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Evaluation of The Effects of Pomegranate Juice on Hepato-Nephrotoxicity in Male Rats Exposed to Aluminum

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ABSTRACT

We aimed to measure biochemical parameters in rat serum such as electrolyte levels, kidney and liver function test, and lipid profile to analyze the effects of pomegranate juice towards $AlCl_3$-induced hepato-nephrotoxicity. The twenty-eight wistar albino rats divided into four groups; control (Group I), pomegranate juice (4 ml/kg) (Group II), $AlCl_3$ (8.3 mg/kg) (Group III) and pomegranate juice + $AlCl_3$ (Group IV). Aluminum toxicity and the protective effect of pomegranate juice did not statistically different among groups in electrolyte levels, except for Mg and Cl ($p<0.05$). $AlCL_3$ considerably increased serum AST, ALT, BUN and CREA levels and decreased ALB and TP ($p<0.05$). Pomegranate juice administration with or before $AlCl_3$ notably restored serum biomarkers of liver and kidney function to near-normal levels. There was only a statistically significant difference in LDL and CHOL levels in lipid metabolism ($p<0.05$). The pomegranate juice reduced aluminum toxicity in terms of electrolyte levels, liver and renal function test, and lipid profile.

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Alüminyuma Maruz Kalmış Erkek Sıçanlarda Nar Suyunun Hepato-Nefrotoksisite Üzerine Etkilerinin Değerlendirilmesi.

ÖZET

Nar suyunun AlCl3 kaynaklı hepato-nefrotoksisiteye olan etkilerini analiz etmek için sıçan serumundaki elektrolit seviyeleri, böbrek ve karaciğer fonksiyon testi ve lipid profili gibi biyokimyasal parametreleri amaçlanmıştır. Yirmi sekiz wistar albino sıçan; kontrol (Grup I), nar suyu (4 ml/kg) (Grup II), $AlCl_3$ (8,3 mg/kg) (Grup III) ve nar suyu + $AlCl_3$ (Grup IV) şeklinde dört gruba ayrılmıştır. Alüminyum toksisitesi ve nar suyunun koruyucu etkisi elektrolit düzeyleri açısından Mg ve Cl hariç gruplar arasında istatistiksel olarak farklı bulunmamıştır ($p <0.05$). $AlCl_3$, serum AST, ALT, BUN ve CREA düzeylerini önemli ölçüde artırdığı ve ALB ve TP'yi düşürdüğü ($p <0.05$) görülmüştür. $AlCl_3$ ile birlikte veya öncesinde nar suyu uygulaması, karaciğer ve böbrek fonksiyonunun serum biyobelirteçlerini neredeyse normale yakın seviyelere getirdiği görülmüştür. Lipid metabolizmasında sadece LDL ve CHOL düzeylerinde istatistiksel olarak anlamlı bir fark görülmüştür ($p <0.05$). Nar suyu, elektrolit seviyeleri, karaciğer ve böbrek fonksiyon testi ve lipid profili açısından alüminyum toksisitesini azalttığı sonucuna varılmıştır.

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INTRODUCTION

The roles of aluminum, which is now no longer located in elemental shape in nature but in the form of compounds, are not clear and may be important in

nowadays. Their compounds make up 8% of the earth's crust and come third during abundance (Priest et al., 2018). In recent years, pharmaceuticals, cosmetics and foodstuffs have also diversified and Al^{+3} is among the components used in production (Exley, 2013). Aluminium is included in many vaccines, especially for pandemic or epidemic reasons, to make vaccines more stabilized and effective (Hotez et al., 2020). Lack of detailed long and short term evidence of its physiological and biochemical role on human metabolism suggests that it causes toxicity in many organs (Nayak, 2002). What's more, concerns are raised about the possible adverse health effects of Al determined even in consuming water. However, Al is thought to be non-toxic and quickly detoxified, and therefore commonly used in routine (Ghorbel et al., 2017). Although aluminum is in all our lives, it has unsuitable properties in terms of chemical properties. Al^{+3} enters the body with food, air, water and medicines. It is collected in tissues and organs in the body. Al^{+3} generally reaches different tissues via the gastrointestinal system like most other metals (Kar et al., 2019). With the widespread use of biochemical tests and biological observations, it is beneficial to detect metal toxicity before significant organ damage occurs. Determination of aluminum concentration in blood samples and interpretation of clinical findings did not provide clarity in the studies (Samir and Rashed, 2018). Therefore, liver and kidney function assessments were established to be the most effective method in this study.

Pomegranate rich nutritional content and therapeutic effectiveness have been the subject of research and are grown in many countries of the world (Vidal et al., 2003). Pomegranate is grown in different parts of Turkey. Pomegranate fruit is used by the public as fruit juice and ingestion of direct fruit. Pomegranate juice (PJ) has several flavonoids as an antioxidant and mineral materials as sodium and potassium (El Kar et al., 2011). Pomegranate has therapeutic properties on metabolism with its high polyphenol content (Matthaiou et al., 2014). The effects of PJ on systolic blood pressure and the enzymes such as angiotensin that regulate (Stowe, 2011) it prompted us to investigate electrolyte levels in aluminum-induced toxicity in this study. In a previous study, PJ consumption diminished the LDL aggregation, . It was shown that regular PJ intake can regulate cholesterol metabolism (Manthou et al., 2017). However, depending on time and concentration, the effects of PJ against aluminum toxicity on the lipid profile synthesized in the liver remain unclear.

The Liver function biomarkers are the first test used to evaluate cell damage due to metal toxicity, and it is the main organ involved in lipid synthesis and detoxification reactions. The kidney function markers are biomonitor that show whether toxic substances are eliminated or not, and kidney is the target organ in which electrolyte metabolism is regulated. Therefore, we designed to measure biochemical parameters in rat serum such as electrolyte levels, kidney and liver function test, and lipid profile to analyze the effects of PJ towards $AlCl_3$ induced hepato-nephrotoxicity in wistar albino rats.

MATERIAL and METHODS

In our research, 28 healthy Wistar Albino adult male rats used (weighing 250±30 g) provided from the Medical and Surgical Experimental Research Center, Adıyaman, Turkey. The rats were followed during the experiment in special rooms where temperature (25 ± 2 ° C), humidity (45 ± 5%) and 12 hour light / dark cycle were controlled and in clean polycarbonate cages. Research involving animals complied with all relevant national regulations and institutional policies (Adıyaman University, Animal Experiments Local Ethics Committee.) for the care and use of animals. (038/2019).

Experimental Procedure

The study was carried out using seven rats in each group, divided into four groups as follows:

- Group I (control), Saline application (1ml) was performed intraperitoneally every other day for 30 days;
- Group II (PJ), For 30 days, pomegranate juice 4 ml/kg was applied with orogastric catheter every other day;
- Group III ($AlCl_3$), Aluminum chloride ($AlCl_3.6H_2O$) was administered intraperitoneally at 8.3 mg/kg every other day for 30 days;
- Group IV ($AlCl_3$ + PJ), Aluminum was administered intraperitoneally at 8.3 mg/kg and pomegranate juice 4 ml/kg with orogastic catheter every other day for 30 days.

PJ was freshly prepared before the experiment and administered at 4 ml/kg doses (Hadipour and Mozaffari, 2010). Pomegranate fruit were obtained from Adıyaman in Turkey. Also, $AlCl_3$ was newly prepared just before the experiment and was administered to rats at a concentration of 8.3 mg/kg (Ozkaya et al., 2014) Rats were anaesthetized with an intramuscular injection ketamine+xylazine (at doses of 70 mg/kg and 10 mg/kg, respectively).

Biochemical Measurements

At the end of experiments, rats were euthanized by decapitation after 30 days from the beginning of the experiment, blood samples were collected and the serum was separated by centrifugation for 15min at 3500 rpm and stored at (80 ^{0}C). Also, the serum was taken from the blood allocated to biochemistry tubes without anticoagulant and was run on an automatic

analyzer for the measurement of biochemical parameters.

Serum electrolyte levels namely; sodium (Na),potassium (K), Chlorine (Cl), calcium (Ca), magnesium (Mg), Iron. Renal and hepatic function biomarker levels namely blood urea nitrogen (BUN), creatinine (Crea), Uric acid (UA) and liver function such as total bilirubin (T-BIL), direct bilirubin (D-BIL), total protein (TP), Albumin (Alb), aspartate transaminase (AST), alanine transaminase (ALT) and lipid profile such as triglyceride (TG), Cholesterol (Chol), low density lipoprotein (LDL) and high density lipoprotein (HDL) measurements were performed using a Roche COBAS C702 auto analyzer (Roche Diagnostics, Germany) in Kırşehir Ahi Evran University Biochemistry Laboratory. All procedures were performed according to the manufacturers' instructions.

Statistical Analyses

SPSS Version 21 (IBM Corporation, Armonk, New York, USA) and Graphpad Prism 7 (GraphPad Software, San Diego, CA, USA) program was applied for the statistical analysis and graphic of biochemical measurements. The values were shown as mean±standard deviation for results. All data were checked for the normality by using the Kolmogorov Simirnov and Shapiro-Wilk tests. Data conforming to normal distribution, one-way ANOVA and TUKEY test for multiple comparision was performed, but to data that is not compatible with normal distribution, Kruskal-Wallis and Dunn's test for multiple comparision test was performed. $P<0.05$ was considered significant statistically.

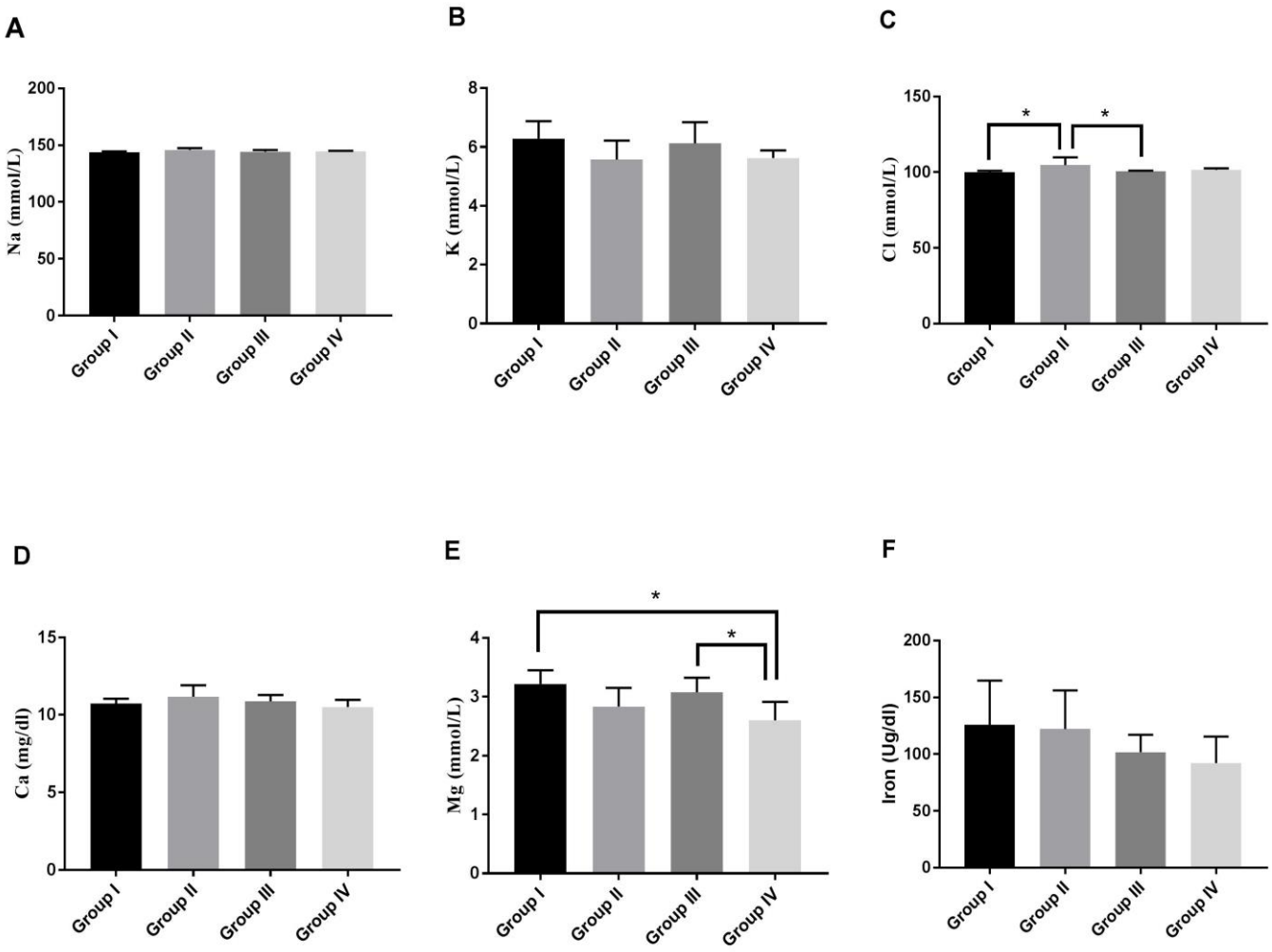

Figure1. The effects of pomegranate juice on electrolyte levels in rats exposed to aluminum-induced toxicity. A: Na (sodium), B: K (potassium), C: Cl (chloride), D: Ca (calcium), E: Mg (magnesium), F: Iron. The values are displayed as mean±SD (n=7). *: significant change at $p< 0.05$.

*Şekil 1. Alüminyum kaynaklı toksisiteye maruz kalan sıçanlarda nar suyunun elektrolit düzeyleri üzerine etkileri. A: Na (sodyum), B: K (potasyum), C: Cl (klorür), D: Ca (kalsiyum), E: Mg (magnezyum), F: Demir. Değerler ortalama±SD (n=7) olarak gösterildi. *: $p< 0.05$'te anlamlı farklılık.*

RESULTS

The Effects of Pomegranate Juice on Electrolyte Levels in Rats Exposed to Aluminum-Induced Toxicity

The electrolyte levels were measured in order to quickly assess cytosolic pressure and acid-base balance. The therapeutic and protective effects of PJ on electrolyte levels in rats exposed to aluminum-induced toxicity were shown in Fig 1. No significant differences were found in the serum levels of minerals such as Na, K, Ca and Iron in the between groups. There was a significant increase in chloride levels in the group II (104.7±5.1). Magnesium levels in group IV (2.6±0.31) were statistically lower compared to group III (3.07±0.24) and group I (3.21±0.23). We thought that although the rich mineral content of PJ did not significantly affect electrolyte levels, the chloride increase was due to $AlCl_3$.

Pomegranate Juice Ameliorates Kidney Function in Rats Exposed to Aluminum-Induced Toxicity

In the light of our findings, the comparison of serum BUN, UA and CREA levels between the groups for the evaluation of renal functions is shown in Figure 2.

The levels of BUN and CREA in the Al treated rat were significantly increased compared to the group II and group IV ($p<0.05$ and $p<0.01$, respectively). There was no statistically significant difference in UA levels between the groups. Al^{+3} toxicity affected the kidney by causing serious damage at BUN and CREA levels. This damage was observed to be reduced by PJ.

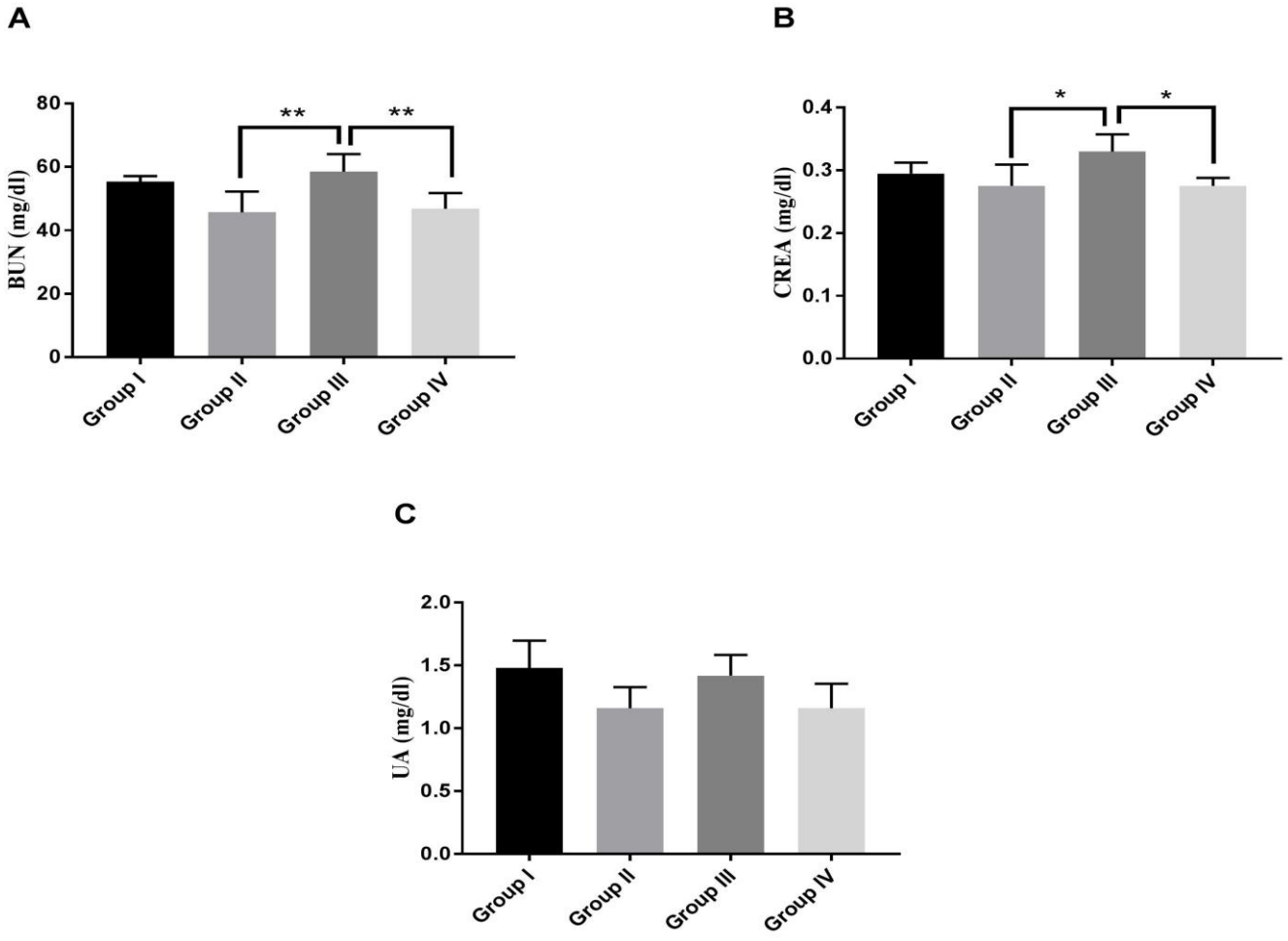

Figure 2. The effects of pomegranate juice on renal function in rats exposed to aluminum-induced toxicity. A: BUN, B: CREA, C: UA. The values are mean±SD (n=7). *,**: significant change at *p <0.05, **p <0.01

*Şekil 2. Alüminyum kaynaklı toksisiteye maruz kalan sıçanlarda nar suyunun böbrek fonksiyonu üzerindeki etkileri. A: BUN, B: CREA, C: UA. Değerler ortalama±SD'dir (n=7). *,**: *p <0.05, **p <0.01'de anlamlı farklılık.*

Pomegranate Juice Modulates Liver Function Test in Rats Exposed To Aluminum-Induced Toxicity

The ALT, AST, total and direct bilirubin levels were profound to liver function and biliary obstruction. As seen Fig. 3, There was no statistically large distinction within the bilirubin metabolism control

versus other groups. ALT and AST levels were notably elevated in the group III versus group II ($p<0.01$). Albumin and total protein levels were statistically higher in group II given PJ.

The Effects of Pomegranate Juice on Lipid Profile in Rats Exposed to Aluminum-Induced Toxicity

As observed in Figure 4, when evaluating lipid profile parameters (TRIG, CHOL, LDL and HDL), it was shown that there was no significant TRIG and HDL levels difference between groups. The CHOL (57.2±4.65) and LDL (8.01±4.06) levels were statistically lower in group II given PJ versus other groups.

DISCUSSION

Aluminum exposure on human metabolism might be from distinct sources such as ingesting water, vaccine, consuming food stuff and cosmetics (Celik et al., 2012) Aluminum chloride taken into consideration as non-hazardous metal for a protracted time, however extra interest has been centered on its negative outcomes on in vivo studies (Imam et al., 2016).

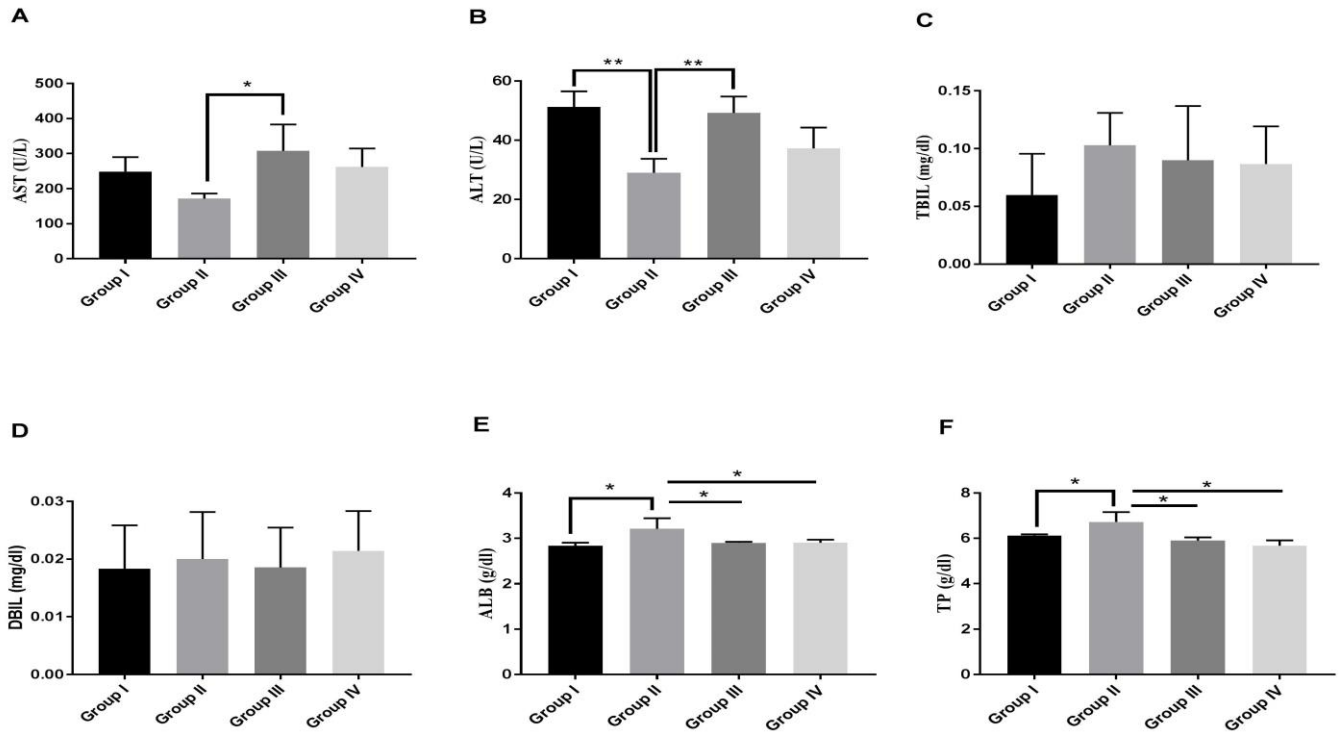

Figure 3. The effects of pomegranate juice on liver function and protein levels in rats exposed to aluminum-induced toxicity. A: AST, B: ALT, C: TBIL, D: DBIL, E: ALB, F: TP. Values are mean±SD (n=7). *: significant change at *p <0.05, **p <0.01

*Şekil 3. Alüminyum kaynaklı toksisiteye maruz kalan sıçanlarda nar suyunun karaciğer fonksiyonu ve protein düzeyleri üzerine etkileri. A: AST, B: ALT, C: TBIL, D: DBIL, E: ALB, F: TP. Değerler ortalama±SD'dir (n=7). *,**: *p <0.05, **p <0.01'de anlamlı farklılık.*

Regulation of extracellular fluid volume, provision of appropriate acid-base balance, serum osmolality levels are carried out by electrolyte metabolism. In the previous study, application of PJ did not cause any change in serum electrolyte levels between the groups after 7, 15, and forty-five days (Ilbey et al., 2009). The PJ decreased electrolyte levels such as K, Ca and P and increased Na levels in rabbits induced by nicotine toxicity (Aboulgasem and Azab, 2015). Hozayen et al. reported that rosemary extract with a significant content, such as pomegranate, caused a significant increase in serum sodium and a decrease in potassium levels in aspartame-induced rats (Hozayen et al., 2014). Abd Elmonem (2014) observed that pomegranate supplementation regulates Ca electrolyte levels . Similarly, PJ provided an increase in Ca levels on bone metabolism (Parvin et al., 2014). In the aluminum-induced toxicity study, Na+/ K+ ATPase and Mg^{2+} ATPase activities were significantly decreased, and intracellular and extracellular ion exchange damage occurred (Sumathi et al., 2011). According to the data we observed, the aluminum toxicity did not significantly affect the electrolyte levels, and although PJ has rich mineral content, it provided stability in electrolyte levels, unlike the mentioned studies.

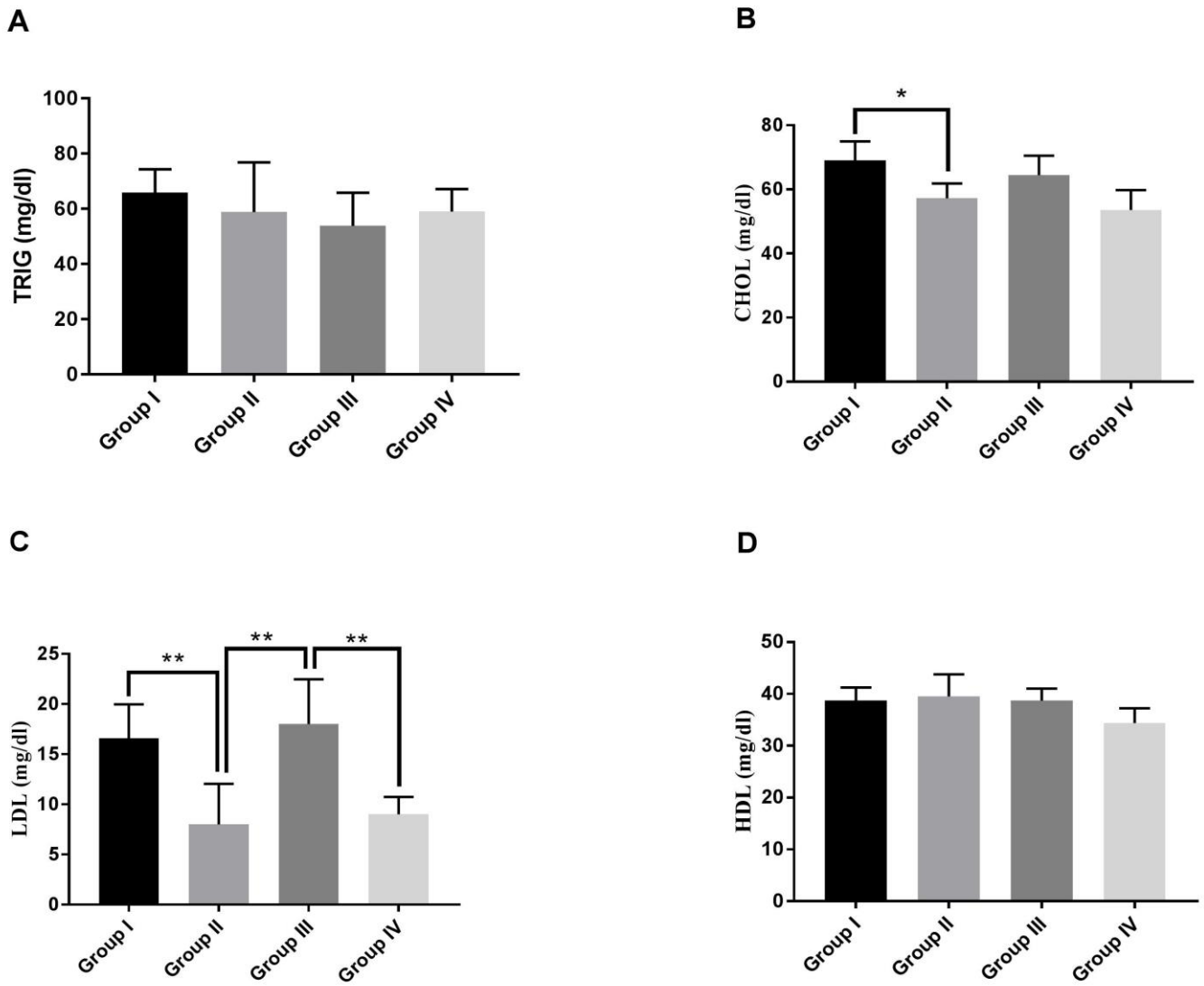

*Figure 4. The effects of pomegranate juice on lipid profile in rats exposed to aluminum-induced toxicity. A: TRIG, B: CHOL, C: LDL, D: HDL. The values are mean±SD (n=7). *,**: significant change at *p <0.05, **p <0.01*

Şekil 4. Alüminyum kaynaklı toksisiteye maruz kalan sıçanlarda nar suyunun lipid profili üzerindeki etkileri. A: TRIG, B: CHOL, C: LDL, D: HDL. Değerler ortalama±SD'dir (n=7). *,**: *p <0.05, **p <0.01'de anlamlı farklılık.

The liver is the essential organ in which chemical, xenobiotics and metals are detoxified further to the synthesis reactions critical for metabolism, even as the kidney presents the removal and elimination of those poisonous materials in reference to the liver. In the light of this information, $AlCl_3$ exposure caused changes in our biochemical results, which are specific indicators of liver function. In Balgoon's study (2019), $AlCl_3$ administration substantially increased serum ALT, AST, ALP, and bilirubin and reduced albumin and total protein levels. In previous studies, high doses of $AlCl_3$ exposure caused liver damage, impaired metabolic functions and altered protein synthesis. This was in agreement with the our findings (Imam et al., 2016; Niedworok and Fijałkowski, 2004; Azza et al., 2017; Al-Hashem, 2009; Parasuraman et al., 2020). The BUN, CREA and UA levels use to acute and chronic renal damage and test the renal functions. The changed levels of these biomarkers representing that the animals applied with AlCl3 have the risk of kidney injury (Al Dera, 2016). The nephrotoxicity induced by $AlCl_3$ is may be due to the accumulation of Al in the kidney, ultimately resulting in renal failure.

The role of PJ on biochemical parameters against long-term $AlCl_3$-induced changes in both liver and kidney was also evaluated. In the neurotoxicity study, the protective application of pomegranate caused a significant decrease in BUN, CREA and UA levels (Moneim and El-Khadragy, 2013). Derik pomegranate

juice improved function tests such as ALT, AST, ALB and bilirubin, which increased in liver damage (Pirinççioğlu et al., 2014). It was stated that pomegranate juice reduces the hepato and renal function parameters caused by metal toxicity to normal levels against not only aluminum but also other metal toxicities (Hassanen et al., 2019). In another study, PJ altered BUN and CREA levels. It did not change the ALT and AST values. These contradictory results showed that PJ could affect liver and kidney function tests in the study without any presence of toxicity (Moneim et al., 2011).

In our toxicity study, we thought that lipid synthesis would be affected as a result of liver damage and that pomegranate could improve lipid levels due to its antilipidemic effects. In a previous study, aluminum exposure did not show a important change on the lipid profile (Parasuraman et al., 2020). On the other hand, Ghorbel et al. Stated that the abnormal results in lipase enzyme activity were caused by the application of $AlCl_3$ and therefore cholesterol levels increased (Ghorbel et al., 2017). $AlCl_3$ induced toxicity increased CHOL and TRIG levels. Thus, lipid metabolism in the liver was disrupted and it was observed that PJ managed to reduce the $AlCl_3$-induced increase in lipid profile (Al-Hashem, 2009). In our findings, there was only a statistically significant difference in LDL and CHOL levels. Antilipidemic properties of pomegranate were demonstrated in in vivo studies. For example, consumption of PJ concentrate for eight weeks extensively decreased CHOL and LDL levels in diabetic patients with hyperlipidemia (Esmaillzadeh et al., 2006; Sumner et al., 2005). A decrease in CHOL, TRIG and LDL serum concentrations of PJ given to rabbits was observed, while HDL levels increased (Aboulgasem and Azab, 2015).

CONCLUSION

Our findings verifies long-term aluminium exposure had toxic and harmful effects on electrolytes, minerals, lipid profile, liver and renal functions in the rat serum. The application of pomegranate juice confirmed a remarkable improvement in both these abnormalities in hepato-nephrotoxicity caused by aluminium and a protective effect. Therefore, we revealed that Pomegranate Juice could be a appropriate healing agent, especially in aluminium exposure from the environment and daily life activities.

Researchers Contribution Rate Declaration Summary

HÇ and ÖA planned and designed the research. ÇÇ, ÖA, FK and GK provided help in the experiment. All authors discussed the results and contributed to the final manuscript.

Conflicts of Interest Statement

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

Abd Elmonem HA 2014. Assessment the effect of pomegranate molasses against diazinon toxicity in male rats. IOSR Journal of Environmental Science, Toxicology and Food Technology 8(2): 135-141.

Aboulgasem GJ, Azab AE 2015. The potential protective effects of pomegranate juice against (S)-(-)-1-methyl-2-(3-pyridyl) pyrrolidine (+)-bitartrate salt induced serum biochemical changes in rabbits. International Journal of Science and Research 4(11): 360-371.

Al Dera HS 2016. Protective effect of resveratrol against aluminum chloride induced nephrotoxicity in rats. Saudi Medical Journal 37(4): 369–378

Al-Hashem F 2009. Camel's milk protects against aluminum chloride-induced toxicity in the liver and kidney ofwhite albino rats. American Journal of Biochemistry and Biotechnology 5(3): 98–109.

Azza AA, Toqa ME, Abeer IAEF, Mona MK, Karema AE 2017. Comparative Study On The Influence Of Different Drugs And Nutrients Against Aluminium- Induced Nephrotoxicity And Hepatotoxicity In Rats. International Journal of Current Research 9(10): 58684-700

Balgoon MJ 2019. Assessment of the protective effect of Lepidium sativum against aluminum-induced liver and kidney effects in albino rat. BioMed Research International 4516730.

Celik H, Celik N, Kocyigit A, Dikilitas M 2012. The relationship between plasma aluminum content, lymphocyte DNA damage, and oxidative status in persons using aluminium containers and utensils daily. Clinical Biochemistry 45(18): 1629–1633.

El Kar C, Ferchichi A, Attia F, Bouajila J 2011. Pomegranate (Punica granatum) Juices: Chemical composition, micronutrient cations, and antioxidant capacity. J Food Sci 76(6): C795-800.

Esmaillzadeh A, Tahbaz F, Gaieni I, Alavi-Majd H, Azadbakht L 2006. Cholesterol-lowering effect of concentrated pomegranate juice consumption in type II diabetic patients with hyperlipidemia. International Journal for Vitamin and Nutrition Research, 76: 147-151.

Exley C 2013. Human exposure to aluminium. Environmental Science: Processes & Impacts 15: 1807–1816.

Ghorbel I, Elwej A, Chaabane M, Jamoussi, K, Zeghal N 2017. Protective effect of selenium against aluminium chloride induced cardiotoxicity in rats. Pharmaceutical and Biomedical Research 3(2): 19–25.

Hadipour JM, Mozaffari KR 2010. Chondroprotective effects of pomegranate juice on monoiodoacetate-induced osteoarthritis of the knee joint of mice. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives 24(2): 182-185.

Hassanen EI, Tohamy AF, Issa MY, Ibrahim MA, Farroh KY, Hassan AM 2019. Pomegranate Juice Diminishes The Mitochondria-Dependent Cell Death And NF-kB Signaling Pathway Induced By Copper Oxide Nanoparticles On Liver And Kidneys of Rats. International Journal of Nanomedicine 14: 8905.

Hotez PJ, Corry DB, Strych U, Bottazzi ME 2020. COVID-19 vaccines: neutralizing antibodies and the alum advantage. Nature Reviews Immunology 20: 399-400.

Hozayen WG, Soliman HAE, Desouky EM 2014. Potential protective effects of rosemary extract, against aspartame toxicity in male rats. Journal of International Academic Research for Multidisciplinary. 2(6): 111-125.

Ilbey YO, Ozbek E, Simsek A, Cekmen M, Somay A, Tasci AI 2009. Effects of pomegranate juice on hyperoxaluria-induced oxidative stress in the rat kidneys. Renal failure 31(6): 522-531.

Imam TS, Khalifa HA, Hussein MM, Ali HA 2016. Aluminum–induced oxidative stress and hepato-renal impairment in male albino rats: possible protective trial with naringenin, Life Science Journal 13(1): 93-104.

Kar F, Hacioglu C, Uslu S, Kanbak G 2019. Curcumin Acts as Post-protective Effects on Rat Hippocampal Synaptosomes in a Neuronal Model of Aluminum-Induced Toxicity. Neurochemical research 44(8): 2020-2029.

Manthou E, Georgakouli K, Deli CK, Sotiropoulos A, Fatouros IG, Kouretas D, Jamurtas AZ 2017. Effect of pomegranate juice consumption on biochemical parameters and complete blood count. Experimental and therapeutic medicine 14(2): 1756-1762.

Matthaiou CM, Goutzourelas N, Stagos D, Sarafoglou E, Jamurtas A, Koulocheri SD, Kouretas, D 2014. Pomegranate juice consumption increases GSH levels and reduces lipid and protein oxidation in human blood. Food and Chemical Toxicology 73: 1-6.

Moneim AEA, Dkhil MA, Al-Quraishy S 2011. Studies on the effect of pomegranate (Punica granatum) juice and peel on liver and kidney in adult male rats. Journal of Medicinal Plants Research, 5(20): 5083-5088.

Moneim AEA, El-Khadragy MF 2013. The potential effects of pomegranate (Punica granatum) juice on carbon tetrachloride-induced nephrotoxicity in rats. Journal of physiology and biochemistry, 69(3): 359-370.

Nayak P 2002. Aluminum: impacts & diseases. Environmental Research 89: 101–115.

Niedworok J, Fijałkowski P 2004. Effect of Long-Term Aluminium Chloride Intoxication on Selected Biochemical Parameters and Oxidative--Antioxidative Balance in Experimental Animals. Polish Journal of Environmental Studies 13(1): 41-3.

Ozkaya A, Celik S, Yuce A, Şahin Z, Yilmaz Ö 2010. The effects of ellagic acid on some biochemical parameters in the liver of rats against oxidative stress induced by aluminum. Kafkas Üniversitesi Veteriner Fakültesi Dergisi 16 (2): 263-268.

Parasuraman S, Qin BNY, Hui LC, Benk JYK 2020. Effect of epigallocatechin gallate on aluminum chloride-induced changes in behavior, biochemical parameters, and spermatogenesis of Sprague-Dawley rats. Beni-Suef University Journal of Basic and Applied Sciences 9(1): 1-10.

Parvin F, Monsefi M, Talaei KT 2014. Effect of Pomegranate Juice on Bone Calcium Content and Body Weight of Adult Mice. Zahedan Journal of Research in Medical Sciences 16(3): 64-66.

Pirinççioğlu M, Kızıl G, Kızıl M, Kanay Z, Ketani A 2014. The protective role of pomegranate juice against carbon tetrachloride–induced oxidative stress in rats. Toxicology and industrial health 30(10): 910-918.

Priest ND, Talbot RJ, Newton D, Day JP, King SJ, Fifield LK 1998. Uptake by man of aluminium in a public water supply. Hum Exp Toxicol 17: 296–301.

Samir AM, Rashed LA 2018. Effects of occupational exposure to aluminium on some oxidative stress and DNA damage parameters. Human & experimental toxicology 37(9): 901-908.

Stowe CB 2011. The effects of pomegranate juice consumption on blood pressure and cardiovascular health. Complementary Therapies in Clinical Practice 17(2): 113-5.

Sumathi T, Shobana C, Kumari BR, Nandhini, DN 2011. Protective role of Cynodon dactylon in ameliorating the aluminium-induced neurotoxicity in rat brain regions. Biological trace element research 144(1-3): 843-853.

Sumner MD, Elliott-Eller M, Weidner G, Daubenmier JJ, Chew MH, Marlin R, Ornish D 2005. Effects of pomegranate juice consumption on myocardial perfusion in patients with coronary heart disease. American Journal of Cardiology, 96: 810-814.

Vidal A, Fallarero A, Peña BR, Medina ME, Gra B, Rivera F, Vuorela PM 2003. Studies on the toxicity of Punica granatum L. (Punicaceae) whole fruit extracts. Journal of Ethnopharmacology 89: 295 300.