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For Rats Which are Implemented Cadmium Chloride Exposure, Polydatin and Grape Seed Extracts Protective Effects on Testis and Brain Tissues

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ABSTRACT

This study is carried out on rats, the polydatin (PD) and grape seed extracts' (GSE) protective effects aganist to cadmium's (Cd) oxidative damage in brain and testis (transgressing blood-testis and blood-brain barriers) is investigated. In our study, 49 wistar-Albino adult male rats were used. Rats were seperated into seven equal groups: Group 1; Control Group (Normal saline was given orally for 30 days.) Group 2; Cd group (5 mg/kg dose of CdCl2 was dissolved in normal saline and was given orally for 30 days.) Group 3; Group PD (g 120 mg/kg PD was dissolved in normal saline and was given orally for 30 days.) Group 4; GSE Group (120 mg/kg GSE was dissolved in normal saline and was given orally for 30 days.) Group 5; Cd+PD Group (5 mg/kg dose of CdCl2 + 120 mg/kg PD were dissolved in normal saline and was given orally for 30 days.) Group 6; Cd+ GSE Group (5 mg/kg dose of CdCl2 + 120 mg were dissolved in normal saline and were given orally for 30 days.) Group 7; Cd+PD+ GSE Group (5 mg/kg dose of CdCl2+120 mg/kg PD + 120 mg/kg GSE were dissolved in normal saline and were given orally for 30 days.) At the end of the experimental period, all the rats were decapitated and their brain and testis tissues samples were examined. In Cd implemented rats, in their brain ($p < 0.05$) and in testis ($p<0.01$), malondialdehyde (MDA) levels statistically increase in significant way, within PD and GSE implemented groups, it decreases /kg GSE was detected. In Cd implemented rats, antioxidant potential values (AOP) decrease in brain and testis, in PD and GSE implemented groups, it increases significantly. ($p<0.001$) According to the ICP-OES data, it couldn't be determined because it was under the brain measurement leels, in Cd impelemented testis groups, there was increasement ($p<0.001$). Consequently, for rats, because of the cadmium exposure, oxidative damage has occured in brain and testis; aganist to this damage, both PD and GSE were protective, but PD was more protective than GSE.

KEYWORDS : Cadmium, Polydatin, Grape Seed Extract, Toxicity, Rat

INTRODUCTION

As a result of industrialisation and urbanisation; environmental pollution has increased and they also caused to soil pollution and it has reached dangerous level for the living creatures. In directly and indirectly, environmental and soil pollution problems could have been occured and it affected all organisms by food chain, this increased the problem's magnitude and danger. The most important factor that caused environmental and soil pollution is heavy metals (Stresty and Madhava Rao, 1999). In recent years, heavy metal content increasement in agricultural plants and these metals' influence on plant, animal and human health with the side effects of known toxic effects; caused to enlarge the studies about this subject. The presence of one of the heavy metal as cadmium in plants, could be main material and also it may be as a result of industrial activities, phosphorus fertilizers, sewage sludge and atmosferic deposits as a result of human activities (Assche and Clijsters, 1990). Cadmium is a moving element in the soil and it can be absorbed easily by the plants. To be absorbed by the plants, it causes an important environmental problem as entering the food chain or be washed in the soil and probablity of reaching water environment. In addition to this, cadmium can be moved up to down with chelating agents easily, and it causes a pollution in watering waters and it can mingle the underground water (Köleli and Kantar, 2005). The main resources that cadmium spreads over the nature are; mines, refineries, industrial wastes, phosphate fertilizers, some pesticides, shellfish and gres oils (Baldwin and Marshall, 1999). Cadmium and its compounds are used in pigment and dye production, printing, textile, photography, jewelry maker, carving, automobile industry and production of fluorescent lamp (Kaya and Akar, 2002; Olabarriete et al., 2001). Cadmium poisoning causes to damage in respiratory system, circulatory system, stomach and intestines, bone tissue, blood, kidney, testis and pancreas etc. (Katsuta et al., 1994). Cytotoxic effects which have been in depends of cadmium; forming free radicals and defects of antioxidant defence system are being responsible (Casalino et al., 2002; Lopez et al., 2006). Cadmium does not produce free oxygen radicals directly, but it affects the mitochondrial electron transfer chain or increases the glutathione and it contributes to producing free radicals indirectly (Romero et al., 2011). Free radicals cause to damage the structures with affecting all important compounds as lipid, protein, DNA and carbohydrates and in living organisms they cause to lipid peroxidation (El-Sokkary et al., 2010; Aydogdu et al., 2007). Malondialdehyde (MDA) is a main metabolite that is oxidized by cell lipids which were damaged and it is also accepted as an index of lipid peroxidation (Zahir et al., 1999). Antioxidant defence system is called that protect the cell itself aganist to composed free radicals and normal oxygen metabolism's toxic effects, intracellular and extracellular enzymes and nonenzyme (without enzyme) defency mechanisme (Fridovich, 1976). Antioxidants can be synthesized in the body, and also they can be taken from diet. "Phytochemicals" are called thet is not itself food, but have functions as food and 1functional, healthy, medical, regulatory, for particular nutrition or pharmacological nutritions" and they are in substance's structure, plant-derived biological active compounds (Aksoy, 2007; Gulcin, 2009). The studies that have been continued for many years, some of these substances in the plants could be distilled, so it provides to get phytochemicals distilled and used them. One of the phytochemicals that have been studied intensively is a grape seed with its rich phenolic content. It has been reported that the high level of antioxidant activity's phenolic content is relate to grape seed extract (Kar et al., 2006). In spite of the plant extracts are potential candidates, they can also include extremely complex compounds of different contents. For this reason, in recent years; the interest focused on herbal medicines' bioactive compounds. Resveratrol (3,4 , 5 -trihidroksi -trans- stilben) is one of them. It occurs naturally as a polyphenol and especially it is in grape, nnut, pomegranate and poligonum cuspidatum. Polydatin is

resveratrol glycoside and derived from cuspidatum's root (RPC) and its stem, it is a stilbenoid. Its content in RPC is more than resveratrol for six times (Zhou et al., 2005). This study aims to survey so far on the impact of PD in rats induced by Cd and PD and is investigated the lack of work on the efficacy of resveratrol in toxicity between the components of the protective blood brain barrier and CD, GSE by comparing the testis tissues.

MATERİALS AND METHODS

Materials: Polydatin and cadmium chloride Sigma-Aldrich (Interlab Inc., Istanbul, Turkey), Aksu Vital bought Grape Seed Extract (Istanbul, Turkey). The other chemical substances can be easiy avaiable commercially in high purity.

Experimental protocol: In our study, health male Wistar – Albino rats which have 250 – 300 grams weights and 2 – 3 months old, have been bought from Laboratory Animals Survey and Application Center (Afyon,Turkey). For the study, a ethics committee permission was taken from Afyon Kocatepe University, Animal Experiments Ethics Committee (AKUHAYDEK). Rats stayed in 12 hours light/dark cycle, with the 50-55% of moisture, at room temperature (25°C), and were fed with Standard rote feed and as libitum water. In this study, total 49 rats were seperated randomly in 7 groups with 7 rats in each group. Before the beginning of the experiment process, for a week, rats were provided to adjust the environment.

Group 1; Control Group (Normal saline was given to rats by gastric gavage (SF))

Group 2; Cadmium (Cd) Group (Cadmium chloride was disssolved in SF in doze of 5mg/kg/day were given to rats by gastric gavage). Group 3; Polydatin (Pd) Group (Polydatin was disssolved in SF in doze of 120 mg/kg/day were given to rats by gastric gavage).

Group 4; Grape Seed Extract (GSE) Group (Grape seed extract was dissolved in SF in doze of 120 mg/kg/day were given to rats by gastric gavage). Group 5; PD + Cd Group (Cadmium chloride in doze of 5mg/kg/day and polydatin in dose of 120 mg/kg/day were disssolved in SF were given to rats by gastric gavage). Group 6; GSE + Cd Group (Cadmium chloride in doze of 5mg/kg/day and grape seed extract in dose of 120 mg/kg/day were disssolved in SF were given to rats by gastric gavage). Group 7; PD + GSE + Cd Group (Cadmium chloride in doze of 5mg/kg/day and grape seed extract in dose of 120 mg/kg/day and polydatin in dose of 120 mg/kg/day were disssolved in SF were given to rats by gastric gavage). Not to effect drug interactions and drug absorbation, cadmium chloride applications were made in the morning, polydatin and grape seed extract aplications were made in the afternoon.

Preparation of homogenates: Animals were sacrificed by cervical dislocation and their brain and testis tissues were washed immediately with ice cold 0.9% NaCl. Each tissue was trimmed free of extraneous tissue, rinsed in chilled 0.15 M Tris–HCl buffer (pH 7.4). These tissues were blotted dry, and homogenized in 0.15 M Tris–HCl buffer (pH 7.4) to yield a 10% (w/v) homogenate. Then, they were centrifuged at 3500 rpm for 10 min at 4 °C. The pellets represented the nuclear fraction and the supernatants were subjected to centrifugation at 20,000 rpm for 20 min at 4 °C. The resultant pellets and the supernatants represented the mitochondrial fraction and the cytosolic (including microsomal fraction) fraction, respectively. Reactive oxygen species generation was observed in these fractions as well as whole homogenate (Kucukkurt et al., 2008).

Preparation of tissues for histopathological analysis: At the end of experimental period, 49 male rats were sacrificed. Then, they were dissected and brain and testis tissues from each animal were collected and fixed into 10% formalin solution for 48 h and then dehydrated through graded alcohol series (70–100%), cleared in xylene and embedded in paraffin. 5–6 µm thick parafin sections were cut and stained with haematoxylin-eosin (H&E) and analyzed under a light microscope (Olympus Bx51 model, Tokyo, Japan) equipped with camera (Olympus DP20, Tokyo, Japan).

Cadmium Concentration Assay in Tissues: 0,5 g sample was taken from each animal's brain and testis tissue, and was putin high heat-resistant pocelain tubes and first 1 ml 30% H2O2(Hydrogen peroxide) was added and after that 7 ml 65% HNO3 (nitric oxide) was added and then waited for 10 minutes. Then, tubes' brims were closed and in microwave oven it has burned in 200*C for 30 minutes. The burning process was made in Milestone Stard D brand microwave oven, and quantitive assay was made in Perkin Elmer ICPOES Optima 8000.

Measurement of LPO in whole tissue homogenates: Malondialdehyde (MDA), as a marker for LPO, was determined according to the methods of in tissue homogenates (Ohkawa et al., 1979). The principle of the methods is based on spectrophotometric measurement of the colour production during the reaction of thiobarbituric acid (TBA) with MDA and its absorbance was measured spectrophotometrically at 532 nm. The concentration of MDA was calculated by the absorbance coefficient of MDA–TBA complex and expressed in nmol/g wet tissue.

AOP (antioxidant potantial) measurement in tissue homogeneous: AOP was determined to the way of Durak et al. Method. This method enriched reaction environment with fish oil. Fish oil has beeen prefered because it is polyunsaturated and therefore it is very sensible to free radical attacks.

Samples have been exposed for an hour to produced xanthine/xanthine oxidase (xanthine/xanthine oxidase) system superoxide radicals ($O_2^{\cdot-}$). As it is known, if it is inability to remove free radicals in stem, unsaturated free fatty acids were oxidized easily and TBARS concentration increases. Using the reaction system as mention in the above, in tissue and stems, we can have more accurate information about total (enzymatic and non-enzymatic) antioxidant potential. For this purpose, TBARS concentration in reaction environment was measured before $O_2^{\cdot-}$ radical process and after it has formed. Difference between two values is inversely proportional to antioxidan potential (Durak et al., 1998).

Statistical analyses: Data obtained from experimental animals were expressed as means and standard deviation of means (±SE) and analysed using one-way analysis of variance (ANOVA), followed by Tukey post hoc tests on the SPSS (11.5) software computer program. A difference in the mean values of $p < 0.05$ was considered to be significant.

RESULTS

Biochemical Findings: MDA level is used commonly as LPO indicated with free radical. Comparing the controls, Cd implemented rats' in brain ($p<0.05$) and testis ($p<0.01$), it has been increasement in MDA level significantly. In contrast to this, related to PD and GSE, in Cd groups (Table 1) tissues, MDA levels have been decreased (Table 1). In Cd implemented rats, MDA level decreases in brain and testis ($p<0.001$) compared to the conrols. But related to PD and GSE, in CD groups, it has been observed an increasement significantly (Table 1).

Table 1: In male rats' brain and testis tissues (nmol/g tissue), Cd exposure polydatine (PD) and grape seed extract (GSE) effect on AOP activity levels

Groups	Control	Cd	PD	GSE	Cd+PD	Cd+GSE	Cd+PD+GSE	P <
Brain MDA	1,05±0,05^{a}	1,00±0,04^{ab}	0,96±0,06^{ab}	0,78±0,06^{b}	0,94±0,04^{ab}	0,91±0,04^{ab}	0,92±0,05^{ab}	0,030*
Testis MDA	1,03±0,07^{a}	0,90±0,06^{ab}	0,69±0,04^{b}	0,89±0,10^{ab}	0,67±0,05^{b}	0,74±0,03^{b}	0,82±0,05^{ab}	0,003**
Brain AOP	2,25±0,21^{c}	2,24±0,43^{c}	10,58±0,43^{a}	6,76±1,21^{ab}	7,45±1,40^{ab}	6,39±0,65^{b}	9,15±1,17^{ab}	0,000***
Testis AOP	3,65±0,95^{c}	5,04±1,01^{c}	12,32±1,83^{a}	11,17±2,40^{ab}	3,04±0,49^{c}	4,13±0,79^{c}	6,07±0,83^{bc}	0,000***

Values are mean ± Standard error; n = 7.

[a,b,c] In the same column values with different letters show statistically significant differences; *: p< 0.05 **: p<0.01 ***: p<0.001

Cd levels in tissues: Rats' brain tissues that are in Cd implemented groups was not determined because the Cd concentration was below the measurement levels (Table 2). In rats' testis (p<0.001) tissues, there is a significant increasement in Cd groups. In contrast to this, depending on PD and GSE, in Cd groups (Table 2), Cd concentration levels have decreased.

Table 2: In male rats' brain and testis tissues (nmol/g tissue), polydatine (PD) and grape seed extract (GSE) effect on Cd (ppb) concentration

Groups	Control	Cd	PD	GSE	Cd+PD	Cd+GSE	Cd+PD + GSE	P <
Brain Cd	ND	ND	ND	ND	ND	ND	ND	
Testis Cd	ND	0,44±0, 02[a]	ND	ND	0,37 ± 0, 02[ab]	0,42 ± 0, 02[ab]	0,33± 0,02[b]	0,000***

Values are mean ± Standard error; n = 7. ND: Under measurement limits

[a,b,c] In the same column values with different letters show statistically significant differences; ***: p<0.001

Histopathological findings: Histopathological changes in experiment groups animals' organs were identified in detail and was showed in Table 1. In Cd group, in brain, it was observed that focal gliosis and hyperemia around the neurons (Figure 1-A2). In testis, it was observed that cell debris and decreasement in density of spermatozoa in the lumen of Tubulus Seminiferus Kontortus (TSK) (Figure 1-B2). In PD and GSE groups, it has been observed that the significant histopathological changes in brain and testis tissues.

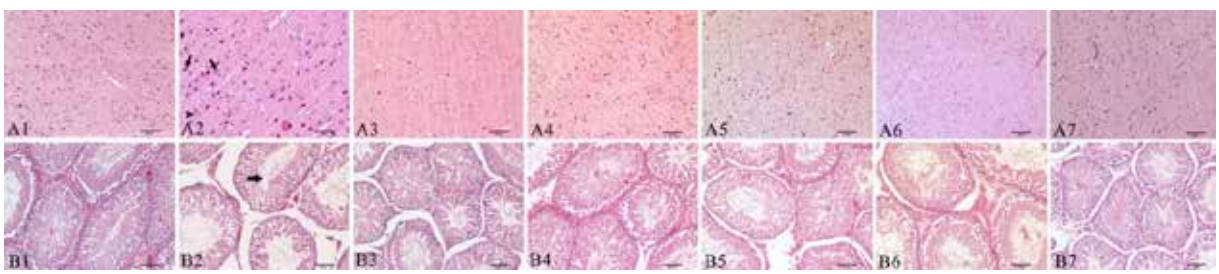

Fig. 1: In male rats, an effect of polydatin (PD) and grape seed extract (GSE) on damages that has been created with cadmium (Cd) in brain (1) and testis (2). All figures are stained with eosin and haematoxyli. For an original magnification ration; 20x and 50um were used. Arrows, respectively indicate that focal glucose and hyperemie around the neurons in brain (Figure 1-2A), in testis, decreasement in indensity of spermatozoa in the lumen of Tubulus Seminiferus Kontortus (TSK) and cell debris (Figure 1-B2). (1) indicates control group, (2) 5 mg/kg/30 day Cd group, (3) 120 mg/kg/30 day PD group, (4) 120 mg/kg/30 day GSE group, (5) 5 mg/kg/30 day Cd + 120 mg/kg/30 day PD group, (6) 5 mg/kg/30 day Cd + 120 mg/kg/30 day GSE group, (7) 5 mg/kg/30 day Cd + 120 mg/kg/30 day PD group + 120 mg/kg/30 day GSE group, implemented rat groups. In all groups, implement was done by gastric gavage orally.

DISCUSSION

As it is known, cadmium is one of the toxic industrial and environmental heavy metal. Many researchers have had experiments on many different animals, it has been demonstrated that cadmium's chronic toxicity on several organs, and histological and thin structure by various researchers (Watari et al., 1989; Asar et al., 2004). Acutely exposure and cadmium induced necrosis in testis and damage cellular, and with chronic exposure, it damages intensively in kidney and bone (Griffin et al., 2001). It is clearly shows that rats that were exposed to cadmium have DNA damage in brain stems analsis. It has been reported that there is a positive relation between cadmium dose and DNA damage level (Fasanya-Odewumi et al., 1998).

Oxidative stres, is expressed to deterioration of the balance between the free radicals' intracellular production and cellular defency mechanisms, especially MDA is one of the significant indicator of oxidative stress (İnce et al., 2010). It is known that oxidative stree has a main role in inducing chronic cadmium (Shaikh et al., 1999). Cadmium can change cells' antioxidant systems and increase the peroxidation of membrane lipids and so it can induce oxidative damage in different tissues (Yiin et al., 1999; Yiin et al., 1999). Cadmium's effects have been known for a long time on different types of animals, especially toxic effects on testis (Niewenhuis et Fende, 1978) and it has been reported that aganist the cadmium's acute toxic effects, the most sensitive organ in rodents is testis (Shiraishi and Waalkes, 1996). A researche that was done by Kunda et al., it has been determined that sub-lethal dose of $CdCl_2$ is 5 mg/kg/day. In our study, we applied $CdCl_2$ exposure to rats in dose of 5mg/kg/day. Previous studies has showed that MDA levels increased in testis tissues after the implement of Cd to rats (Patra et al., 1999; El-Maraghy et al., 2001; Casalino et al., 2002; Ognjanovi´c et al., 2003). It has been identified that there was an organ damage and system dysfunction related to increasing LPO, Cd origin in tissues (Casalino et al., 2002; Ognjanovi´c et al., 2008). In our survey, Cd implemented rats' MDA level increased, but with Cd and GSE implemented group, as a significant indicator of lipid peroxidant, MDA decreased significantly in testis tissues. In addition to this, in the same groups; testis AOP levels increased in GSE groups, but with Cd and GSE implemented groups, there was a significant decreasement. Oxygen radicals have an important role in brain damage. As a result of a research that surveyed GSE implemented newborn rats effects on brain damage inducated by oxygen radicals, with using grape seed extract, it stops lipid peroxidation snd it decreases brain damage on newboen rats hypoxic (due to lack of oxygen) ischemic brain damage. (Yangzherg et al., 2005). A research has been conducted which depends on the hypothesis if the rats was fed with grape seed extract, their brains will be protected. As a result of this research, if the rats would fed with feed that contains 5% grape seed extract, they found that it is a protective effect on brain proteins on neurodegeneration or Alzheimer (Dehane et al., 2004). In this presented study, GSE implemented group's brain tissues show that MDA decreasement as a significant indicator of lipid peroxidant. With Cd and GSE implemented groups, it has been observed that lipid peroxidant has been stopped. In Cd implemented groups, AOP levels decreased in brain; with Cd and GSE implemented groups, there was a significant increasement. Enzymatic oxidation is more resistant than a water-soluble form of PD resveratrol. Unlike resveratrol, it penetrates to the cell pasively. Cellular ingestion occurs with the way of gucose carriers active mechanism (Falchetti et al., 2001). In previous studies, there are many activities of PD: hyperlipidemia decreases lipid profile in rabbits (Xing et al., 2009), in cerebral damages with induced ischemia/reperfusion provides a neuroprotective effect (Cheng et al., 2006), causes weight loss and enrich the diet among the low birth weight newborns (Jordan et al., 2008), CCl_4 implemented rats, it shows protective effects in primer hepatocyte cultures (Huang et al., 1999) and decrease lipid oxidation (Pan et al., 2007). However, as a result of our surveys; there wasn't found any studies about polydatin activity in cadmium exposed rats. In our study, there was not a significant PD activity on MDA levels in rats' brain tissues, when the Cd group's AOP levels are low, Cd and PD implemented groups, it is shown that PD increased AOP levels significantly. In testis tissues, Cd implemented group's MDA levels increased, but with Cd and PD implemented groups, it has been showed that PD decreased the MDA

levels significantly. In addition to this, testis tissues AOP levels have not any significant importance on PD's Cd toxicity. In the studies, it has not been observed that, depending on cadmium toxicicty; in acute terms; there is not any edema in interstitial region, hemorrhagic necrosis, neutrophil granulocyte infiltration, hyperemia, dilation in vessels and thrombosis, and degeneration in TSKs and necrosis, in chronic terms; there is an increasement of connective tissue on interstitial region, fibrosis and lymphocyte infiltration and there is a necrosis in TSKs. (Gupta et al., 1967; Gunn and Gould 1970; Saygı et al., 1991; Foley 2001; Lanning et al., 2002). According to the research of Kusabe et al.'s, they observed that after 24 hours of intraperitoneal cadmium injection, seminiferous tubules detached from basal membrane, atrophied and spermatogenic cells decreased significantly and also interstitial tissue damaged (Kusakabe et al., 2008). In this research, with the implement of Cd, histopathologically; in Cd group it has been observed that focal hyperemie around the neurons in brain and in testis, the indensity of spermatozoa lumen has decreased and cell fluff. It has not been observed any change histopathologically in PD and GSE groups.

CONCLUSION

In this study, in Cd implemented rats, PD and GSE have protective effect aganist oxidative stress. This research's results have showed that PD and GSE not only blocked LPO but also icrease the activity of antioxidant defency system and produced protective effects. In addition to this, it has been determined that PD has more positive activity than GSE.

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REFERENCES

Aksoy, M., 2007. Fitokimyallar: Ansiklopedik Beslenme, Diyet ve Gıda Sözlüğü Kitabı. 1. Baskı. ISBN: 975-8322-19-2 Ankara ss: 193-194. Asar, M., U.A. Kayisli, V.N. Izgut-Uysal and G. Akkoyunlu, 2004. Immunohistochemical and ultrastructural changes in the renal cortex of cadmium-treated rats. Biol Trace Elem Res; 97: 249-263. Assche, F.V. and H. Clijsters, 1990. Effects of metals on enzyme activity in plants, Plant and Cell Environment. 13: 195-206. Aydoğdu, N., H. Erbaş and K. Kaymak, 2007. Taurin, Melatonin ve N-Asetilsisteinin Kadmiyuma Bağlı Akciğer Hasarındaki Antioksidan Etkileri. Trakya Üni. Tıp Fak. Dergisi, 24(1):43-48. Baldwin, D.R. and W.J. Marshall, 1999. Heavy metal poisoning and it's laboratory investigation. Ann Clin Biochem, 36, 267-300. Casalino, E., G. Calzaretti, C. Sblano and C. Landriscina 2002. Molecular inhibitory mechanisms of antioxidant enzymes in rat liver and kidney by cadmium. Toxicol; 179: 37-50. Cheng, Y.F., H.T. Zhang, L.S. Sun, S.L.Guo, S. Ouyang, Y.J. Zhang and J. Xu, 2006. Involvement of cell adhesion molecules in polydatin protection of brain tissues from ischemia-reperfusion injury. Brain Res 1110: 193-200. Dehane, J., L. Chaves, K.V. Sarikonda, S. Isbell, L. Wilson , M. Kirk, C. Grubbs, S. Barnes, S. Meleth and H. Kim, 2004. Proteomic Analysis of Rat Brain Protein Modulations by Grape Seed Extract. J. Agric. Food Chem. 52, 7872-7883. Durak, I., H.I. Karabacak, S. Büyükkocak, M.Y.B. Çimen, M. Kaçmaz, E. Ömerolu and H.S. Öztürk, 1998. Impaired antioxidant defence system in the kidney tissues from rabbits treated with cyclosporine. Nephron.;78:207-11. El-Maraghy, S.A., M.Z. Gad, A.T. Fahim and M.A. Hamdy, 2001. Effect of cadmium and aluminium intake on the antioxidant status and lipid peroxidation in rat tissues. J Biochem Mol Toxicol;15:207–14. El-Sokkary, G.H., A.A. Nafady and E.H. Shabash, 2010. Melatonin administration ameliorates cadmium-induced oxidative stress and morphological changes in the liver of rat. Ecotox Environ Safe: 73; 456-463. Falchetti, R., M.P. Fuggetta and G. Lanzilli, 2001. Effects of resveratrol on human immune cell function. Life Science 70: 81–96. Fasanya-Odewumi, C., L.M. Latinwo and C. Ikediobi, 1998. The genotoxicity and cytotoxicity of dermally-administered cadmium: Effects of dermal cadmium administration. Int J Mol Med; 1: 1001-1006. Foley, G.L., 2001. Overview of male reproductive pathology. Toxicol Pathol, 29, 49-63. Fridovich, I., 1976. In free radical in biology; Pryor, W.A., Ed; Academic: New York,1, 239-271. Griffin, J.L., L.A. Walker, R.F. Shore and J.K. Nicholson, 2001. Metabolic profiling of chronic cadmium exposure in the rat. Chem Res Toxicol; 14: 1428-1434. Gunn, S.A., T.C. Gould and W.A.D. Anderson, 1970. Comparative mechanisms of action on monochlorhydrin and cadmium induced necrosis of the caput epididiymis of the rat. Biol Reprod, 3, 35-42. Gupta, R.K., G.W. Barnes and F.R. Skelton, 1967. Light-microscopic and immunopathologic observations on cadmium chloride-induced injury in mature rat testis. American Soc Invest Pathol, 51, 191-205. Gülçin, İ., 2009. Antioxidant activity of L-adrenaline: A structure–activity insight. Chemico-Biological Interactions, 179, 71-80. Huang, Z.S., Z.W. Wang, M.P. Liu, S.Q. Zhong, Q. M. Li and X.L. Rong, 1999. Protective effects of polydatin against CCl(4)-induced injury to primarily cultured rat hepatocytes. World J Gastroenterol; 5: 41-44. Ince, S., I. Kucukkurt, I.H. Cigerci, A.F. Fidan and A. Eryavuz, 2010. The effects of dietary boric acid and borax supplementation on lipid peroxidation, antioxidant activity, and DNA damage in rats. J Trace Elem Med Biol; 24: 161-4. Jordan, K.C., J.H. Freeland-Graves, D.M. Klohe-Lehman, G.W. Cai, V.S.Voruganti and J.M. Proffitt, 2008. A nutrition and physical activity intervention promotes weight loss and enhances diet attitudes in low-income mothers of young children. Nutr Res; 28: 13-20. Kar, P, D. Laight, K.M. Shaw and M.H. Cummings, 2006. Flavonoid-rich grape seed extracts: A new approach in high cardiovascular risk patients? Int J Clin Pract ;60:1484-92. Katsuta, O., H. Hiratsuka, J. Matsumoto, H. Iwata, N. Toyota, M. Tsuchitani, T. Umemura and F. Marumo, 1994. Cadmiuminduced osteomalasic and osteopetrotic lesions in ovariectomized rats. Toxicol Appl Pharmacol, 126, 58-68. Kaya, S. and F. Akar, 2002. Metaller, Diğer Inorganik ve Radyoetkin Maddeler. In: Kaya S, Pirinçci İ, Bilgili A. Editörler, Veteriner Hekimliğinde Toksikoloji. Medisan Yay, 2. baskı, s.207-250. Köleli, N. and Ç. Kantar, 2005. Fosfat Kayası, Fosforik Asit ve Fosforlu Gübrelerdeki Toksik Ağır Metal (Cd, Pb, Ni, As) Konsantrasyonu. Ekoloji Dergisi, 14(55). Kucukkurt, I., S. Ince, A.F. Fidan and A. Ozdemir, 2008. The effects of dietary supplementation of different amount of Yucca schidigera powder (Sarsaponin 30®) on blood and tissue antioxidant defense systems and lipid peroxidation in rats. J Anim Vet Adv; 7: 1413-17. Kundu, S., S. Sengupta, S. Chatterjee, S. Mitra and A. Bhattacharyya, 2009. Cadmium induces lung inflammation independent of lung cell proliferation: a molecular approach. J Inflamm (Lond), 6:19. Kusakabe, T., K. Nakajima, K. Nakazato, K. Suzuki, H. Takada, T. Satoh, M. Oikawa, K. Arakawa and T. Nagamine, 2008. Changes of heavy metal, metallothionein and heat shock proteins in Sertoli cells induced by cadmium exposure. Toxicol In Vitro.; 22 (6): 1469-75. Lanning, L.L., D.M. Creasy, R.E. Chapin, P.C. Mann, N.J. Barlow, K.S. Regan and D.G. Goodman, 2002. Recommended approaches for the evaluation of testicular and epididymal toxicity. Toxicol Pathol, 30, 507-520. Lopez, E., C. Arce, M.J. Oset-Gasque, S. Canadas and M.P. Gonzalez, 2006. Cadmium induces reactive oxygen species generation and lipid peroxidation in cortical neurons in culture. Free Radic Biol Med; 40: 940-51. Niewenhuis, R.J. and P.L. Fende, 1978. The protective effect of selenium on cadmium-induced injury to normal and cryptorchid testes in the rat. Biol Reprod, 19, 1-7. Ognjanovi´c, B., S.D. Markovi´c, S.Z. Pavlovi´c, R.V. ˇZiki ´c, A. ˇStajn and Z.S. Sai˘ci ´c, 2008. Effect of chronic cadmium exposure on antioxidant defense system in some tissues of rats: protective effect of selenium. Physiol Res;57:403–11. Ognjanovi´c, B., S.Z. Pavlovi´c, S.D. Maleti´c, R.V. ˇZiki ´c, A. ˇStajn and R.M. Radoji˘ci ´c, 2003. Protective influence of vitamin E on antioxidant defense system in the blood of rats treated with cadmium. Physiol Res;52:563–70. Ohkawa, H., N. Ohishi and K. Yagi, 1979. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem; 95: 351-58. Olabarriete, J., B. Lazou, C. Yuric, J. Cambar and M. Cajaraville, 2001. In vitro effects of cadmium on two different animal cell models. Toxicol In Vitro, 511-517. Pan, Y.M., X.P. Zhang, H.S. Wang, Y. Liang, J.C. Zhu, H.Y. Li, Z. Zhang and Q. Wu, 2007. Antioxidant potential of ethanolic extract of Polygonum cuspidatum and application in peanut oil. Food Chem 105: 1518-1524. Patra, R.C., D . Swarup and S.K. Senapati, 1999. Effects of cadmium on lipid peroxides and superoxide dismutase in hepatic, renal and testicular tissue of rats. Vet Hum Toxicol;41:65–7. Romero, A., A. Caride, N. Pereiro and A. Lafuente, 2011. Modulatory effects of melatonin on cadmium-induced changes in biogenic amines in rat hypothalamus. Neurotox Res; 20: 240-9. Saygı, Ş., G. Deniz, O. Kutsal and N. Vural, 1991. Chronic effects of cadmium on kidney, liver, testis and fertility of male rats. Biol Trace Elem Res, 31, 209-214. Shaikh, Z.A., T.T. Vu and K. Zaman, 1999. Oxidative stress as a mechanism of chronic cadmium-induced hepatotoxicity and renal toxicity and protection by antioxidants. Toxicol Applied Pharmacol; 154: 256-263. Shiraishi, N. And M.P. Waalkes, 1996. Acquired tolerance to cadmium induced toxicity in rodent testes. Toxicol Subs Mech, 15, 27-42. Stresty, T.V.S. and K.V. Madhava Rao, 1999. Ultrastructural alterations in response to zinc and nickel stress in the root cell of pigeonpea, Environmental and Experimental Botany. 41: 3-13. Watari, N., Y. Hotta and Y. Mabuchi, 1989. Ultrastructural studies on a cadmium-storing cell in rat pancreatic tissues following cadmium chloride administration. J Electron Microsc; 38: 235-241. Xing, W.W., J.Z. Wu, M. Jia, J. Du, H. Zhang and L.P. Qin, 2009. Effects of polydatin from Polygonum cuspidatum on lipid profile in hyperlipidemic rabbits. Biomed Pharmacother 63: 457-462 Yangzheng, F., Y.M. Liu, J.D. Fratkins and M.H. Le Blanc, 2005. Garpe seed extract suppresses lipid peroxidation and reduces hypoxic inshemic brain injury in neonatal rats. Brain Research Bulletin, 66; 120-127. Yiin, S.J., C.I. Chern and J.Y. Sheu, 1999. Cadmium-induced renal lipid peroxidation in rats and protection by selenium. J Toxicol Environ Health; 57: 403-413. Yiin, S.J., C.L. Chern, J.Y. Sheu and T.H. Lin, 1999. Cadmium induced lipid peroxidation in rat testes and protection by selenium. Biometals; 12: 353-359. Zahir, A.S., T. Thanhtam and K. Zaman, 1999. Oxidative stress as a mechanism of chronic cadmium-induced hepatotoxicity and renal toxicity and protection by antioxidants. Toxicol Appl Pharmacol; 154: 256-63. Zhou, C.S., H.Y. Xiang, J.B. Xiao and Q.F. Lei, 2005. Quantitative determination of resveratrol and piceidin Polygonum cuspidatum Sieb. et Zucc.by HPLC.Chin J Pharm Anal 25: 534–536.