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Araştırma Makalesi– Research Paper

PARTIAL PROTECTIVE EFFECTS OF *L. PLANTARUM* ADMINISTRATION ON SOME BLOOD PARAMETERS AND ANAE-POSITIVE LYMPHOCYTE RATIOS IN FEMALE RATS EXPOSED TO CADMIUM (Cd)

KADMİYUMA (Cd) MARUZ KALAN DIŞI SIÇANLARDA *L. PLANTARUM* UYGULAMASININ BAZI KAN PARAMETRELERİ VE ANAE-POZİTİF LENFOSİT ORANLARI ÜZERİNE KISMİ KORUYUCU ETKİLERİ

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Özet

Bu çalışmada, kronik olarak kadmiyuma (Cd) maruz kalan dişi sıçanlarda oral *L.plantarum* uygulamasının bazı kan parametreleri ile alfa-naftil asetat esteraz (ANAE)-pozitif lenfosit oranları üzerindeki etkilerini araştırmayı amaçladık. Bu araştırmanın yapılabilmesi için ratlar kontrol (C, n = 8), kadmiyum (Cd, n = 8), *L.plantarum* (n = 8) ve Cd+ *L.plantarum* (n = 8) olmak üzere dört eşit gruba ayrıldı. Cd (2.04 mg/mL) oral olarak Cd ve Cd+ *L.plantarum* gruplarına 28 gün uygulandı. Ayrıca *L.plantarum* ve Cd+ *L.plantarum* gruplarına aynı anda aktif-canlı *L.plantarum* (yaklaşık 108 - 109 cfu/mL) oral olarak uygulandı. C grubu hayvanlara çalışma süresince sadece taze su ve standart rat yemi verildi. Uygulamaların ardından hayvanlar dekapite edilerek bazı kan parametreleri (WBC ve farklı alt tipleri, RBC, HCT, MCV, MCH, MCHC ve PLT) ve ayrıca ANAE-pozitif lenfosit oranlarının değerlendirilmesi için kan örnekleri alındı. WBC sayıları diğer deney gruplarına göre Cd grubunda en yüksek olarak belirlendi ($p < 0.05$). Öte yandan, *L.plantarum* uygulaması Cd+ *L.plantarum* grubu hayvanlarda WBC sayılarında Cd grubuna göre önemli bir iyileşmeye neden oldu ($p < 0.05$). NEU sayıları en yüksek Cd grubunda saptanmakla birlikte, Cd+ *L.plantarum* grubunda oral *L.plantarum* uygulamasına bağlı olarak bu sayılarda düşüş gözlemlendi ($p < 0.05$). Çalışmada Cd uygulamasına bağlı olarak artan PLT değerleri, Cd+ *L.plantarum* grubunda Cd grubuna oranla *L.plantarum* diyeti kullanılarak düzeltildi ($p < 0.05$). Sonuç olarak *L.plantarum* uygulaması, dişi sıçanların kan parametrelerini Cd'nin zararlı etkilerinden kısmen korumuştur.

Anahtar Kelimeler: *Lactobacillus plantarum*, kadmiyum, dişi rat, hematoloji, ANAE pozitif

Abstract

We aimed to research the influences of oral *L.plantarum* administration on some blood parameters and alpha-naphthyl acetate esterase (ANAE)-positive lymphocyte ratios in female rats exposed chronically to Cd. In order to perform this investigation, rats were separated into four equal groups as control (C, n = 8), cadmium (Cd, n = 8), *L.plantarum* (n = 8), and Cd+ *L.plantarum* (n = 8). Cd (2.04 mg / mL) was orally applicated to Cd and Cd+ *L.plantarum* groups for 28 days. In addition, active-live *L.plantarum* (approximately 108 - 109 cfu / mL) was applicated orally to *L.plantarum* and Cd+ *L.plantarum* groups at the same time. C group animals received only fresh water and standard rat food during the study. After the applications, animals were decapitated and blood samples were collected for evaluating of some blood parameters (WBC and its different sub-types, RBC, HCT, MCV, MCH, MCHC, and PLT) and also ANAE-positive lymphocyte ratios. WBC counts were determined the highest in the Cd group compared to other experimental groups ($p < 0.05$). On the other hand, LP administration caused a significant amelioration in WBC counts of Cd+ *L.plantarum* group animals when compared to Cd group ($p < 0.05$). Although NEU counts were detected the highest in the Cd group, these counts decreased due to oral *L.plantarum* administration in Cd+ *L.plantarum* group ($p < 0.05$). Increased PLT values due to CD administration were fixed by using LP diet in the Cd+ *L.plantarum* group compared to the Cd group in the study ($p < 0.05$). In conclusion, *L.plantarum* partially affects female rats' blood parameters from the harmful effects of Cd.

Keywords: *Lactobacillus plantarum*, cadmium, female rats, hematology, ANAE positivity

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1. INTRODUCTION

Cadmium (Cd) is a naturally occurring and well-known toxic heavy metal. In addition, it is generally obtained from zinc (Zn) and lead (Pb) byproducts. World Health Organization (WHO) have been listed the main sources of Cd as manufacturing batteries, pigments, corrosion-protection coating, platings, solar cells, plastic stabilizers, neutron absorbers, and cosmetics (WHO, 2010, pp. 3-6). It could get into the water sources, be taken up by plants, and released into the atmosphere as gases, or adsorbed by soil components. Due to above mentioned harmful effects, it causes environmental pollution around the World. (Satarug et al., 2003, pp. 65-83; Kisadere et al., 2001, pp.1-9).

Cd is detected as a carcinogen (class-one) by the International Agency for Research on Cancer (IARC) (IARC, 1993, pp.58). The human and animals generally exposure the Cd through the oral route. Also, inhalation or skin contact can be given as examples of Cd absorbsion routes (Satarug et al., 2010, pp. 182-190). Cd-contaminated water and foods, cigarettes, and spending a long time in metal-processing units significantly increases expose to Cd (IARC, 1993, pp.58; Kisadere et al., 2020, pp. 262-266).

As it is well-known, acute or chronic Cd accumulation causes epigenetic changes in DNA expression. Besides, it induces inhibition of cell metabolism in living-beings. Oxidative stress (OS) and increased lipid peroxidation (LPO) are main results of the Cd exposure in the body (Kisadere et al., 2019, pp.10; Kisadere et al., 2020, pp. 262-266). Depend on the above mentioned detrimental effects of Cd on different organisms, Cd exposure can cause damage in many vital organs including the kidney, liver, lung, brain, bone, duodenum, placenta, and blood (Bernard, 2008, pp. 557-564, WHO, 2010, pp. 3-6).

Researchers, studying on this topic, have reported that the deleterious effects of Cd on different tissues can be ameliorated by using of some antioxidants and chelating agents. In addition, they have advised probiotics (including Lactobacillus / Bifidobacterium strains), melatonin, chitosan, selenium (Se), ß-carotene, chitosan oligosaccharides, quercetin for elimination of Cd toxicity (Zhai et al., 2014, pp. 4063-4071; Donmez et al., 2019, pp. 381-386; Kisadere et al., 2019, pp. 66-70; Kisadere et al., 2021, pp. 1-9; Kisadere et al., 2022, pp. 3). Interestingly, recent studies showed that some lactic acid bacteria (LAB) strains have features the bind and remove Cd *in vivo*/*in vitro* conditions. *L. plantarum*, is a prominent well-known lactic acid bacterium, which exists as part of the microbiota of many organic materials including meat, fish, sauerkraut, pickles, Korean kimchi, Nigerian Ogi, sourdough, and pickled olives. At the same time, it also naturally presents in human and also animal's gastrointestinal tracts and saliva (Zhai et al., 2014, pp. 4063-4071). Its anti-oxidant, anti-fungal, immuno-modulator and also metal binding capacity were also informed in previous studies (Ojekunye et al., 2017, pp. 379-385; Liu et al., 2020, pp. 211; Banwo et al., 2021, pp. 779-791).

Although the liver, kidney, lung, and testis are the most affected organs by Cd toxicity, its deleterious effects have been defined in the blood and the hematopoietic system in recent years (Donmez et al., 2019, pp. 381-386; Kisadere et al., 2022, pp. 3; Kisadere et al., 2022, pp. 87-95). The count of white blood cells (WBC), the count and also ratios of its different sub-types such as lymphocytes (LYM), monocytes (MON), neutrophils (NEU), the count of red blood cells (RBC), hematocrit value (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and

the counts of platelets (PLT) were very important markers for evaluating the health status of living beings (Donmez et al., 2016, pp. 8-12; Kisadere et al., 2017, pp. 165-168).

ANAE (alpha-naphthyl acetate esterase) is a lymphocyte lysosomal enzyme. It has been shown in mature and also in immuno-competent T lymphocyte activity in the blood. It is specific for mature T lymphocytes, but not for B lymphocytes (Donmez and Sur, 2008, pp. 56-60). Donmez et al. (2019) reported that acute Cd toxicity caused some detrimental changes in some hematological characteristics and the percentage of ANAE-positive lymphocytes in male rats. Kisadere et al. (2022, pp:87-95) also reported that the percentage of ANAE-positive lymphocytes in peripheral blood altered remarkably in the Cd received male animals.

For this purpose, we aimed to investigate the potential protective effects of oral *L. plantarum* administration on some blood parameters and ANAE-positive lymphocyte ratios in female rats exposed to cadmium.

2. MATERIAL AND METHODS

2.1. Ethics

All procedures about the present study were approved by Balıkesir University/Ethics Committee of Experimental Animals Center (Approval no: 2021/3-5).

2.2. Animals and experimental design

Six - seven weeks aged thirty-two female Wistar rats (average weight of 100 - 120 g) were taken from Balıkesir University Experimental Animal Research Center for using in the present study. Then, rats were divided into four groups including control (C; n= 8), cadmium (Cd; n= 8), *L. plantarum* (n= 8), and Cd+ *L. plantarum* (n= 8). The animals were separated into four different equal groups, however, they were held in individual rat cages. After the adaptation period (two weeks), standard rat pellets and fresh water were given to C group animals *ad libitum* during the study. Besides, at a dose of 2.04 mg/mL Cd ($CdCl_2$) was dissolved in fresh drinking water. After, prepared Cd-water solution was applicated to Cd and Cd+ *L. plantarum* group animals for 28 days (Banwo et al., 2021, pp. 779-791). In addition, active - live *L. plantarum* (approximately 10^8 - 10^9 cfu / ml), in skim milk powder medium, was applicated orally to *L. plantarum* and Cd+ *L. plantarum* groups for 28 days (Banwo et al., 2021, pp. 779-791). All administrations were done in an end-of-day controlled manner.

After the 28 days, rats were terminated with cervical dislocation technique under general anesthesia [ketamine/xylazine (0.1 ml / 100 mg / b.w)]. Due to performing analysis in the plasma samples, blood samples were collected from the heart by cardiac puncture to anti-coagulant tubes.

2.3. Preparation of *L. plantarum* diet

In our study, *L. plantarum* was grown in a medium containing 10 ml of De Man Rogosa and Sharpe Broth (MRS Broth) at 30 °C for 18 - 20 hours. After the incubation period, MRS Broths that were containing approximately 10^9 - 10^{10} cfu /mL bacterial culture were centrifuged at 5000 rpm in a cooled centrifuge for 5 min. After, the obtained supernatant was discarded. Then, the remaining bacterial pellets were dissolved in 10 mL skim milk powder (Merck-115363), and 100 ml was completed. Then, it was applicated to the experimental animals (Fazeli et al., 2010, pp. 22; Banwo et al., 2021, pp. 779-791).

2.4. Determination of the blood parameters

The count of WBC, the count and also ratios of its different sub-types such as LYM, MON, NEU, the count of RBC, HCT, MCV, MCH, MCHC, and the counts of PLT were detected from the plasma samples by using automatic blood analyzer (Abacus Junior Vet-5, USA).

2.5. Determination of the ANAE-positive lymphocyte ratios

ANAE demonstration was carried out by using the technique of Donmez and Sur (2008) with minor changes. Air dried blood smears were fixed in phosphate buffered glutaraldehyde-acetone solution (pH 4.8) at -10°C for 3 min. The cells that have lymphocyte morphology and the different counts (1-3) of reddish-brown granules were classified as ANAE-positive (Fig. 1) under the light microscope (Leica DM 2500, Wetzlar, Germany) by counting 200 lymphocytes.

2.6. Statistical analysis

The SPSS 25.0 program (SPSS, Inc., Chicago, IL) was used for all of the statistical analyses. Parameters were analyzed by using the analyses of variance (ANOVA) followed by Duncan's test. The obtained data were considered important at $p \leq 0.05$, statistically.

3. RESULTS

3.1.Blood parameters

In our study, WBC counts were determined the highest in the Cd group compared to other experimental groups ($p < 0.05$). On the other hand, *L. plantarum* administration caused a significant amelioration in WBC counts of Cd+*L. plantarum* group animals when compared to CD group ($p < 0.05$). In the present study, LYM counts were higher in the Cd group than the C group, statistically ($p < 0.05$). Although NEU counts were detected the highest in the Cd group, these counts decreased due to oral *L. plantarum* administration in Cd+*L. plantarum* group ($p < 0.05$). Besides, we did not define any changes in MON counts and also ratios (%) of LYM, NEU, and MON in the study ($p > 0.05$). On the other hand, Cd administration led to an increase of PLT values in the Cd group animals compared to the C group in our study ($p < 0.05$). In the contrary, increased PLT values due to Cd administration were fixed by using LP diet in Cd+*L. plantarum* group compared to Cd group in the study ($p < 0.05$). We could not determine any alterations in the other blood parameters (RBC, HGB, HCT, MCV, MCH, and MCHC) among the experimental groups ($p > 0.05$).

Table-1. Some blood parameters and ANAE positive lymphocyte ratios of the experimental groups

Parameters	Groups	*n*	Mean ± SE
WBC (109/L)	**Cd+*L. plantarum***	8	3.59±0.70b
	Cd	8	5.67±0.75a
	C	8	2.76±0.51b
	L. plantarum	8	3.50±0.51b
LYM (#)	**Cd+*L. plantarum***	8	2.57±0.61ab
	Cd	8	3.82±0.50a
	C	8	2.06±0.41b
	L. plantarum	8	2.45±0.33ab
MON (#)	**Cd+*L. plantarum***	8	0.09±0.03
	Cd	8	0.26±0.11
	C	8	0.13±0.02
	L. plantarum	8	0.36±0.12
NEU (#)	**Cd+*L. plantarum***	8	0.88±0.14b
	Cd	8	1.56±0.24a
	C	8	0.88±0.13b
	L. plantarum	8	0.60±0.10b
LYM (%)	**Cd+*L. plantarum***	8	73.07±2.82
	Cd	8	68.36±2.62
	C	8	67.88±4.69
	L. plantarum	8	70.61±2.19
MON (%)	**Cd+*L. plantarum***	8	3.25±0.83
	Cd	8	4.68±1.43
	C	8	4.36±0.77
	L. plantarum	8	4.11±0.96
NEU (%)	**Cd+*L. plantarum***	8	23,68±2.39
	Cd	8	27.58±2.69
	C	8	27.72±4.43
	L. plantarum	8	25.26±1.92
RBC (1012/L)	**Cd+*L. plantarum***	8	8.69±0.32
	Cd	8	8.66±0.23
	C	8	8.74±0.38
	L. plantarum	8	9.65±1.18
HGB (g/dl)	**Cd+*L. plantarum***	8	13.55±0.67
	Cd	8	12.90±0.41
	C	8	11.94±0.97
	L. plantarum	8	12.92±0.43
HCT (%)	**Cd+*L. plantarum***	8	47.19±1.87
	Cd	8	45.83±1.38
	C	8	47.02±2.02
	L. plantarum	8	49.63±5.65
MCV (fL)	**Cd+*L. plantarum***	8	53.25±0.75
	Cd	8	52.50±0.82
	C	8	53.88±0.58
	L. plantarum	8	53.63±0.42
MCH (pg)	**Cd+*L. plantarum***	8	15.52±0.42
	Cd	8	14.87±0.09
	C	8	13.81±0.96
	L. plantarum	8	14.37±1.27

MCHC (g/dl)	**Cd+*L. plantarum***	8	28.60±0.59
	Cd	8	24.87±3.14
	C	8	25.60±1.79
	L. plantarum	8	27.73±2.32
PLT (109 /L)	**Cd+*L. plantarum***	8	731.50±60.49b
	Cd	8	1122.87±147.28a
	C	8	584.75±94.34b
	L. plantarum	8	564.37±52.24b
ANAE positive lymphocyte (%)	**Cd+*L. plantarum***	8	48. 50 ± 1.00
	Cd	8	48.10 ± 1.37
	C	8	49.14 ± 0.34
	L. plantarum	8	49.12 ± 0.36

[a,b,c]$P < 0.05$ considered statistically significant in the same column.

3.2.ANAE-positive lymphocyte ratios

We could not define any changes regarding to ANAE positive lymphocyte ratios among the experimental groups in the present study ($p > 0.05$).

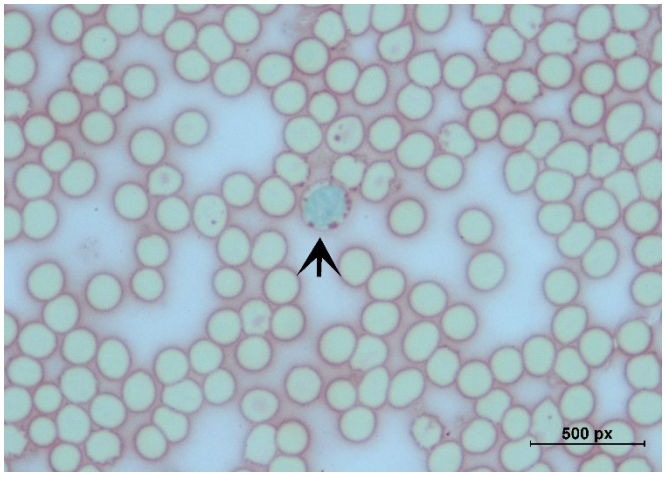

Fig-1. ANAE staining in animal's peripheral blood in the control group (C). Arrowhead: ANAE positive lymphocyte.

4. DISCUSSION

In the present study, WBC counts were higher in the only Cd (2.04 mg / mL, p.o, for 4 weeks) received animal group (female) than another groups. Kisadere et al. (2022) reported that Cd (2 mg/kg/day, p.o, for 4 weeks) administration significantly increased the WBC counts in the Cd group animals (male) when compared to the C group. Donmez et al. (2019) also found same results about the WBC counts after Cd administration (4 mg/kg/day, i.p, for 3 days) in male rats. On the other hand, oral *L. plantarum* administration (at a level of approximately 10^8 - 10^9 cfu / ml in skim milk powder medium) led to decrease of WBC counts in Cd+*L. plantarum* group compared to Cd group in the present study. Singh et al. (2019) reported that either *L. plantarum* or *L. casei* supplemention to the normal rat diet for four-weeks increased to the WBC counts in Charles Foster male rats. Besides, it was informed that supplementation of Lactobacillus sporogenes along with arsenic (As) resulted in improvement of WBC counts compared to toxic group (Bora et al., 2022, pp. 4744-4749). Also, Ghazanfarpour et al. (2019)

reported that L. fermentum may inhibit the harmful effects of lead (Pb) on rat's WBC counts. On the other hand, LYM and NEU counts of rats increased, however MON counts were not affected from Cd administrations in our study. Kisadere et al. (2021) suggested that LYM counts decreased, but NEU and MON counts were not affected from the Cd administrations in rats. In our study, NEU counts decreased due to oral *L. plantarum* administration in Cd+*L. plantarum* group compared to C. It can be expressed as a partial effect of *L. plantarum*. Besides, we did not detect any alterations in ratios (%) of LYM, NEU, and MON among the groups in the present study. Kisadere at al. (2022) also informed same results about the LYM, NEU, and MON ratios in male rats exposed to Cd. Bora et al. (2022) suggested that LS administration improved the LYM, NEU, and MON ratios in As-induced Wistar male rats. It may be due to application route, dose, microorganism types or chemicals.

In the present study, RBC, HGB, and HCT values of the all experimental group animals (females) were not affected from the chronic oral Cd (2.04 mg / mL, p.o, for 4 weeks) administrations. Donmez et al. (2019) reported that injection of CdCl (24 mg/kg/day, for 3 days, s.c) decreased the RBC, HGB, and HCT values in male rats. Kisadere et al. (2022) also suggested that administration of Cd (2mg/kg/day, for 4 weeks, p.o) did not lead to significant change in RBC, HGB, and HCT values in Wistar male rats. It may be occurred due to different dose or application methods. Besides, oral *L.plantarum* administration did not cause any alteration above mentioned parameters (RBC, HGB, and HCT) among the groups in our study. On the other hand, Sayed et al. (2020) reported that dietary administration of *L. acidophilus* (0.009 x10^6CFU/g of rat b.w for 30 days, p.o) improved the HGB and RBC values in Carbon Tetrachloride (Ct) exposed rats. Bora et al. (2022) suggested that supplemention of Lactobacillus sporogenes to diet improved the RBC and HGB values in arsenic (As) exposed male Wistar rats. Similarly, Ghazanfarpour et al. (2019) informed that oral Lactobacillus fermentum (1.5 ×108 cfu/mL for 8 weeks) administration led to recovery of Pb-induced changes in RBC, HGB, and HCT values in rats. It can be observed due to use of different dosage regimes, types of microorganisms or toxic metals. MCV, MCH, and MCHC values of the female rats also were not affected neither Cd (2.04 mg / mL, p.o, for 4 weeks) nor *L. plantarum* (at a level of approximately 108 - 109 cfu / mL in skim milk powder medium) applications in our study. Kisadere et al. (2022) reported that Cd administration (2 mg/kg/day, for 4 weeks, p.o) did not effect the MCH values, however decreased the MCV and MCHC values in male Wistar rats. Andjelkovic et al. (2019) offered that Cd administration caused significant changes in MCH values of the rats in both Cd-treated groups (15 mg Cd/kg and 30 mg Cd/kg/b.w, p.o) compared C group. In addition, they observed that neither MCV nor MCHC was affected by the Cd treatment. Differences may be occurred due to different dose, sex, and application routes. As above mentioned, oral *L. plantarum* administration did not effect the MCV, MCH, and MCHC values of experimental groups in the present study. Bora et al. (2022) suggested that supplemention of LS to diet improved the MCV, MCH, and MCHC values in rats exposed to As. Ghazanfarpour et al. (2019) also reported that oral LF administration ameliorated the MCV and MCH values in male rats exposed to Pb. Singh et al. (2019) informed that oral administration of either *L. plantarum* or *L. casei* (LC) milk powders improved the MCV, MCH, and MCHC values in male Charles Foster rats. It can be obtained due to use of different types of microorganisms. In our study, Cd administration caused an increase of PLT values in rats. Conversely, Donmez et al. (2019) found decreased PLT values in rats exposed to acute Cd-toxicity. Interestingly, Andjelkovic et al. (2019) detected to increase of PLT values in low dose

application (15 mg Cd/kg/b.w, p.o) similar with our results, but it was also defined decreased PLT values in high-dose applications (30 mg Cd/kg/b.w, p.o). Kisadere et al. (2022) also reported that oral Cd administration (2 mg/kg/day for 4 weeks, p.o) did not cause significant changes in PLT values of male Wistar rats. Changes may have been detected due to different doses and duration of administration. Increased PLT values due to Cd administration were ameliorated by using oral *L. plantarum* diet in Cd+*L. plantarum* group compared to Cd group in the present study. Ghazanfarpour et al. (2019) informed that increased PLT values of the rats due to Pb administration were fixed by using oral LF in rats that was consistent with our results. In addition, we could not find any information about the effects of oral *L. plantarum* administrations on PLT values in rats exposed to different types of toxic heavy metals. It can be expressed as the protective effect of *L. plantarum* on PLT values in female rats exposed to chronic CD toxicity.

5. CONCLUSION

In conclusion, *L. plantarum* partially effects female rats' blood parameters from the harmful effects of Cd. In addition, these obtained findings will be provided useful information for the use of *L. plantarum* in metal intoxications. Also, further studies designed to identify the specific molecular mechanism of the prevention of Cd accumulation in the different tissues by *L. plantarum* are required.

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