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# Effect of Gingko Biloba Extract (Egb761) Supplementation on Hemato-Biochemical Parameters Following Acute Treadmill Exercise in Rats *, **

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This study was aimed to investigate the effect of Gingko biloba extract (EGb761) on hemato-biochemical parameters following acute treadmill exercise in rats. Thirty-two male rats were divided into four groups with equal number of rats. The animals of control and exercise groups orally received 2 cc/kg bw 0.9% saline while EGb761 and EGb761+exercise groups received 100 mg/kg bw EGb761 by oral gavage for 5 days/week for 4 weeks. On the last day of experiment, the animals of the exercise groups were promoted to acute exhaustive exercise, and blood samples were collected by intracardiac puncture from all rats. Following the hematological analysis, plasma samples were separated for biochemical analysis. The results showed that exercise, EGb761 supplementation or both did not lead to alteration on red blood cells (RBC), packed cell volume (PCV), hemoglobin (HGB), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) (P>0.05). However, acute exhaustive exercise reduced mean corpuscular cell volume (MCV) in rats while increased red cell distribution width (RDW) (P<0.05). In addition, plasma alanine aminotransferase (ALT) activity, total cholesterol, and total protein levels did not change in any group (P>0.05), and alkaline phosphatase (ALP) activity was significantly increased in exercise groups while glucose and triglyceride levels were decreased (P<0.05). In conclusion, our results showed that acute exhaustive exercise affected MCV and RDW values, plasma ALP activity, glucose, and triglyceride levels. Gingko biloba extract supplementation ameliorated only the exercise-induced changes in ALP activity and RDW value. Therefore, it is suggested that the effects of usage after exercise or different doses of EGb761 should be investigated in the future comprehensive studies.

***Key Words:*** *Biochemistry, exhaustive exercise, gingko biloba, hematological parameters*

### Sıçanlarda Gingko Biloba ekstresi (EGb761) takviyesinin akut koşu bandı egzersizi sonrası hemato-biyokimyasal parametreler üzerine etkisi

Bu çalışmanın amacı, sıçanlarda Gingko Biloba ekstresi (EGb761) takviyesinin akut koşu bandı egzersizi sonrası hemato-biyokimyasal parametreler üzerine etkisini araştırmaktadır. Otuz iki erkek sıçan, eşit sayıda sıçanla dört gruba ayrıldı. Kontrol ve egzersiz gruplarının hayvanlarına 4 hafta boyunca 5 gün/hafta oral yolla 2 cc/kg va %0.9'luk serum fizyolojik verilirken, EGb761 ve EGb761+egzersiz gruplarına, 100 mg/kg va EGb761 oral gavaj ile verildi. Denemenin son gününde, egzersiz gruplarının hayvanlarına akut yorucu egzersiz yaptırıldı ve tüm hayvanlardan kalp içinden kan örnekleri toplandı. Hematolojik analizin ardından, biyokimyasal analiz için plazma örnekleri ayrıldı. Sonuçlar, egzersizin, EGb761 takviyesinin veya her ikisinin eritrosit (RBC), hematokrit (PCV), hemoglobin (HGB), ortalama alyuvar hemoglobini (MCH) ve ortalama alyuvar hemoglobin konsantrasyonu (MCHC)'yi değiştirmediğini gösterdi (P> 0.05). Bununla birlikte, akut yorucu egzersiz sıçanlarda, alyuvar dağılım genişliği (RDW)'yi artırırken ortalama alyuvar çapı (MCV)'yi azalttı (P<0.05). Ayrıca, plazma alanin aminotransferaz (ALT) aktivitesi, toplam kolesterol ve toplam protein seviyeleri hiçbir grupta değişmedi (P>0.05) ve alkalin fosfataz (ALP) aktivitesi, egzersiz gruplarında anlamlı olarak artarken, glikoz ve trigliserit seviyeleri azaldı (P<0.05). Sonuç olarak, bulgularımız akut yorucu egzersizin MCV ve RDW değerlerini, plazma ALP aktivitesini, glukozu ve trigliserit seviyelerini etkilediğini gösterdi. Gingko Biloba ekstresi takviyesi, yalnızca ALP aktivitesindeki ve RDW değerindeki egzersiz kaynaklı değişiklikleri iyileştirdi. Bu nedenle, EGB761'in egzersiz sonrası kullanımının veya farklı dozlarının etkilerinin ilerde yapılacak kapsamlı çalışmalarda incelenmesi önerilmektedi.

***Anahtar Kelimeler****: Biyokimya, yorucu egzersiz, gingko biloba, hematolojik parametreler*

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## Introduction

In the last few decades, sport has become a major social event among the people, so the exercise has been an attractive issue for the scientists who studied its effects in terms of various aspects in many studies conducted on human and animals (1, 2). Although regular physical exercises have beneficial effects on the health of organs such as heart, liver, bone, muscle, and brain in terms of reducing risk of coronary heart disease, osteoporosis, diabetes mellitus and cancer, or increasing learning, memory, neurogenesis, and production of neurotrophic factors, the acute exercises may lead to

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damages in these organs. Therefore, the type, intensity and duration of exercise may affect the physiological, hematological, and biochemical parameters in the body (3, 4).

Exercise leads to several physiological changes in response to homeostatic imbalances. For example, exercise stimulates acute polycythemia and increases hematocrit because of the increased oxygen demands, metabolic stress, alterations in fluid compartments, and leukocytosis (5, 6). It was reported that exercise caused anemia in humans (7) while increased of RBC and PCV in horses during the first stages of the race (8). Wu et al. (9) showed that a 24-h ultramarathon race increased leukocytes and thrombocytes. Exercise can also alter biochemical components of blood: exhaustive exercise considerably increased blood creatinine, total cholesterol, and HDL-cholesterol in athletes (10). Serum ALP activity in young dogs was increased post treadmill exercise (11) and the activities of creatinine kinase (CK), lactate dehydrogenase (LDH) and liver related enzymes in the serum were increased in male Wistar rats following running exercise (12).

*Ginkgo biloba* is a native tree originated from China, and the standardized leaves extract of Gingko biloba (EGb761) has a common usage of worldwide as an herbal medicine due to its health-promoting properties (13, 14). Antioxidative effect of EGB761 is a well-known property of it which is able to scavenge free radicals and prevent lipid peroxidation. It has also anti-inflammatory and modulatory effects on immune response, and vasodilative and platelet inhibition activity (15-17). Due to these features, EGb761 is used to improve cognitive functions and care the symptoms of eye, heart and Alzheimer's diseases, vascular dementia, vertigo, chronic cerebral insufficiency, and peripheral vascular disorders, and accidents including brain trauma, and tinnitus of vascular origin (18, 19).

According to literature, EGb761 is mainly studied in terms of neurobehavioral, vascular and antioxidative effects in many previous investigations. However, there are still limited research related to its effects on the exercise metabolism (20, 21). Therefore, this study was designed to investigate the effects of EGb761 supplementation on hemato-biochemical parameters following acute exhaustive treadmill exercise in male rats.

## Material and Methods

**Research and Publication Ethics:** This study was conducted with the approval of Local Ethical Committee of Kırıkkale University with the document number of 2020/02 – 27.03.2020.

**Animals:** Thirty-two male Wistar Albino rats at the age of 2-3 months old were obtained from Gülhane Laboratory Animals Production and Research Center, Ankara, Turkey. The animals were housed in plastic cages (four rats/cage) at a controlled room temperature (22-25 °C) and 55-60 % humidity with 12:12-h light-dark cycle in Kırıkkale University Hüseyin AYTEMIZ Experimental Research and Application Center. They were fed with commercial standard dry pellet rat food and water *ad libitum* during the study and acclimated for two weeks before experiment. Afterwards, they were randomly divided into four groups within the equal number of rats as control, EGb761, exercise, and EGb761+exercise.

**Experimental design:** The experimental design of the present study was approved by the Local Ethical Committee of Kırıkkale University with the document number of 2020/02-11. Before the treatment, EGb761 tablets (Tebokan intens, Abdi İbrahim, Turkey) after crushing were dissolved in 0.9% saline solution as 100 mg/2 cc by vortex. The animals of the control groups were received only 2 cc/kg-body weight (b.w.) 0.9% saline solution by oral gavage for 4 weeks (5 days/week) and not applied exercise. The exercise group was also received 0.9% saline solution like control groups and applied acute exhaustive exercise protocol. The EGb761 and EGb761+exercise groups were orally administered with 100 mg/kg-b.w. via gavage. EGb761 in 2 cc 0.9% saline solution for 5 days in a week for 4 weeks, and the latter were applied exercise protocol as well. All the treatments were carried out at 09:00-12:00 am during the investigation.

**Exercise Protocol:** The acute exhaustive exercise protocol was performed as described by Fei-Wei et al. (22) with some modifications. In brief, all rats of exercise and EGb761+exercise groups were underwent an exercise program on a rodent treadmill (MAY, TME 0805, USA) for 4 weeks. Before the exhaustive exercise they were familiarized with 10-min exercise per day for 3 days in a week by the following speeds: 10 m/min in 1$^{st}$ week, 15 m/min in 2$^{sd}$ week, 20 m/min in 3$^{rd}$ week, and 25 m/min in 4$^{th}$ week. On the last day of the experiment, these rats were ran at 25 m/min and 5% grade until exhaustion. The animals were forced to run by low-voltage electrical shock in order to motivate them and create an acute exhaustive exercise. The criterion for exhaustion was determined as the touching of animal to the electrified grid at the rear of the treadmill five times within 2 min (23).

**Sample Collection and Measurements:** The animals of control and EGb761 groups were anesthetized with an intraperitoneal (i.p.) injection of 90 mg/kg ketamine plus 10 mg/kg xylazine at the last day of the experiment while the rats of the exercise and EGb761+exercise groups were anesthetized with the same method after exhaustive exercise. Blood samples were collected into the $K_3$EDTA and heparinized test tubes for hematological and biochemical analysis, respectively, via cardiac puncture after thoracotomy. The former samples were immediately analyzed for RBC, PCV, HGB, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width (RDW) using auto hematology analyzer (Mindray BC-6800, China). The latter samples were centrifuged at 3000 rpm at 4 °C for 10 min to isolate plasma. The plasma samples were then analyzed for alkaline phosphatase (ALP), alanine aminotransferase (ALT), glucose, total cholesterol, triglyceride, and total

**Table 1**. Changes in selected hematological parameters in control and experimental groups

| | Control (n=8) | Gingko (n=8) | Exercise (n=8) | Gingko + Exercise (n=8) | P Value |
|---|---|---|---|---|---|
| | Mean ± SEM | Mean ± SEM | Mean ± SEM | Mean ± SEM | |
| RBC (×$10^6$/µL) | 6,75 ± 0.13 | 6.72 ± 0.49 | 7.27 ± 0.35 | 7.25 ± 0.10 | >0.05 |
| PCV (%) | 41.28 ± 0.72 | 41.75 ± 3.09 | 42.88 ± 2.14 | 42.33 ± 0.60 | >0.05 |
| HGB (g/dL) | 12.59 ± 0.43 | 12.47 ± 0.74 | 13.78 ± 0.65 | 13.85 ± 0.26 | >0.05 |
| MCV (fL) | 61.15 ± 0.52 $^{ab}$ | 62.10 ± 0.58 $^{a}$ | 58.98 ± 0.85$^{bc}$ | 58.39 ± 0.35 $^{c}$ | <0.05 |
| MCH (pg) | 18.56 ± 0.41 | 18.72 ± 0.81 | 18.98 ± 0.24 | 19.11 ± 0.18 | >0.05 |
| MCHC (%) | 30.35 ± 0.62 | 30.15 ± 1.38 | 32.19 ± 0.19 | 32.74 ± 0.29 | >0.05 |
| RDW (%) | 13.19 ± 0.23$^{b}$ | 13.75 ± 0.21$^{ab}$ | 14.21 ± 0.29 $^{a}$ | 13.78 ± 0.14$^{ab}$ | <0.05 |

$^{a,b,c}$: Different letters in the same row are represented statistically significant which is considered P<0.05. SEM: standard error mean.

**Table 2.** Changes in selected biochemical parameters in control and experimental groups

| | Control (n=8) | Gingko (n=8) | Exercise (n=8) | Gingko + Exercise (n=8) | P Value |
|---|---|---|---|---|---|
| Variables | Mean ± SEM | Mean ± SEM | Mean ± SEM | Mean ± SEM | |
| ALP (U/L) | 285.86 ± 13.60 $^{b}$ | 336.29 ± 27.77 $^{ab}$ | 380.37 ± 16.77 $^{a}$ | 292.00 ± 8.28 $^{b}$ | <0.01 |
| ALT (U/L) | 71.86 ± 5.28 | 63.14 ± 9.14 | 73.00 ± 6.08 | 70.00 ± 10.39 | >0.05 |
| Glucose (mg/dL) | 256.00 ± 25.37 $^{a}$ | 214.43 ± 18.35 $^{ab}$ | 136.38 ± 11.98 $^{c}$ | 162.25 ± 10.82 $^{bc}$ | <0.05 |
| Total Cholesterol (mg/dL) | 52.14 ± 4.53 | 53.43 ± 4.35 | 53.88 ± 3.34 | 46.38 ± 2.46 | >0.05 |
| Triglyceride (mg/dL) | 60.71 ± 7.39 $^{a}$ | 55.00 ± 6.14 $^{a}$ | 35.13 ± 2.28 $^{b}$ | 32.88 ± 3.44 $^{b}$ | <0.05 |
| Total Protein (g/dL) | 5.40 ± 0.19 | 5.30 ± 0.30 | 5.69 ± 0.06 | 5.46 ± 0.12 | >0.05 |

$^{a,b,c}$: Different letters in the same row are represented statistically significant which is considered P<0.05 and P<0.01. SEM: standard error mean.

protein with auto biochemistry analyzer (Mindray BS-2000, China) for biochemical evaluation.

**Statistical Analysis:** Descriptive analysis and normality tests of all data obtained from each group were performed with SPSS 18.0 package program for Windows. Results were presented as mean ± standard error mean (SEM), and compared using One-way analysis of variance (ANOVA), following post-hoc Tukey test in order to determine the difference between groups (22). The lower P value than 0.05 was considered as statistically significant.

## Results

The hematological findings presented in Table 1 showed that the measured values of RBC, PCV, HGB, MCH, and MCHC did not change statistically between the experimental groups (P>0.05). The statistically similar values of MCV in control and EGb761 group which has highest level of it were significantly (P<0.05) higher than that of exercise and EGb761+exercise groups which has the lowest level of MCV. As shown in the same table, acute exhaustive exercise resulted in increased RDW values in rats significantly (P<0.05). However, EGb761 supplementation caused it to decrease to similar level within the other groups.

According to biochemical analysis showed in Table 2, there was no significant changes in ALT activity, and total cholesterol and total protein levels between the compared groups (P>0.05). On the other hand, ALP activity was significantly higher in the exercise group compared to control (P<0.01) and EGb761+exercise groups (P<0.05). It was also high level in the EGb761 group but not different from other groups (P>0.05). The level of glucose was statistically decreased by the exercise compared to control group (P<0.05). It was slightly increased after EGb761 supplementation in EGb761+exercise group, but still similar with exercise (P>0.05), and different from control groups (P<0.05). Plasma triglyceride levels were statistically higher in non-exercised groups (control and EGb761 groups) than that of exercised groups (exercise and EGb761 + exercise groups, P<0.05).

## Discussion

Exercise is recommended for a healthy life because of its health-promoting effects. However, unlike the regular and long-term exercise, acute and especially exhaustive exercise may lead to damages in several organs such as heart, liver, brain, and muscle as well as physiological alterations in response to homeostatic imbalances (2, 3). The EGb761 supplment is widley used throughout the world due to its antioxidative effects. However, there are still limited research related to its effects on blood hematology and biochemistry during the exercise. Therefore, it was studied the effects of EGb761 on hemato-biochemical parameters following acute exhaustive treadmill exercise in male rats.

As presented in Table 1, hematological findings of this study showed that exercise, EGb761 supplementation or both did not lead to alteration on RBC, PCV, HGB, MCH, and MCHC. However, acute exhaustive exercise reduced MCV value in rats while increased RDW value. Similarly, Wu et al. (9) showed

that a 24-h ultramarathon race did not change the blood levels of RBC, HCT, HGB, MCV, MCH, and MCHC. In addition, similar levels of RBC (24), PCV (24, 25), HGB (25), MCH (26), and MCHC (25, 26) were reported after acute exercises in human and animals. On the other hand, acute exhaustive swimming exercise decreased the amounts of RBC, PCV, and HGB in male rats (26, 27). Dzhelebov et al. (1) have also reported that exhaustive exercise was decreased RBC, HGB, MCH, and MCHC values in dogs unlike MCV value which was elevated right after the exercise. Contrary to this, Koc et al. (25) have demonstrated that RBC counts were increased in handball player after acute exhaustive exercise whereas MCV and MCH values were decreased. Although not significantly, the levels of RBC, PCV, and HGB in exercised rats slightly increased in the present study. These values were probably elevated to compensate the increasing oxygen demands. However, MCV value was significantly reduced in exercise group. Exercise-induced iron deficiency may be responsible for this decrease, since it may lose via sweat, gastrointestinal bleeding and hematuria, and leads to microcytes in erythrocytes (28). In accordance with these findings, RDW was increased in exercised rats, but it was decreased to similar level of control groups following EGb761 supplementation in EGb761+exercise group. As mentioned above, short-term effects of exercise on blood parameters are still controversial (29), which is probably due to differences of the type, intensity and duration of exercises and species as well as individual differences.

It was observed in this study that plasma ALT activity, and total cholesterol and total protein levels did not change in each group, and ALP activity was significantly increased in exercise groups while glucose and triglyceride levels were decreased (Table 2). These results were confirmed by some previous studies, in which serum/plasma liver enzymes such as ALT, AST (24, 30), and GGT (10) activities and total protein (24) level did not change after exercise, while ALP activity increased (10-12) and triglyceride level decreased (30). On the other hand, there are several reports incompatible with our results. It has been demonstrated that acute exhaustive exercises decreased plasma total cholesterol level (30); increased plasma ALT activity (2, 12) and total cholesterol level (10); did not change glucose (2, 24, 30) and triglyceride (10) levels in human and animals. In the present study, in addition to statistically increased ALP, ALT activity was also increased non-significantly in the exercise group. The elevated activities of these enzymes are generally responsible for dysfunctions or damages of tissues, especially liver (31). It has been also reported that exercise caused oxidative tissue damage in liver (23, 32). Therefore, possible acute exhaustive exercise-induced oxidative damage in liver may lead to increase of ALP and ALT activities significantly and slightly, respectively, in this study. On the other hand, the elevated ALP and ALT activities were reduced via EGb761 supplementation in EGb761+exercise group. This was probably related to antioxidative effects of EGb761 since it was reduced MDA and increased SOD activities in liver of exercised-mice (32), and successfully lowered the ALT activities by recovering degeneration, necrosis, mononuclear cell infiltration, and hemorrhage in hepatic tissue of rats (33). Furthermore, exercise induces insulin sensitivity due to increasing glucose needs muscles to support work (34). Therefore, the reduction of plasma glucose and triglyceride levels in exercised rats may resulted from using of them in the production of required energy for exercise.

In conclusion, results of the present study showed that acute exhaustive exercise affected some hematological and biochemical parameters. However, EGb761 supplementation ameliorated the exercise-induced changes in ALP activity and RDW value in EGb761+exercise group while it could not increase the reduced MCV, glucose and triglyceride levels in rats. In this study, 100 mg/kg b.w. EGb761 was used before the exercise. Therefore, it is suggested that the effects of usage after exercise or different doses of EGb761 should be investigated in the future comprehensive studies.

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