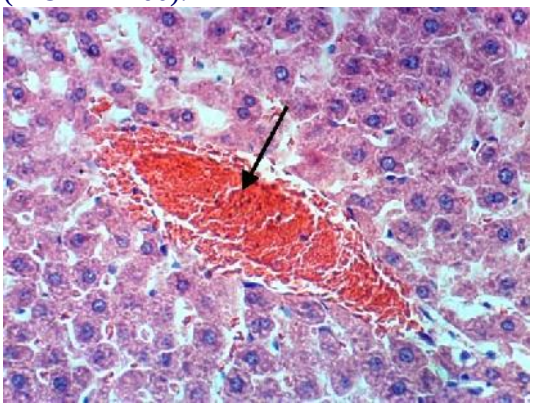

Figure 3: Liver of rat from G III showing congestion of central vein (H & E X 400).

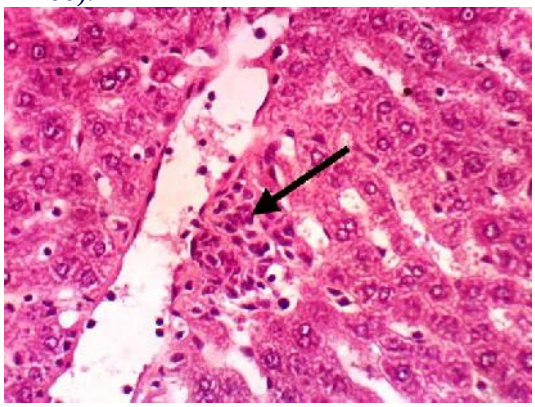

Figure 4: Liver of rat from G III showing focal hepatic necrosis associated with inflammatory cells infiltration (H & E X 400).

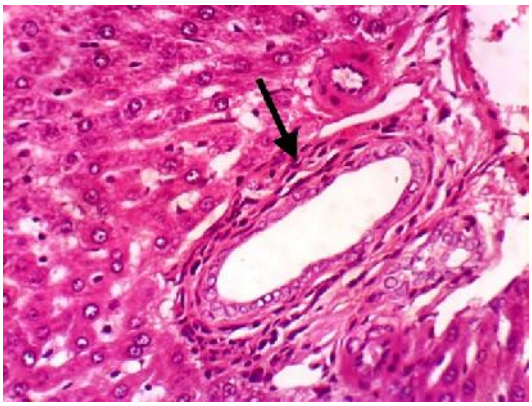

Figure 5: Liver of rat from G III showing fibroplasia in the portal triad (H & E X 400).

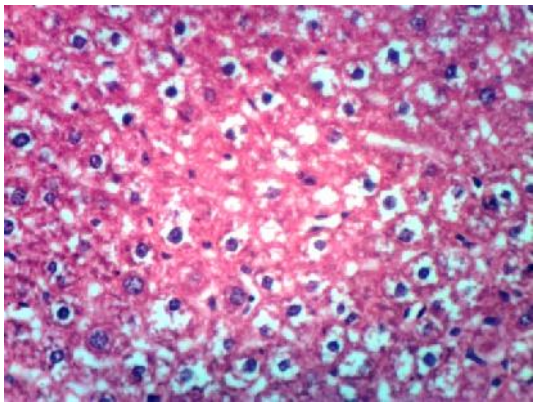

Figure 6: Liver of rat from G IV showing hydropic degeneration of hepatocytes (H & E X 400).

Kidneys: Microscopically, kidneys of rats from G I revealed the normal histological structure of renal parenchyma. Moreover, kidneys of rats from G II (RSV treated) revealed no histopathological changes (Figure 7). On the other hand, kidneys from G III (Al treated) revealed cytoplasmic vacuolation of epithelial lining renal tubules (Figures 8&9) and endothelial lining glomerular tuft (Figure 9), atrophy of glomerular tuft with distension of Bowman's space (Figure 10), necrosis of epithelial lining renal tubules with pyknosis of the nuclei (Figure 11). However, kidneys from G IV (RSV and Al treated) showed no histopathological changes (Figure 12) except slight cytoplasmic vacuolation of epithelial lining renal tubules and endothelial lining glomerular tuft (Figure 13).

Testes: Histological examination of testes of rats from control group (GI) showed the normal architecture of seminiferous tubule with normal spermatogoneal cells and complete spermatogenesis. Moreover, testes of RSV group (G II) showed no histopathological changes (Figure 14). In contrary, testes of Al group (G III) revealed degeneration of spermatogoneal cells lining seminiferous tubules with incomplete spermatogenesis (Figure 15). However, testes from G IV which co-administrated with RSV and Al showed no histopathological changes (Figure 16).

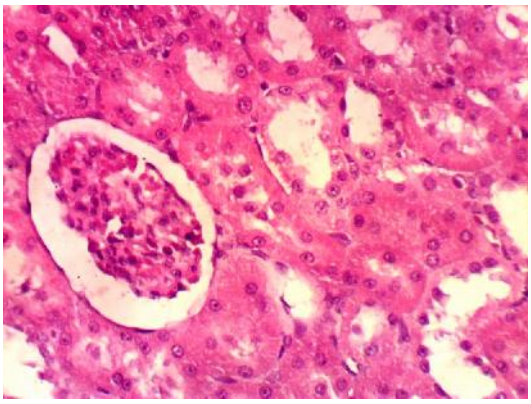

Figure 7: Kidney of rat from G II showing no histopathological changes (H & E X 400).

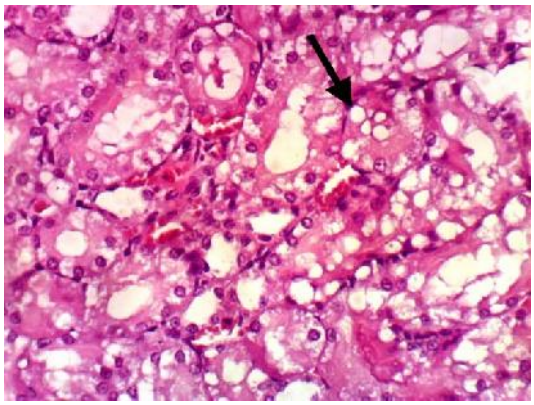

Figure 8: Kidney of rat from G III showing cytoplasmic vacuolation of epithelial lining renal tubules (H & E X 400).

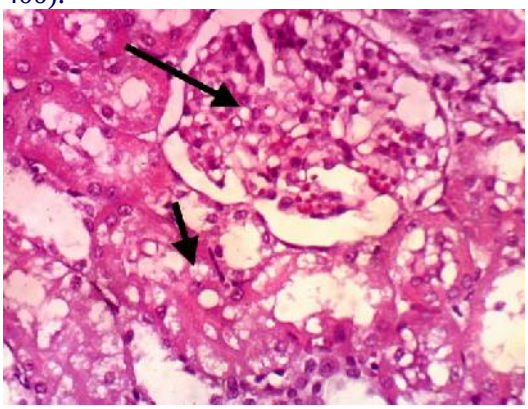

Figure 9: Kidney of rat from G III showing cytoplasmic vacuolation of epithelial lining renal tubules and endothelial lining glomerular tuft (H & E X 400).

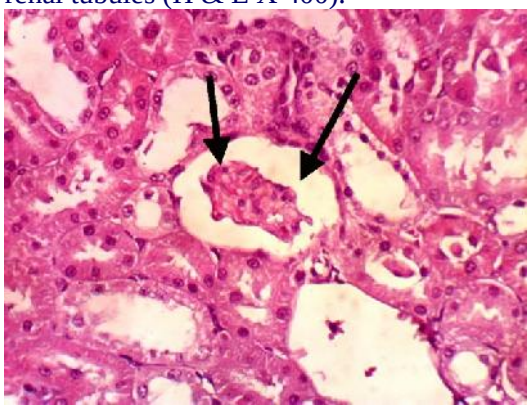

Figure 10: Kidney of rat from G III showing atrophy of glomerular tuft and distension of Bowman's space (H & E X 400).

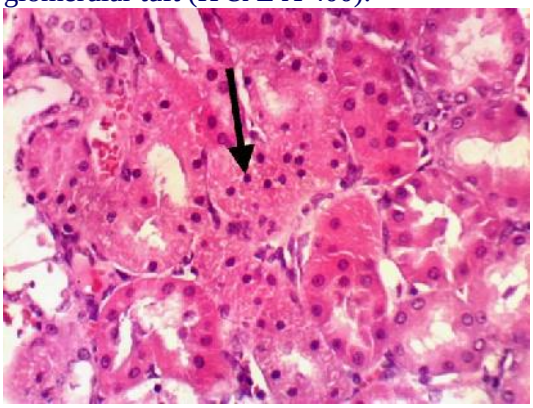

Figure 11: Kidney of rat from G III showing necrosis of epithelial lining renal tubules with pyknosis of the nuclei (H & E X 400).

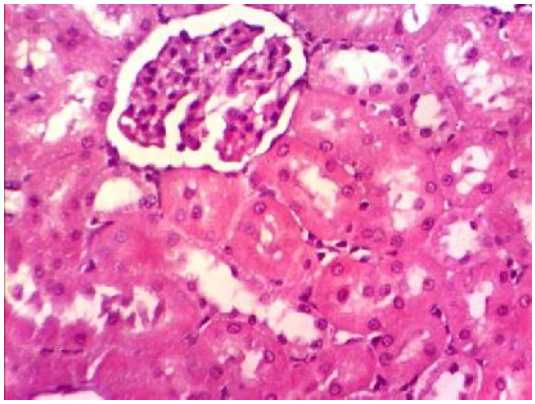

Figure 12: Kidney of rat from G IV showing no histopathological changes (H & E X 400).

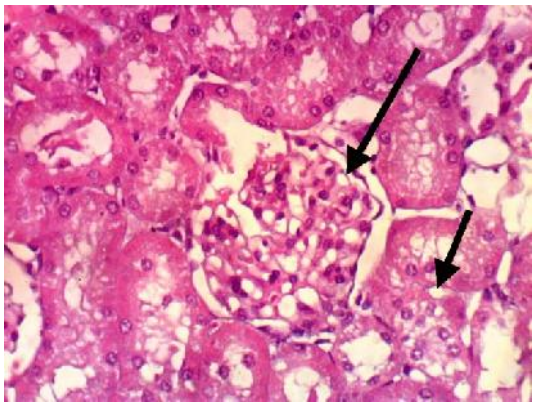

Figure 13: Kidney of rat from G IV showing slight cytoplasmic vacuolation of epithelial lining renal tubules and endothelial lining glomerular tuft (H & E X 400).

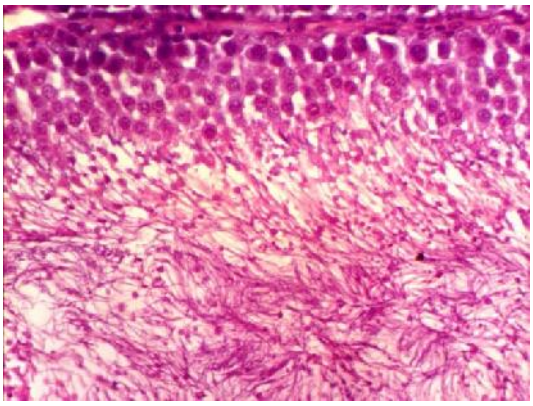

Figure 14: Testis of rat from G II showing the normal histological structure of seminiferous tubule with normal spermatogoneal cells and complete spermatogenesis (H & E X 400).

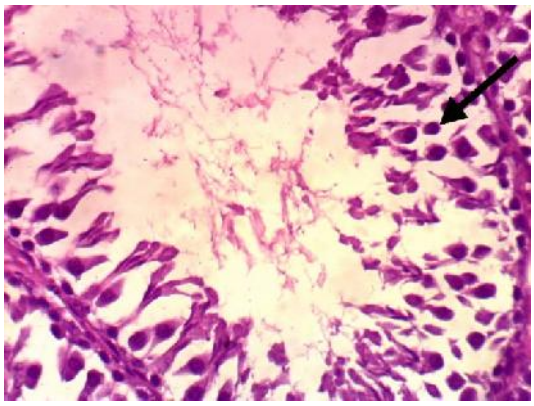

Figure 15: Testis of rat from G III showing degeneration of spermatogoneal cells lining seminiferous tubules with incomplete spermatogenesis (H & E X 400).

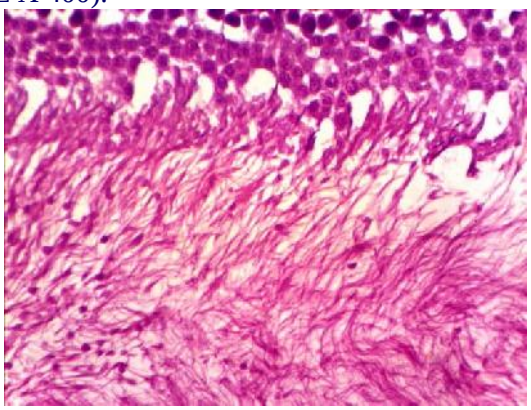

Figure 16: Testis of rat from G IV showing no histopathological changes (H & E X 400).

Brain: Microscopically, brain of rats from G I (control) and G II (RSV treated) revealed no histopathological changes (Figure 17). In contrary, examined sections from G III (Al treated) revealed necrosis of neurons and neurofibrillary tangles (Figure 18), focal gliosis (Figure 19) and focal haemorrhage (Figure 20). Meanwhile, examined sections from G IV which simultaneously treated with RSV and Al revealed necrosis of some neurons (Figure 21).

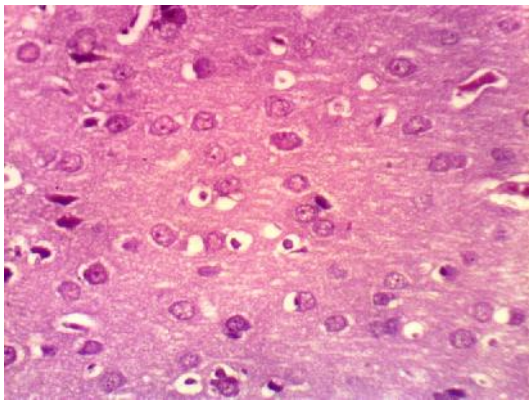

Figure 17: Brain of rat from G II showing no histopathological changes (H & E X 400).

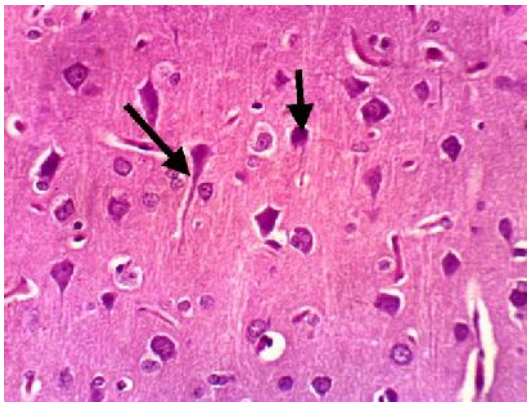

Figure 18: Brain of rat from G III showing necrosis of neurons and neurofibrillary tangles (H & E X 400).

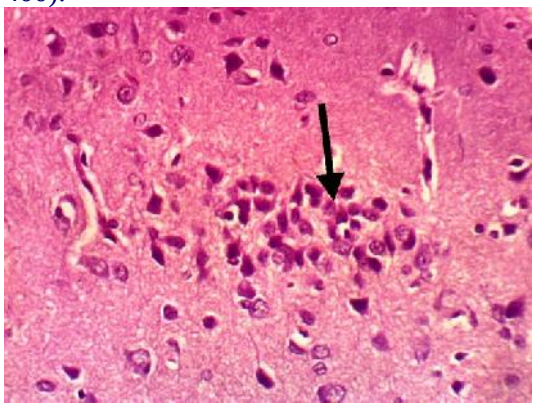

Figure 19: Brain of rat from G III showing focal gliosis (H & E X 400).

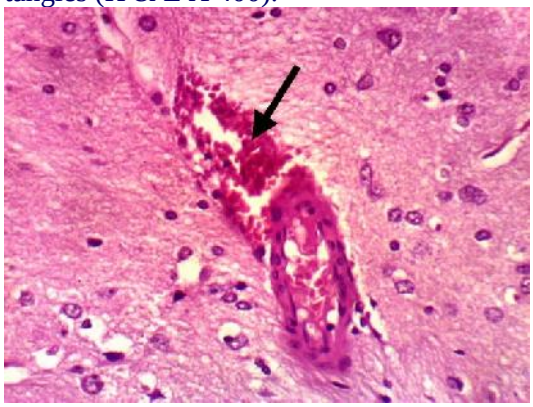

Figure 20: Brain of rat from G III showing focal haemorrhage (H & E X 400).

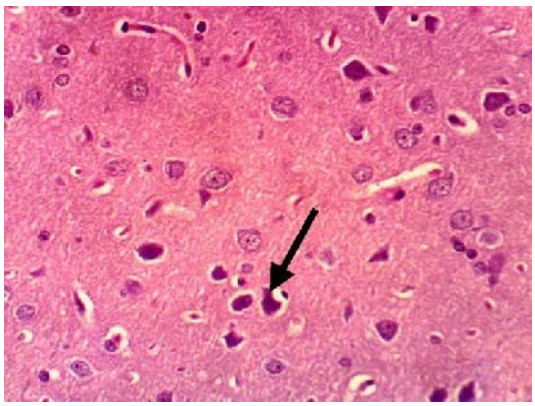

Figure 21: Brain of rat from G IV showing necrosis of some neurons (H & E X 400).

Discussion

In the present study the effect of Al exposure on rats (100 mg/kg b.w) as well as the protective effect of RSV (20 mg/kg b.w) against Al toxicity was investigated.

The present study reveals the administration of $AlCl_3$ for 6 weeks impaired liver function parameters. Al significantly elevated ALT, AST and ALP activities and reduced TP and albumin concentrations which indicate hepatocellular damage and consequent release of enzymes to blood stream (Soheir and Haya, 2013). On the other hand examination of H&E stained hepatic sections showed hydropic degeneration of hepatocytes, congestion of central vein, focal hepatic necrosis associated with inflammatory cells infiltration and fibroplasia in the portal triad. These results are similar to data reported by El-Demerdash (2004) who indicated disruption of liver functions as a result of Al administration (34 mg/kg b.w) for 30 days. Kalaiselvi *et al.* (2015) stated that oral administration of Al (100 mg/kg b.w) for 60 days resulted in accumulation of Al in liver and hepatotoxicity which evidenced by elevations of ALT, AST and ALP activities. Al-Qhtani and Farran (2017) reported an increase of ALT, AST and ALP activities as a consequence of hepatic failure induced by Al administration for 45 days in rats and mice. Disruption of hepatic architecture and degenerative changes was previously reported by Buraimoh *et al.* (2012) in wistar rats after oral Al administration for 8 weeks. Similar to our histopathological finding, Abdel-Wahab (2012) reported morphological changes in liver (necrosis, vacuolization of hepatocytes, congestion of the central vein and infiltration of inflammatory cells) of rats treated by $AlCl_3$ (20 mg/kg b.w) orally for 30 days. Such changes were attributed to induction of lipid peroxidation by Al as indicated by increasing of hepatic MDA with a concomitant decrease in the GSH and antioxidant enzymes (Abdel-Wahab, 2012 and Osama *et al.,* 2014).

In the current study, RSV attenuated hepatocellular damage induced by Al which hypothesized by mean of inhibition of lipid peroxidation in hepatic tissue, improvement of antioxidant defense system and further prevention of oxidative injury (Kasdallah-Grissa *et al.,* 2006 and Zhang *et al.,* 2013). Moreover, RSV inhibits inflammatory processes by interfering with transcription factors such as NF-kB and preservation of GSH (Hassan-Khabbar *et al.,* 2010). RSV dramatically prevented changes in liver function parameters. These data were consistent with finding of Al-Qhtani and Farran (2017) and Yang and Kang (2018) they recorded RSV improved hepatic enzymes and functions in rats treated with Al and streptozotocin, respectively. Furthermore, RSV restored and improved hepatic parenchyma however the lesion of hydropic degeneration of hepatocytes remains. The protective effect of RSV against hepatic distortion was previously reported by Zhang *et al.* (2013) and Highab *et al.* (2017) in rats treated with arsenic trioxide and lead, respectively.

In our experimental model, Al induced renal toxicity proved by increased serum creatinine and urea levels and distortion of renal tissue. Creatinine considered as sensitive indicator of kidney failure. Al-Qayim and Mashi (2014) denoted deleterious effect of $AlCl_3$ administration (50 mg /kg b.w) for 60 days on functions and structure of kidney of rats. Same results obtained by Al Dera (2016) after 40 days of treatment. Kalaiselvi *et al.* (2015) and Al-Qhtani and Farran (2017) reported increased creatinine, uric acid and urea in blood of Al exposed rats. Further, Al accumulates in kidney and stimulates lipid peroxidation injury of renal tubular cell through induction of free radicals causing development of renal failure **(**Alfrey *et al.*, 1976 and Kloppel *et al.*, 1997). Beside kidney dysfunction, increased urea could be also attributed to toxic effect of Al on liver and as urea is the end product of protein catabolism (Katyal *et al.*, 1997).

Present study clarified that co- administration of Al and RSV resulted in improvement of renal function and restore normal kidney structure except of slight cytoplasmic vacuolation of epithelial lining renal tubules and endothelial lining glomerular tuft. Such renal protective effect of RSV was previously reported by Al Dera (2016) and Al-Qhtani and Farran (2017) against nephrotoxicity induced by Al due to its powerful antioxidant properties Moreover, Yang and Kang (2018) recorded improvement of kidney function in diabetic rats co-treated with streptozotocin and RSV.

In view of the current results, Al administration provoked disturbance of metabolism indicated by increasing of blood cholesterol, triglycerides and glucose. In agreement with present study, El-Demerdash (2004), Abdel-Wahab (2012), Osama *et al.* (2014) and Kalaiselvi *et al.* (2015) reported disturbance of the lipid and carbohydrate metabolism as a result of Al toxicity in rats. Regarding liver damage in our experiment, Wilhelm *et al.* (1996) attributed the hypercholesterolemic and hyperlipidaemic effect of Al to accumulation of Al in

liver, oxidative damage of liver and subsequent lipid metabolism disturbance. The hyperglycemic effect of Al could be resulted from breakdown of liver glycogen and hence elevation of blood glucose due to increasing of secretion of adrenal and glucagon hormones and/or depression of insulin (Raja *et al.*, 1992). Fortunately, serum cholesterol, triglycerides and glucose were ameliorated upon RSV administration. Similarly, Szkudelska *et al.* (2017) claimed that RSV at low dose could be beneficial in alleviation of hormonal and metabolic changes induced by alcohol consumption. Rivera *et al.* (2009) addressed that the elevated concentrations of triglycerides, total cholesterol were reduced in obese rats supplemented with RSV for long-term and stated that such effect was related to enhancement of inflammatory status, lowering hepatic lipid content and increase of phosphorylation of 50-AMP-activated protein kinase and acetyl-CoA carboxylase in the liver of obese Zucker rats. Moreover, Poulsen *et al.* (2012) suggested that, RSV protects against fatty liver disease due to its anti-inflammatory potential. Whilst the mechanisms underlying the hypoglycemic effect of RSV were mediated via increased uptake of glucose by tissues, especially skeletal muscle (Deng *et al.*, 2008), increase of insulin/glucagon ratio due to improvement of pancreatic hormone level (Szkudelska *et al.*, 2017) and protection of pancreatic β-cells structure and glucose metabolic enzymes (Yang and Kang, 2018).

The extent of testes damage is assessed by histopatholgical examination. Al treatment induced degeneration of spermatogoneal cells lining seminiferous tubules and incomplete spermatogenesis. Such results were previously provided by Khattab (2007) after interpertonieal injection of rats with different doses of Al, Khattab *et al.* (2010), AL Dera and Abushouk (2015) and Pandey and Jain (2017) after oral administration of Al. Al affect male fertility and disturb steroidogenesis and spermatogenesis through oxidative stress mechanism and decrease of serum testosterone, follicle stimulating hormone (FSH) and luteinizing hormone (LH) (AL Dera and Abushouk, 2015 and Pandey and Jain, 2017).

Current study revealed that RSV fully protected testes against negative impact of Al. AL Dera and Abushouk (2015) and Meydanli *et al.* (2017) reported same protective effect of RSV on testes against Al toxicity and against high-fructose diet, respectively. Kasdallah-Grissa *et al.* (2006) proposed that RSV induce its useful effect by depressing MDA production on testis and thus prevent oxidative injury.

Al recorded as one of environmental pollutants etiology of brain injury, this study confirms that Al administration induce pathological changes in the brain represented by necrosis of neurons, neurofibrillary tangles, focal gliosis, and focal haemorrhage. Several recent studies recorded damage and altered structure of cerebral cortex, cerebellum and hippocampus of rat brain after experimental exposure to Al (Sumathi *et al.*, 2013, Amjad and Umesalma, 2015, Bassiouny and Zaky, 2015 and Said and Abd Rabo, 2017). The neurodegenerative disorder induced by Al is subsequent to prolonged inflammation following enhancement of immune mediators (Blaylock, 2012) and associated with increased lipid peroxidation, protein carbonyl levels, and acetylcholine esterase activity and attenuation of antioxidant defense system in the brain (Al-Otaibi *et al*., 2018).

This work revealed RSV protected brain partially against Al toxicity where the brain of rats co-treated with RSV and Al showed necrosis of some neurons only, even though RSV possessed great power against neurological disorders and brain damage which recorded in many previous studies. RSV showed protective effect against neurological function and histopathological changes induced by streptozotocin (Sharma and Gupta, 2002), spinal cord injury (Liu *et al*., 2011), Al (Bassiouny and Zaky, 2015) and Al along with fluoride (Nallagouni and Reddy, 2017). The reduction of neuronal damage was correlated with reduction of lipid peroxidation and gliosis enhancement of antioxidant mechanism due to antioxidant, anti-inflammatory and anti-apoptosis potential of RSV (Kasdallah-Grissa *et al.*, 2006, Zhang *et al*., 2010 and Liu *et al*., 2011).

In the current study, the recorded increase of MDA along with depleting of GSH and SOD in plasma of Al- intoxicated rats provided an explanation of negative effect of Al on tested parameters and organs. This hypothesis runs with previous studies of El-Demerdash (2004), Abdel-Wahab (2012), Sumathi *et al.* (2013) and Shrivastava (2013). Al accumulates in different organs and induces free radicals mediated cytotoxcicty (Kloppel *et al.*, 1997 and Kalaiselvi *et al.*, 2015) which cause damage of cellular membrane, lipid peroxidation, denaturation of protein and DNA and depleting of cellular antioxidant enzymes (Moumen *et al*., 2001). Moreover, Al interferes with minerals balance inside body such as magnesium, calcium, and

iron and replaces them in their biological systems leading to deactivation of their functions (Ward *et al*., 2001).

Luckily, RSV was able to alleviate Al toxicity on antioxidant defense system and reduce lipid peroxidation production and thus prevent oxidative stress (Hassan-Khabbar *et al.*, 2010). After ingestion of RSV, it is metabolized in liver and intestine then carried to tissue through plasma protein, namely albumin (Boocock *et al*., 2007). The free radicals scavenging activity of RSV attributed to its unique structural active three phenolic hydroxyl groups (Karlsson *et al*., 2000).

Conclusion

In conclusion, oxidative stress damage is the favored scenario justifying the toxicity of aluminum. On the other hand, resveratrol (natural polyphenol) showed exceptionally antioxidant activity contributing to limitation of aluminum toxic effects on different biochemical parameters, metabolism, antioxidant defense system and organs structure.

Conflicts of Interest

The authors declare no conflict of interest.

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