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The influence of Zinc adsorbed nano zeolite on some haematological and biochemical parameters and mineral levels in Cadmium toxicity

Influencia del zinc adsorbido con nanozeolita en algunos parámetros hematológicos y bioquímicos y en los niveles de minerales en toxicidad por Cadmio

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ABSTRACT

The aim of the study was to investigate the influence of zinc adsorbed nano – zeolite administration on some hematological and biochemical values as well as mineral levels in female Wistar rats exposed to cadmium. For this purpose, 32 female rats were selected and divided into four equal groups as control, cadmium, adsorbed nano – zeolite, and cadmium + adsorbed nano – zeolite. The rats in the cadmium and cadmium + adsorbed nano – zeolite groups received cadmium (2.04 mg·mL^{-1}) orally by gastric gavage for 4 weeks. Besides, adsorbed nano – zeolite (8 g·kg^{-1} bw·day^{-1}) was administered to adsorbed nano – zeolite and cadmium + adsorbed nano – zeolite groups for 4 weeks. At the end of the experiment, they were sacrificed and blood samples were taken to assess the erythrocytes, leukocytes, platelets, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, creatinine, blood urea nitrogen, creatinine / blood urea nitrogen, glucose, carbon dioxide, lactat, and pH values as well as calcium, phosporus, magnesium, sodium, chlorine, and potassium levels. As a result, cadmium administration reduced the erythrocytes counts in female Wistar rats (P<0.01). On the other hand, adsorbed nano – zeolite administration ameliorated the erythrocytes values in the cadmium + adsorbed nano – zeolite group when compared to the cadmium group (P<0.01). In addition, serum lactat and glucose levels were determined to be lowest in the adsorbed nano – zeolite group when compared to other experimental groups, interestingly (P<0.01). In this study, administration of cadmium and adsorbed nano – zeolite (alone or together) caused a significant decrease in serum magnesium levels of the experimental groups (P<0.001). In conclusion, adsorbed nano – zeolite administration caused remarkable changes in some blood and biochemical parameters of female Wistar rats exposed to cadmium.

Key words: Cadmium; zinc adsorbed nano – zeolite; hematology; biochemical parameters; mineral levels

RESUMEN

El objetivo del estudio fue investigar la influencia de la administración de zinc adsorbido por nanozeolita en determinados valores hematológicos y bioquímicos, así como en los niveles de minerales en ratas Wistar hembras expuestas al cadmio. Para ello, se seleccionaron 32 ratas hembras y se dividieron en cuatro grupos iguales: control, cadmio, zinc adsorbido por nanozeolita y cadmio + zinc adsorbido por nanozeolita. Las ratas de los grupos cadmio y cadmio + zinc adsorbido por nanozeolita recibieron cloruro de cadmio (2.04 mg·mL^{-1}) por vía oral mediante sonda gástrica durante cuatro semanas. Además, se administró zinc adsorbido por nanozeolita (8 g·kg^{-1} de peso corporal/día) a los grupos zinc adsorbido por nanozeolita y cadmio + zinc adsorbido por nanozeolita durante cuatro semanas. Al finalizar el estudio, se les sacrificó y se les extrajo sangre para evaluar los siguientes parámetros: eritrocitos, leucocitos, plaquetas, hemoglobina, hematocrito, hemoglobina corpuscular media, concentración corpuscular media de hemoglobina, volumen corpuscular medio, creatinina, nitrógeno ureico en sangre, creatinina / nitrógeno ureico en sangre, glucosa, dióxido de carbono, lactato y valores de pH, así como los niveles de calcio, fósforo, magnesio, sodio, cloro y potasio. Como resultado, la administración de cadmio redujo el recuento de glóbulos rojos en ratas Wistar hembras (P<0,01). Por otro lado, la administración de zinc adsorbido por nanozeolita mejoró los valores de glóbulos rojos en el grupo cadmio + zinc adsorbido por nanozeolita en comparación con el grupo cadmio (P<0,01). Además, se observó que los niveles séricos de lactato y glucosa eran más bajos en el grupo de zinc adsorbido por nanozeolita en comparación con los demás grupos experimentales, lo cual resulta interesante (P<0,01). En este estudio, la administración de cadmio y zinc adsorbido por nanozeolita (por separado o juntos) provocó una disminución significativa de los niveles séricos de magnesio en los grupos experimentales (P<0,001). En conclusión, la administración de zinc adsorbido por nanozeolita provocó alteraciones notables en algunos parámetros sanguíneos y bioquímicos de las ratas Wistar hembras expuestas al cadmio.

Palabras clave: Cadmio; nanozeolita adsorbida con zinc; hematología; parámetros bioquímicos; niveles minerales

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INTRODUCTION

Cadmium (Cd) is a hazardous transition metal (non – essential) that occurs naturally in the earth's crust in low concentrations, mostly together with zinc (Zn), lead (Pb), and copper (Cu) sulfide ores [1].

This dangerous heavy metal reaches the environment through natural (volcanic eruptions), agricultural (heavy metal – containing materials), and industrial (waste and metal smelting facilities) sources [2].

Long – term exposure to Cd – contaminated water, plant / animal products, and also air primarily causes oxidative stress (OS), increased lipid peroxidation (LPO), suppression of cell metabolism, and epigenetic changes in DNA expression in humans and also animals [3].

It is well known that the hematopoietic system is sensitive to many heavy metals. Previous studies on the subject have reported that Cd disrupts hematopoietic system functions and causes microcytic anemia, accelerated platelet aggregation, and leukocytosis [4, 5].

Cadmium is carried by blood after ingestion and absorption into the body, where it attaches itself to plasma albumin (Alb) and the membranes of red blood cells (RBCs). RBCs and lymphocytes (T and B) suffer OS as a result of the bloodstream's production of reactive oxygen species (ROS) and metallothioneins (MT) due to Cd accumulation [6]. Besides, it was declerated that Cd accumulation significantly altered some hematological (RBC, hemoglobin (HGB), mean corpuscular hemoglobin (MCH), leukocytes (WBC), platelets (PLT), mean corpuscular hemoglobin concentration (MCHC), hematocrit (HCT), mean corpuscular volume (MCV) and biochemical parameters alanine amino transferase (ALT), creatinine (Creat), gamma glutamyl transferase (GGT), aspartate amino transferase (AST), and blood urea nitrogen (BUN) in rats [7, 8].

Furthermore, it has been demonstrated that Cd throws off the mineral balance of living organisms, including calcium (Ca), phosphorus (P), magnesium (Mg), Zn, and leads to some major health problems (osteoporosis, osteomalacia, and itai – itai disease) [4, 5].

Recently, scientists have used a variety of organic and inorganic substances in an attempt to eradicate or at least lessen the harmful effects of Cd on living things. The evaluation of these studies' findings showed that certain chelating agents and antioxidants such as acetylcysteine, garlic, tomatoes, β – carotene, vitamin E, lycopene, chitosan, quercetin, and selenium (Se) can ameliorate the negative effects of Cd [7, 8, 9].

On the other hand, zeolites (clinoptilolite), which have been used as feed additives for a long time to increase performance, provide mineral support, and prevent ammonia toxicity in farm animals, are also used in many other different areas due to their ion exchange, metal binding, detoxifying, antioxidant, and anti – inflammatory properties [10, 11].

Depending on the development of technology, the production of synthetic zeolite (clinoptilolite) and its use in different industrial areas (including health) have also increased day by day in the world [12].

An important metal that is necessary for protein structure, catalysis, and function control is Zn. It plays a main role in many functional biochemical events, including regulating excessive inflammatory status by reducing inflammatory cytokines, reducing OS by participating in the synthesis of antioxidant enzymes, and acting as an enzyme catalyst in lipid, carbohydrate, and protein metabolism. The underlying mechanisms have not been thoroughly investigated, despite the fact that numerous studies have demonstrated that Zn can lessen the toxicity of Cd. However, recent studies have shown that Zn reduces Cd toxicity by directly competing with Cd adsorption, inducing MT, and reducing the harmful effects of ROS [13].

It was aimed to investigate the potential protective effects of Zn adsorbed nano-zeolite administration on some hematological and biochemical values as well as mineral levels in female Wistar rats (*Rattus norvegicus*) exposed to Cd toxicity.

MATERIAL AND METHODS

Ethics

The Experimental Medicine Research and Application Center of the Balıkesir University Experimental Animal Ethics Committee's criteria were followed in all animal procedures, which were authorized (Approval no: 2023 / 9 – 4).

Animals

In the present study, 32 healthy female rats (6 – 7 weeks old on average) obtained from Balıkesir Experimental Animal Production Center, were used. The weights of the animals were adjusted to be approximately 100 – 120 g in each group. During the experiment, female Wistar rats were housed in standard plastic rat cages and kept in an environment with a constant room temperature (23 ± 2°C) and relative humidity (55 ± 10%) on a 12 – hour (h) light / dark cycle. After the adaptation period (approximately 2 weeks), the animals were subjected to the following applications:

- Control group (C): isotonic saline solution was administered orally to the animals via gastric gavage for 28 days (d).
- Cadmium group (Cd): Cd, dissolved in fresh drinking water at a dose of 2.04 $mg \cdot mL^{-1}$, was administered orally to the animals via gastric gavage for 28 d.
- Zinc adsorbed nano – zeolite group (ZnNC): ZnNC suspension, at a dose of 8 $g \cdot kg^{-1}$ body weight (bw)/d, was administered orally to the animals via gastric gavage for 28 d [14, 15].
- Cd + ZnNC Group: Cd, dissolved in fresh drinking water (at a dose of 2.04 $mg \cdot mL^{-1}$), and ZnNC suspension (at a dose of 8 $g \cdot kg^{-1}$ $bw \cdot d^{-1}$) were administered orally to the animals via gastric gavage for 28 d [14, 15]. An oral gavage in a volume of 1 $mL \cdot kg^{-1}$ b.w. was used to treat every rat.

In addition, standard rat feed and fresh drinking water were given to the rats ad libitum throughout the study. The amount of adsorbed Zn was adjusted to 12 $mg \cdot kg^{-1}$ to fix the daily needs of the animals [14]. At the end of the study, while the animals were under general

anesthesia (Ketamine / Xylazine (0.1 mL·100 mg^{-1}·bw^{-1}), blood samples were taken from the heart tissue by cardiac puncture.

After, the animals were euthanazied by the cervical dislocation technique while under anesthesia. Then, the blood samples were transferred to tubes with and without an anticoagulant. The blood samples were centrifuged (ALLEGRA – X64R, USA, 3500 × g·s^{-1}), and plasma / serum samples were collected in eppendorf tubes. For the purpose of analysis, the serum samples that had been separated were kept in a refrigerator (ZK Meiling, DW – HL218, Zhongke Meiling Cryogenics Company Limited, China) at a temperature of -80°C.

Vaginal smear tests

A 0.2 mL aliquot of physiologic saline was administered to each rat's vagina using a separate Pasteur pipette. A smear slide was used to examine two drops of cell suspension in order to determine the estrous cycle stages. The current study includes thirty – two rats after the proestrous and / or estrous stages were determined based on rounded / nucleated epithelial cells and cornified cells [16].

Zeolite (Clinoptilolite)

The zeolite (clinoptilolite) samples were taken from the Bigadiç region in northwest Anatolia, which is Turkey's most significant zeolite resource. Zeolites (clinoptilolite) with a size of 0 – 1.5 mm were supplied from the producer in Bigadiç to be added to feeds. Powder and solid densities were determined using a pycnometer (Micromeritics, AccuPyc II 1340, USA) Also, hardness was determined using a Leeb Rebound Hardness Meter (LRHT) (Proceq SA, Switzerland). Specific surface area was measured with a Micromeritics BET (Micromeritics Instrument Corporation, USA) surface area analyzer. Besides, color analysis was performed using a colorimeter (Konica Minolta CR - 10 Plus, Konica Minolta, Inc., Japan). In addition, fluidization temperature was evaluated with a fluidized bed tester (Freund – Vector FBD – 100, USA). Cation exchange capacity was determined using a Kettler CEC Analyzer (Heinz Kettler GmbH & Co. KG, Germany). Porosity was measured using a Micromeritics mercury intrusion porosity meter (Micromeritics Instrument Corporation, USA). Finally, pH values were determined using a Hanna Instruments pH meter (Hanna Instruments, USA). Chemical composition was analyzed using the X – ray fluorescence (XRF) technique (Thermo Fisher Scientific, USA) shown in TABLE I.

Physical preparation of nano-zeolite

The raw zeolite (clinoptilolite) minerals were processed to obtain nano – zeolite through physical methods. A 10 g·500 mL^{-1} ratio of zeolite (clinoptilolite) to pure water was stirred (Isolab Laborgerâte GmbH 605.01.001, Germany) at 100 rpm for 24 h. Following this process, the mixture was allowed to settle for 3 h, and then 100 mL of the suspension phase was carefully taken from the top. This suspension was placed in an oven (Memmert OLS, Germany) at 105°C until all water had evaporated and the zeolite particles were completely dry. The dried and clean zeolite particles were then analyzed for particle size (PS) distribution and morphological characteristics. Finally, the dried particles were collected and stored in a desiccator (Fisher Scientific, USA).

TABLE I
Physical and chemical properties of the used zeolite (clinoptilolite)

Physical Properties		Chemical properties components contents wt %	
Powder density	1.42 g·cm^{-3}	SiO_2	69.20
Solid density	2.14 g·cm^{-3}	Al_2O_3	10.81
Hardness	3.5 – 4.0 mohs	TiO_2	0.08
Specific surface area	14.5 m^2·g^{-1}	Fe_2O_3	1.18
Color	Ivory	Na_2O	0.37
Fluidization temp.	1506°C	K_2O	2.78
Cation exchange capacity	1.57 meq·g^{-1}	CaO	2.98
Porosity	40%	MgO	1.48
pH	7.0	P_2O_5	0.02
		SO_3	0.04
		LoI (1050°C)	11.06
		SiO_2	69.20

Conventional hydrothermal synthesis

The synthesis of nano-zeolite was carried out using the hydrothermal crystallization technique as described below. A complete seed solution was created with a molar ratio of 5.5 Na_2O:1.0 Al_2O_3:4.0 SiO_2:190 H_2O:0.2 SDS by blending freshly prepared homogeneous solutions of aluminate, silicate, and SDS reagents with deionized water. To prepare a uniform aluminosilicate solution, 50 mL of deionized water was first placed into a Falcon tube. Initially, NaOH pellets were dissolved in 50 mL of deionized water using an ice bath. Following this, $NaAlO_2$ was gradually introduced into the NaOH solution while stirring vigorously at 250 rpm. $Na_2SiO_3·5H_2O$ was then incorporated into the mixture.

The entire mixture was maintained at 50°C for 48 h for adequate aging. All chemicals utilized in the synthesis of nano zeolites were sourced from Sigma – Aldrich (SA, USA) and were used as received unless otherwise stated. The primary chemical reagents employed included sodium aluminate ($NaAlO_2$) (SA, USA) as the alumina source (SA, USA), sodium metasilicate ($Na_2SiO_3·5H_2O$) (SA, USA) as the silica source (SA, USA), sodium hydroxide (NaOH) (SA, USA), and sodium dodecyl sulfate (SDS) ($CH_3(CH_2)11OSO_3Na$) (SA, USA). Deionized water was employed in every instance. All chemicals used were analytical grade reagents [14, 15].

Size distribution analysis of nano-zeolite samples

Due to PS distribution analysis, a Malvern Zetasizer (Nano – ZS ZEN3600, UK) was employed. The samples were dispersed in water. The zeolite (clinoptilolite) material had a refractive index of 1.48. Measurements were conducted at 25.0°C. A disposable sizing cuvette was used to ensure accuracy and prevent contamination. In this study, sample 1 (NZP), representing the nanozeolite produced by the physical preparation method, and sample 2 (NZH), obtained by the conventional hydrothermal synthesis method, exhibited different size distributions. For NZP, a primary peak with a width of 8.50 nm and 100% intensity was observed at 131.8 nm. Similarly, NZH exhibited a dominant peak with a width of 10.32 nm at 126.3 nm. This indicates that most of the particles are in the nanoscale range in FIG. 1.

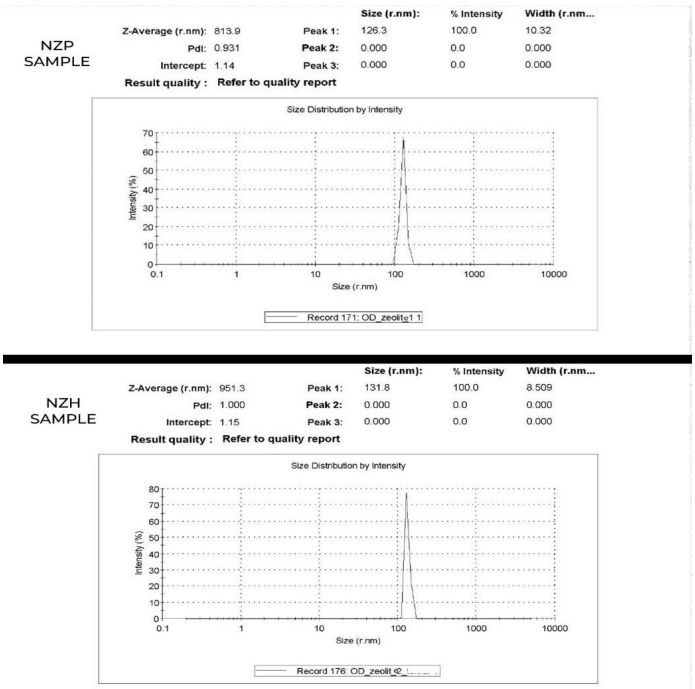

FIGURE 1. Size distribution of NZP and NZH samples. NZP: the physical preparation of nano – zeolite, NZH: the conventional hydrothermal synthesis of nano – zeolite, PDI: Polydispersity index, nm: Nanometer

The absence of additional significant peaks in both samples suggests a relatively uniform size distribution at the nanoscale. The findings confirm that both preparation methods were effective in producing nano – sized zeolite (clinoptilolite) particles. However, it is noteworthy that NZP, derived via physical preparation, was selected for use in animal tests and other experimental processes due to its simplicity in production and suitability for such applications.

Morphological analysis of physical preparation of nano – zeolite and conventional hydrothermal synthesis of nano – zeolite samples

Scanning Electron Microscope (SEM) imaging was performed to investigate the morphological characteristics, PS distribution, and surface structures of the NZP and NZH samples. The figures were conducted using the Zeiss LS EVO 10 (Carl Zeiss AG, Gemany) device at Balıkesir University. The SEM image of NZP (FIG. 2) reveals a structure consisting of irregularly shaped and agglomerated particles with a broad size distribution.

The PS range from nano to submicron levels, exhibiting rough surface features. This may be attributed to the limited size control mechanisms of the physical preparation method. In contrast, the SEM image of NZH (FIG. 2) displays more regular, spherical, or near-spherical particles. Produced via the hydrothermal synthesis method, these particles exhibit a narrower size distribution and higher crystallinity.

Preparation of zinc suspensions containing the physical preparation of nano – zeolite

In the experimental study, the prepared NZP samples were added to the Zn solution. To prepare the solution, solid zinc sulfate

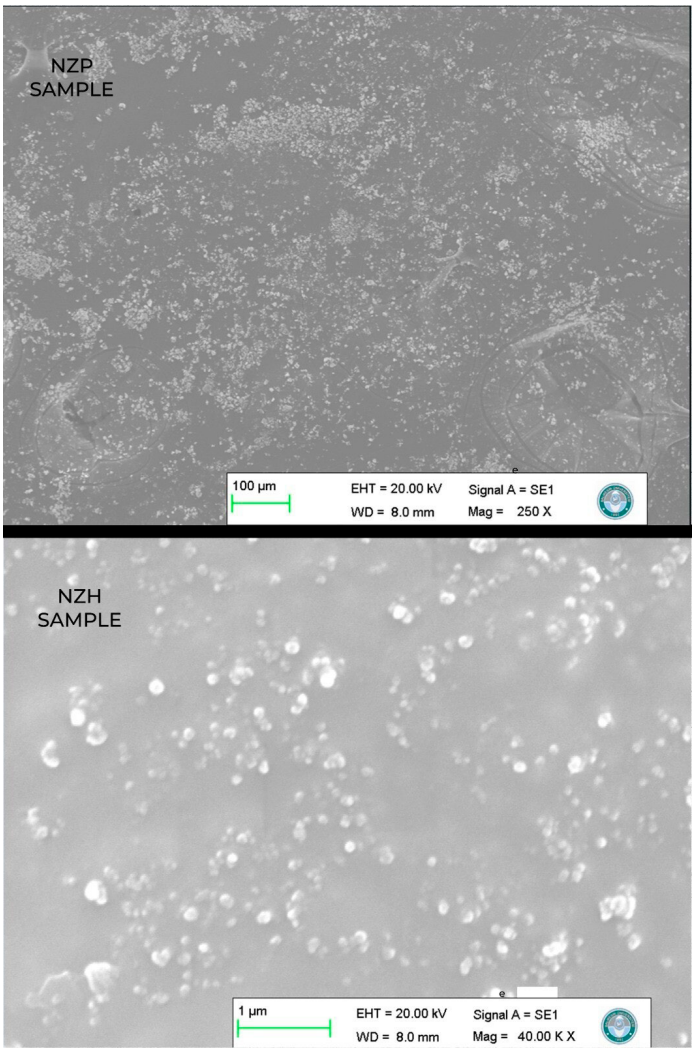

FIGURE 2. SEM image of NZP and NZH samples. NZP: the physical preparation of nano – zeolite, NZH: the conventional hydrothermal synthesis of nano – zeolite, PDI: Polydispersity index, µm: Micrometer, mm: Milimeter, kV: Kilo volt, Mag: Magnitude; WD: Width distribution

pentahydrate ($H_{10}O_9SZn$) (Sigma-Aldrich, USA) was utilized. During the preparation of the solution and suspension, the solid/liquid ratio was adjusted in accordance with the literature. Suspensions were prepared with a concentration of 10 $g \cdot L^{-1}$ NZP in each solution. The amount of Zn given to the female rats was adjusted to 12 $mg \cdot kg^{-1}$ b.w., which is sufficient to meet their daily requirement [17, 18].

Determination of some hematological parameters

Hematological parameters such as WBC, HGB, HCT, PLT, RBC, MCH, MCHC, MCV, and differential WBC [lymphocyte (Lym), monocyte (Mon), and neutrophil (Neu)] counts were determined in blood samples using an automatic cell counter (Hasvet VH5R, Türkiye).

Determination of some biochemical parameters

Some serum biochemical parameters such as Creat, BUN, Creat/BUN, Glu, CO_2, pH, and Lact levels were determined by using an

automatic biochemical analyzer (Seamaty, Sichuan, China) and kits (Lot: 9250119).

Determination of some mineral parameters

Some serum mineral content including Ca, P, Mg, Na, CL, and K was found from the serum samples by using an automatic biochemical analyzer (Seamaty, Sichuan, China) and kits (Lot: 9250119).

Statistical analysis

Using the SPSS 25.0 software, statistical analysis was carried out using the analysis of variance (ANOVA) and Duncan's test (SPSS, Inc., Chicago, IL). At $P<0.05$, the data was considered significant.

RESULTS AND DISCUSSION

Hematological parameters

White Blood Cell, Lym, and Mon counts remained unchanged as a result of neither Cd nor Zn nano – zeolite (ZnNC) administrations ($P>0.05$); nevertheless, Neu counts increased in both Cd and ZnNC groups compared to the C group in this study ($P<0.05$). In addition, the percentage of Lym was detected lower in Cd and ZnNC groups when compared to C ($P<0.05$). On the contrary, the percentage of Neu was found higher in the Cd group compared to other experimental groups ($P<0.05$). Besides, we could not determine any change in the percentage of Mon among the experimental groups ($P>0.05$). Cd administration reduced the RBC counts in female Wistar rats ($P<0.01$). On the other hand, ZnNC administration ameliorated the RBC values in Cd + ZnNC groups when compared to the Cd group ($P<0.01$).

In the present study, administration of ZnNC was unable to make up for the decline in MCV levels brought on by Cd ($P>0.05$). Moreover, HTC values increased in Cd, ZnNC, and also Cd + ZnNC groups when compared to C group ($P<0.01$). Although there was no discernible difference in the MCHC values among the groups in the present investigation ($P>0.05$), the Cd + ZnNC group had the lowest MCH values when compared to the other groups ($P<0.01$). On the other hand, HGB values were found to higher in Cd, ZnNC, and also Cd + ZnNC groups compared to the C in this study ($P<0.01$). Interestingly, all of the administrations (Cd, ZnNC, and also Cd + ZnNC) led to a decrease in PLT values in this study ($P<0.01$), shown in TABLE II.

Biochemical parameters

In present investigation, BUN levels dropped based on the Cd administrations in both the Cd and Cd + ZnNC groups compared to the C group ($P<0.01$), even though serum Creat and Creat / BUN levels were unaffected by the various administrations (Cd, ZnNC, and Cd + ZnNC) ($P>0.05$). In addition, serum Glu levels were found higher in the C and Cd groups than ZnNC and Cd + ZnNC groups in the present study ($P<0.001$). On the other hand, serum Lac levels were determined the lowest in ZnNC groups when compared to other experimental groups, interestingly ($P<0.01$). While the various treatments (Cd, ZnNC, and Cd + ZnNC) had no effect on the CO_2 levels in the groups ($P>0.05$), we found rises in pH values when compared to the C group in this investigation ($P<0.01$), shown in TABLE III.

TABLE II
Hematological findings in rats

Parameters / Groups		Mean ± SE	*P*
WBC ($10^9 \cdot L^{-1}$)	C	8.83 ± 0.57	NS
	Cd	10.93 ± 0.76	
	ZnNC	11.21 ± 0.51	
	Cd + ZnNC	11.08 ± 1.14	
Lym (#)	C	7.51 ± 0.51	NS
	Cd	8.23 ± 0.58	
	ZnNC	8.71 ± 0.35	
	Cd + ZnNC	9.04 ± 0.85	
Mon (#)	C	0.46 ± 0.22	NS
	Cd	0.53 ± 0.21	
	ZnNC	0.41 ± 0.09	
	Cd + ZnNC	0.43 ± 0.15	
Neu (#)	C	0.96 ± 0.13^{b}	($P<0.05$)*
	Cd	2.16 ± 0.33^{a}	
	ZnNC	2.08 ± 0.17^{a}	
	Cd + ZnNC	1.61 ± 0.34^{ab}	
Lym (%)	C	85.21 ± 2.35^{a}	($P<0.05$)*
	Cd	75.58 ± 2.85^{b}	
	ZnNC	77.90 ± 1.37^{b}	
	Cd + ZnNC	82.11 ± 2.14^{ab}	
Mon (%)	C	1.78 ± 0.10	NS
	Cd	4.45 ± 1.44	
	ZnNC	3.58 ± 0.72	
	Cd + ZnNC	3.93 ± 1.47	
Neu (%)	C	10.98 ± 1.24^{c}	($P<0.05$)*
	Cd	19.86 ± 2.95^{a}	
	ZnNC	18.56 ± 1.16^{ab}	
	Cd + ZnNC	13.97 ± 1.50^{bc}	
RBC ($10^{12} \cdot L^{-1}$)	C	9.25 ± 0.15^{b}	($P<0.01$)**
	Cd	8.46 ± 0.14^{c}	
	ZnNC	9.87 ± 0.12^{a}	
	Cd + ZnNC	9.46 ± 0.18^{ab}	
MCV (fL)	C	54.87 ± 0.39^{a}	($P>0.05$)*
	Cd	52.00 ± 0.96^{b}	
	ZnNC	54.25 ± 0.75^{a}	
	Cd + ZnNC	51.37 ± 0.46^{b}	
HCT (%)	C	46.44 ± 0.50^{b}	($P<0.01$)**
	Cd	49.04 ± 0.91^{a}	
	ZnNC	49.76 ± 0.81^{a}	
	Cd + ZnNC	50.82 ± 0.72^{a}	
MCH (pg)	C	16.15 ± 0.24^{a}	($P<0.01$)**
	Cd	15.30 ± 0.16^{bc}	
	ZnNC	15.80 ± 0.16^{ab}	
	Cd + ZnNC	15.06 ± 0.24^{c}	
MCHC (pg)	C	29.56 ± 0.37	NS
	Cd	29.53 ± 0.42	
	ZnNC	29.15 ± 0.36	
	Cd + ZnNC	29.31 ± 0.49	
HGB ($g \cdot dL^{-1}$)	C	13.65 ± 0.13^{b}	($P<0.01$)**
	Cd	14.50 ± 0.30^{a}	
	ZnNC	14.60 ± 0.15^{a}	
	Cd + ZnNC	14.86 ± 0.10^{a}	
PLT ($10^9 \cdot L^{-1}$)	C	889.37 ± 19.47^{a}	($P<0.01$)**
	Cd	671.12 ± 45.62^{b}	
	ZnNC	640.75 ± 44.57^{b}	
	Cd + ZnNC	703.50 ± 63.48^{b}	

Groups: C: Control, Cd: Cadmium, ZnNC: Zn adsorbed nano-zeolite. $^{a-c}$Means in the same column with different superscripts differ significantly ($P<0.05$; $P<0,01$). NS: Non-significant, (#): Count, WBC: White blood cell, Lym: Lymphocyte, Neu: Neutrophil, Mon: Monocyte, RBC: Red blood cell, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, PLT: Platelet count

TABLE III
Biochemical parameters in rats

Parameter	C	Cd	ZnNC	Cd+ZnNC	*P*
Creat	39.05 ± 0.51	39.17 ± 0.80	35.77 ± 3.76	40.40 ± 5.76	N.S
BUN	8.27 ± 0.18^{b}	10.39 ± 0.45^{a}	8.37 ± 0.28^{b}	9.85 ± 0.69^{a}	**
Creat/BUN	213.22 ± 5.12	266.27 ± 12.81	252.97 ± 25.85	280.33 ± 37.77	N.S
Glu	11.42 ± 0.79^{a}	10.82 ± 1.18^{a}	6.80 ± 0.11^{b}	7.27 ± 0.41^{b}	***
Lact	10.29 ± 0.81^{a}	7.17 ± 0.14^{bc}	6.45 ± 0.67^{c}	9.00 ± 0.98^{ab}	**
CO_2	15.53 ± 0.19	16.55 ± 0.10	16.52 ± 0.34	15.92 ± 0.59	N.S
pH	7.78 ± 0.03^{b}	7.97 ± 0.03^{a}	7.93 ± 0.02^{a}	7.95 ± 0.03^{a}	**

Groups: C: Control, Cd: Cadmium, ZnNC: Zn adsorbed nano-zeolite. $^{a-c}$Means in the same line with different superscripts differ significantly (P<0.05*, P<0.01**, P<0.001***). NS: Non-significant. Creat: Creatinine, BUN: Blood urea nitrogen, Glu: Glucose, Lact: Lactate, CO_2: Carbondioxide, pH; The negative logarithm of the hydrogen ion concentration

Mineral levels

Serum Ca levels were determined the lowest in the Cd + ZnNC group compared to other groups, especially the C group, in this study (P<0.05). Besides, Cd administration led to an increase of serum P levels in both Cd and Cd + ZnNC groups (P<0.01). In present study, administration of Cd and ZnNC alone or together caused a significant decrease in Mg levels of the experimental groups (P<0.001). While K values increased in all experimental groups compared to the C group, the increase in the ZnNC – applied groups was remarkable in the present study (P<0.001). While the administrations carried out in the study did not cause any change in CL levels (P>0.05), Cd treatment caused a significant decrease in Na levels (P<0.05), shown in TABLE IV.

Hematological characteristics are particularly important when evaluating the normal state of health and the effects of specific developed – synthesized biological and chemical substances on living beings [8]. In present study, Cd administration (2.04 mg·mL^{-1} for 28 d; p.o) did not affect the WBC, Lym, and Mon, but increased the Neu counts in female Wistar rats. In a previous study, Kısadere *et al.* [19] reported that administration of Cd (2.04 mg·mL^{-1} for 28 d; p.o) increased the WBC, Lym, and Neu, but did not cause any change in Mon counts of female Wistar rats. Also, Kısadere *et al.* [8] detected the highest WBC, but lowest Lym counts in Cd – induced (2 mg·kg^{-1} bw·d^{-1} for 4 weeks; p.o) male Wistar rats.

TABLE IV
Mineral levels in experimental groups

Minerals	C	Cd	ZnNC	Cd+ZnNC	P
K	5.42 ± 0.16^{c}	6.03 ± 0.10^{b}	6.63 ± 0.09^{a}	6.88 ± 0.27^{a}	***
Na	143.21 ± 0.27^{a}	142.05 ± 0.17^{b}	142.60 ± 0.33^{ab}	142.42 ± 0.56^{ab}	*
Cl	106.48 ± 3.42	101.70 ± 0.48	104.02 ± 0.37	103.02 ± 0.77	NS
Ca	3.08 ± 0.02^{a}	2.93 ± 0.04^{ab}	2.93 ± 0.03^{ab}	2.80 ± 0.09^{b}	*
P	2.38 ± 0.09^{b}	2.89 ± 0.12^{a}	2.33 ± 0.05^{b}	2.66 ± 0.09^{a}	**
Mg	1.25 ± 0.03^{a}	0.92 ± 0.02^{b}	0.90 ± 0.01^{b}	0.97 ± 0.04^{b}	***

Groups: C: Control, Cd: Cadmium, ZnNC: Zn adsorbed nano-zeolite. $^{a-c}$Means in the same line with different superscripts differ significantly (P<0.05*, P<0.01**, P<0.001***). NS: Non-significant. K: Potassium, Na: Sodium, Cl: Chlorine, Ca: Calcium, P: Phosphorus, Mg: Magnesium

Furthermore, administration of Cd reduced the proportion of Lym, but did not affect the Mon in female Wistar rats in the present study. Conversely, the Cd group had the largest percentage of Neu. In a prior study, it was reported that administration of Cd (2.04 mg·mL^{-1} for 28 d; p.o) did not lead to an alteration in the percentages of Neu, Lym, and Mon in female Wistar rats [19]**.** Besides, Kısadere *et al.* [8] found the same results regarding to the Lym, Neu, and Mon percentages in male Wistar rats exposed to Cd (2 mg·kg^{-1} bw·d^{-1} for 4 weeks) toxicity. Dosage regimes, individual characteristics, or the analyzer type could be the cause of the different outcomes obtained.

In literature reviews, no evidence was found regarding the effects of normal or nano-sized zeolite on the Lym, Mon, and Neu ratios of rats that were exposed to Cd toxicity. On the other hand, ZnNC administration did not change WBC, Lym, and Mon; however, it increased the Neu counts in this study. Bazri *et al.* [17] suggested that the supplementation of natural nano – sized clinoptilolite (2% daily intake for 8 weeks; p.o) could not affect WBC counts of male Wistar rats. On the contrary, Martin-Kleiner *et al.* [20] found that only long period (30 and / or 40 d; p.o) normal-sized zeolite (clinoptilolite) administration led to an increase of WBC and Lym counts in mice.

In the present study, RBC counts were determined lower in the Cd group animals than the C group. In a previous study, Kısadere *et al.* [19] demonstrated that Cd ($CdCl_2$; 2.04 mg·mL^{-1} for 4 weeks; p.o) administration did not alter the RBC counts in female Wistar rats. According to Saedi *et al.* [21] an increase in the dose of Cd administration (25, 50, and 75 mg·kg^{-1} bw·d^{-1} for 13 d) was observed to be linked to a decrease in the RBC count in female rats.

Also, Chater *et al.* [22] reported that Cd treatment (20 mg·L^{-1}; from d 6 to 19 of pregnancy) induced a significant reduction in RBC counts in female rats. It might be due to the individual characteristics, dosage regimes, or administration period. In present study, ZnNC treatment improved the reduced RBC counts in female Wistar rats caused by Cd. On the other hand, Martin-Kleiner *et al.* [20] demonstrated that RBC counts (in the peripheral blood) were not influenced by the food containing clinoptilolite powder (12.5, 25, or 50%) for 40 d in mice.

In a previous study, Brezvyn *et al.* [23] also found similar results with Martin-Kleiner *et al.* [20] regarding to RBC counts in male rats. These variations could be due to nano – size or Zn – adsorption. In the present study, Cd administration decreased the MCV and MCH, but did not affect the MCHC values in female Wistar rats. Interestingly, Kısadere *et al.* [19] could not observe any change in MCV, MCH, and MCHC values in female rats exposed to Cd (2.04 mg·mL^{-1}) in a previous study.

Similarly, Mikolic *et al.* [24] reported that administration of Cd (50 mg·L^{-1} for 4 weeks) to dams (female rats) did not lead to a change in hematological parameters (MCV, MCH, and MCHC). Results may be affected by different analyzers or individual characteristics. Moreover, ZnNC administration could not ameliorate the above – mentioned parameters in female Wistar rats in the present study. Martin-Kleiner *et al.* [20] also did not reach any alteration in MCH and MCHC values of mice exposed to food containing clinoptilolite powder (12.5, 25, or 50%).

Also, Bazri *et al.* [17] suggested that supplementation of natural nano – sized clinoptilolite (2% daily intake for 8 weeks; p.o) did not affect the MCV and MCH, but decreased the MCHC values in male rats. Based on the afore mentioned parameters, it can be assumed that ZnNC has a partial effect on above – mentioned parameters. In this study, Cd group animals had higher HGB and HCT values than the C group. On the contrary, it was concluded that Cd administration did not affect the HGB and HCT concentrations in female Wistar rats [19].

In addition, it was also reported that HGB concentration decreased inversely with gradually increasing dose of Cd (25, 50, and 75); however, HCT values did not change in female rats [21]. The difference in results appears to be dose – dependent. In the present study, ZnNC administration increased the HGB and HCT values similar to the Cd in female Wistar rats. Moreover, Martin-Kleiner *et al.* [20] could not detect any alterations in HGB values of mice exposed to clinoptilolite powder (12.5, 25, or 50%). Based on HGB and HCT values, the results of Brezvyn *et al.* [23] and Martin-Kleiner *et al.* [20] were comparable.

In addition, Bazri *et al.* [17] noted that rats' HGB and HCT values remained unchanged after receiving nano – sized clinoptilolite in a previous study. It is possible to express that the Zn – adsorption, dose, administration time, and delivery technique have a bigger impact on the differences in outcomes.

In present study, ZnNC administration reduced the PLT values in both ZnNC and Cd + ZnNC groups in female Wistar rats. Similarly, it was reported that nano – sized clinoptilolite administration decreased the PLT values in male Wistar rats in a previous study [17]. Martin-Kleiner *et al.* [20] also determined a non – statistical decrease in PLT values in rats exposed to clinoptilolite administration. The effects of zeolite administration on PLT values in rats exposed to Cd poisoning are not well documented in the literature; nonetheless, it can be stated that bone marrow proliferative activity was affected by ZnNC administration.

As it is well known, biochemical parameters are also of great importance in evaluating the effects of synthetic or natural substances on living things. In present study, serum Creat and Creat / BUN levels of the female Wistar rats were not affected by Cd administrations. However, serum BUN levels increased due to Cd toxicity in rats. Wang *et al.* [25] reported that Cd administration (50 mg / l through drinking water for 8 weeks) led to an increase in both BUN and Creat levels in immature female rats.

Also, Andjelkovic *et al.* [26] also determined the destructive effect of Cd on BUN and Creat levels of male rats in acute Cd toxicity (15 and 30 $mg \cdot kg^{-1}$ $bw \cdot d^{-1}$. The different doses and the period of administration can be utilized to clarify disparate results. In this study, ZnNC administration did not cause any crucial changes in serum Creat, Creat / BUN, and BUN levels in female Wistar rats exposed to Cd.

Conversely, Ibrahim *et al.* [27] suggested that zeolite administration (100 $mg \cdot kg^{-1}$ $bw \cdot d^{-1}$) markedly ameliorated the altered renal markers (BUN and Creat) in Cd – exposed pregnant rats and their fetuses. In the literature, we could not reach any information about the effects of zeolite (normal or nano – sized) administration on BUN and Creat levels in both female and male rats exposed to Cd except for the above – mentioned study.

In the present investigation, the administration of Cd had no effect (only partially) on the serum levels of Glu or Lact in female Wistar rats. On the contrary, Chater *et al.* [22] reported that Cd administration (20 $mg \cdot L^{-1}$ for 13 d) increased the Glu and lactate dehydrogenase (LDH) levels in female rats.

According to da Costa *et al.* [28] female rats in the C and Cd groups did not exhibit any differences in their fasting Glu levels; nevertheless, the Cd group rats showed an increase in their Glu levels during the insulin sensitivity test (IST) and area under the curve (AUC). It might have occurred due to different dosage regimes, period, sex, or hormonal changes. In the present study, ZnNC administration reduced the serum Glu and Lact levels in female Wistar rats, interestingly.

Furthermore, there was no research on the effects of zeolite at normal or nano levels on serum Glu or Lact levels in rats exposed to Cd in the literature. For this reason, it was the first report regarding to Glu and Lact levels in female Wistar rats. In a previous study, it was suggested that in diabetic rats treated with nano – sized clinoptilolite (1% clinoptilolite / food) decreased blood Glu levels to normal references (12.4 vs 27.5 $mmol \cdot L^{-1}$) in rats [29]. It may be due to a dose or size – dependent inhibition of Na – dependent d – glucose absorption by ZnNC.

In this study, serum CO_2 levels were not affected by Cd administration, while pH levels increased in female Wistar rats. In addition, Yuan *et al.* [30] concluded that the specific gravity, pH, and urine volume were all nearly within normal ranges in Cd and Pb – exposed female rats. Besides, the rates of positive urine occult blood and urine pH ≤ 9.0 only rose in the high – dose group.

No information about the direct effects of Cd on serum CO_2 and pH levels was identified in the literature review. On the other hand, ZnNC administration also increased the pH levels; nonetheless it did not affect the CO_2 levels in female rats in this study. Anfray *et al.* [31] suggested that the use of nano – zeolites is safe in rodents and shows a great affinity to O_2 and CO_2 for in vivo applications. The effects of zeolite / nano – zeolite on serum pH and CO_2 levels in rats exposed to Cd poisoning were also not documented in any literature.

In this study, serum P levels tended to increase, whereas Ca levels tended to fall, particularly due to Cd administration in experimental groups. Asagba *et al.* [32] reported that Cd administrations (100 ppm $CdSO_4$ for 16 weeks) did not affect the plasma P and Ca levels in male Wistar rats. Similarly, Brzóska and Moniuszko – Jakoniuk [4] suggested that Ca concentration in the serum of female rats was not influenced by any administrations with Cd (1, 5, or 50 mg $Cd \cdot L^{-1}$ for 3, 6, 9, and 12 months) (range 8.96 – 10.76 $mg \cdot 100^{-1}$). Besides, Andjelkovic *et al.* [26] could not observe any change in Ca levels ($CdCl_2$; 15 and 30 $mg \cdot kg^{-1}$ $bw \cdot d^{-1}$), however, P levels tended to decrease only after at a 30 $mg \cdot kg^{-1}$ $bw \cdot d^{-1}$ dose of Cd exposure in male rats. It is possible to attribute the detrimental effects of Cd on serum Ca and P minerals to dose – dependent. Moreover, administration of ZnNC did not affect the serum Ca and P levels in female Wistar rats exposed to Cd in the present study. Besides, Co – administration / interaction of Cd and ZnNC caused a decrease in serum Ca levels, interestingly.

Despite the fact that the effects of zeolite and / or zinc administrations on serum Ca and P levels in several animals have

been established no studies have been conducted on how these levels are affected in rats exposed to Cd. [20]. Serum Mg levels of female Wistar rats decreased depending on the administration of Cd in the present study. Moreover, ZnNC administration (alone / together with Cd) also decreased the serum Mg levels of rats in the present study. It has been reported that a decrease in the levels of Mg is observed only after at a dose of 30 $mg \cdot kg^{-1}$ $bw \cdot d^{-1}$ acute Cd exposure in male rats. The antagonistic actions of Cd and Mg compounds have been shown in earlier animal studies, which supports this study's findings [26].

Furthermore, administration of ZnNC alone or together with Cd increased the K levels even more in female rats in the present study. In a previous study, Martin-Kleiner *et al.* [20] could not detect any alterions in serum K levels in rats exposed to zeolite (12.5, 25, or 50% clinoptilolite powder) administration for 40 d.

In present study, Cd administration decreased the serum Na levels, but did not affect the serum Cl levels in female rats. On the contrary, Abd – Elhakim *et al.* [33] suggested that serum Na levels increased only after 60 d of oral administration of Cd (5 $mg \cdot kg^{-1}$ bw) in male rats. The effect of Cd on serum Na and Cl levels appears to be dependent on the dose and period of administration.

In this study, ZnNC administration alone or together with Cd did not affect the serum Na and Cl in female Wistar rats. On the contrary, Ahmadi *et al.* [34] demonstrated that clinoptilolite administration (at a rate of 0.25 $g \cdot kg^{-1} \cdot d^{-1}$) ameliorated the serum Na levels in rats intoxicated with Cd (at a dose of 1.7 $mg \cdot kg^{-1}$). Moreover, Martin-Kleiner *et al.* [20] could not reach any remarkable changes in serum Na and Cl levels in rats exposed to zeolite (12.5, 25, or 50% clinoptilolite powder) administration for 40 d. Although further research is required, it may be concluded that ZnNC has a partial impact on serum Na and Cl levels.

CONCLUSION

Zinc Adsorbed Nano Zeolite administration induced significant changes in some blood parameters of female Wistar rats exposed to Cd. Moreover, the findings suggest that ZnNC may be used as a potential agent for the treatment of Cd toxicity. Furthermore, further studies are needed to determine the molecular mechanism by which ZnNC prevents the adverse effects of Cd on the hematopoietic system.

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Conflict of interest

No conflict of interest was reported by the authors.

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