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The Effect of Artichoke Against the Toxicity of Oxfendazole, a Promising Agent for the Treatment and Control of Helminth Infections

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This study was carried out to determine the protective and/or therapeutic roles of artichoke against oxidative stress that oxfendazole (OX) can cause in rats. No intervention was made in the first group. Artichoke extract was applied to the second group at dose of 1.5 g/kg/day for seven days by gavage, to the third group for 15 days at 100 mg/kg/day dose an OX by gavage. The fourth group was formed as Artichoke+OX and the fifth group was OX+Artichoke. In the fourth group, artichoke treatment was started seven days before the OX application and continued for seven days, followed by 15 days after OX application. In the fifth group, artichoke and OX applications were started simultaneously. Upon completion of investigation, levels of malondialdehyde (MDA), reduced glutathione (GSH), and activities of antioxidant enzymes, including catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) were assessed in blood tissue. In comparison to control group, the group treated with OX exhibited significantly elevated levels of MDA ($p<0.001$) and GSH ($p<0.001$), alongside reduced activities of CAT ($p\leq0.001$), GSH-Px ($p<0.01$), and SOD ($p<0.001$). While the values in all parameters in the fifth group approached the control group values, MDA levels in the fourth group could not reach the control group values. In addition, there was no statistical difference in CAT and GSH-Px activities between the OX-administered group and fourth group. As a result, considering the doses and durations applied in our study against oxidative stress caused by OX, it was observed that therapeutic effect of artichoke was stronger than its protective effect.

Key Words: *Oxfendazole, artichoke, oxidative stress, antioxidant*

Helmint Enfeksiyonlarının Tedavisi ve Kontrolünde Umut Vaat Eden Bir İlaç Olan Oksfendazolün Toksisitesine Karşı Enginarın Etkisi

Bu çalışma, ratlarda oksfendazol (OX)'ün oluşturabileceği oksidatif strese karşı enginarın koruyucu ve/veya tedavi edici rollerini belirlemek amacıyla yapılmıştır. Birinci gruba herhangi bir uygulama yapılmamıştır. İkinci gruba 1,5 g/kg/gün dozunda yedi gün boyunca gavaj yoluyla enginar ekstraktı, üçüncü gruba ise 100 mg/kg/gün dozunda 15 gün boyunca gavaj yoluyla OX uygulanmıştır. Dördüncü grup; Enginar+OX, beşinci grup ise OX+Enginar olarak oluşturuldu. Dördüncü grupta enginar tedavisine OX uygulamasından yedi gün önce başlanıp yedi gün boyunca uygulanmış, ardından 15 gün OX uygulaması yapılmıştır. Beşinci grupta enginar ve OX uygulamalarına eş zamanlı olarak başlanmıştır. Araştırmanın tamamlanması üzerine, kan dokusunda malondialdehit (MDA), redükte glutatyon (GSH) seviyeleri ve katalaz (CAT), süperoksit dismutaz (SOD) ve glutatyon peroksidaz (GSH-Px) dahil olmak üzere antioksidan enzimlerin aktiviteleri değerlendirilmiştir. Kontrol grubuyla karşılaştırıldığında, OX ile tedavi edilen grupta MDA ($p<0.001$) ve GSH ($p<0.001$) seviyeleri önemli ölçüde yüksek bulunurken, CAT ($P\leq0.001$), GSH-Px ($p<0.01$) ve SOD ($p<0.001$) aktiviteleri azalmıştır. Beşinci gruptaki tüm parametrelerdeki değerler kontrol grubu değerlerine yaklaşırken, dördüncü gruptaki MDA seviyeleri kontrol grubu değerlerine ulaşamamıştır. Ayrıca, OX uygulanan grup ile dördüncü grup arasında CAT ve GSH-Px aktivitelerinde istatistiksel olarak bir fark saptanmamıştır. Sonuç olarak, çalışmamızda OX'un neden olduğu oksidatif strese karşı uygulanan dozlar ve süreler göz önüne alındığında, enginarın tedavi edici etkisinin koruyucu etkisinden daha güçlü olduğu gözlenmiştir.

Anahtar Kelimeler: *Oksfendazol, enginar, oksidatif stres, antioksidan*

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Introduction

Pesticides are chemicals used to prevent, control or reduce harmful organisms. Pesticides can be found in any environment (water, air and soil) and can be transported to different ecosystems. All living things are directly or indirectly affected by pesticide applications (1, 2). One of the most widely used anthelmintic drug groups is benzimidazoles due to their low cost, wide spectrum range and ease of administration. Oxfendazole (OX [methyl 5-(phenyl sulfonyl)-2-benzimidazolecarbamate]), fenbendazole (FEN), thiabendazole and oxybendazole are the most commonly used benzimidazole anthelmintic drugs. Among the benzimidazole group of anthelmintic drugs, mebendazole and albendazole are commonly used in both human and veterinary medicine (3). In the past few years, it has been suggested that OX can also be used against human helminths (4). OX is effective against adults, larvae and eggs of gastrointestinal and lungworms of cattle and sheep, adults of liver flukes and Moniezia spp. When OX is administered orally to ruminant animals, it reaches a maximum in the blood in 6 hours and the concept of half-life is approximately 6-7 hours. The excretion of the metabolites and active substances from the animal's body is slow. OX from the

animal's body; It is removed with urine 26% and feces 63% (5). OX has antinematodal and anticestodal effects by affecting energy metabolism in parasites. Its effect inhibits the activity of fumarate reductase, which mediates the reduction of fumarate to succinate in parasites, preventing energy generation and causing paralysis of muscles in parasites and then death of parasites (6). Although OX is not thought to have carcinogenic potential in rats and mice, it has been emphasized that OX may have tumor-promoting potential in rats. Thus, acceptable daily intake levels have been determined for OX and many other benzimidazole derivative anthelmintic drugs. However, although the mechanisms underlying the tumor-promoting activity of OX in rats have not yet been elucidated, administration of OX above the therapeutic dose and at a frequency exceeding the therapeutic dose may disrupt the oxidative balance and lead to lipid peroxidation (1, 3, 5).

Oxidative stress arises when the production of reactive oxygen species (ROS) exceeds the ability of a cell or tissue to counteract these species with antioxidants. Through the stimulation or inhibition of important enzyme systems, antioxidants can lessen oxidative damage. There is a balance between the rate of ROS generation and enzymatic activity, such as catalase (CAT), glutathione peroxidase (GSH-Px), glutathione-S-transferase (GST), and superoxide dismutase (SOD), under normal physiological conditions. The generation of ROS is regulated by non-enzymatic antioxidants, including vitamins (such as C, A and E) and reduced glutathione (GSH). An imbalance occurs when there is an overproduction of ROS and/or insufficient antioxidant protection, leading to the onset of oxidative stress. The primary indicator of oxidative stress is lipid peroxidation (LPO). The best-known and easiest parameter to measure the degree of LPO under oxidative stress circumstances is malondialdehyde (MDA), which yields data that is pertinent for clinical use (7).

Today, prevention or reduction of oxidative stress due to toxications resulting from exposure to chemical toxic substances and carcinogens is one of the most studied subjects. For this purpose, studies on the research and development of substances with antioxidant properties are needed now as in the past, and there have been several *in vitro* and *in vivo* models employed (7, 8).

Artichoke (*Cynara scolymus L.*) has strong antioxidant properties and it has been stated that it has liver protective, antimicrobial, cholesterol-lowering properties thanks to its flavonoids (luteolin, apigenin) and caffeoyl quinic acid derivatives (cynarin and chlorogenic acid). However, it is also frequently used in conditions such as dyspepsia and intestinal syndrome. Owing to the active compounds' water solubility and bitter flavor, the majority of teas and aqueous extracts of dried leaves are utilized medicinally (9). Numerous research efforts have concentrated on the antioxidant and liver-protective properties of artichoke, demonstrating its efficacy in these areas (10-14).

The objective of the study was to explore the protective and/or therapeutic effects of artichoke in mitigating the toxicity potentially induced by OX, through the analysis of plasma MDA levels, blood GSH concentrations, and the various antioxidant defence enzymes activities in rats.

Materials and Methods

Research and Publication Ethics: The Local Ethics Committee for Animal Experiments approved this study at Fırat University (Approval number: 2014/01-196).

Experimental animals: 35 male Wistar Albino rats, weighing an average of 250–300 g and 8–10 weeks old, were used in the investigation. Rats were purchased from the Firat University Experimental Application and Research Center (Elazig, Türkiye). Before the application, the rats spent a week for adaptation to their new surroundings. The outside temperature was 24±1°C with a 45±5% relative humidity. There was also a 12-hour cycle of light and dark in the rats' surroundings. Rats were given a regular pellet diet and unlimited access to tap water.

Experimental Protocol: There were five different groups of rats, each including seven rats. There are four experimental groups and a control in the experimental design, as shown in Table 1; No intervention was made in the first group (control). Artichoke extract (Arı Engineering, Ankara/Türkiye) was applied to second group at dose of 1.5 g/kg/day for seven days by gavage needle, to third group for 15 days at 100 mg/kg/day dose an OX (Vetranal, 34176, Merck, Germany) by gavage needle. The fourth group was formed as Artichoke+OX (protective group) and fifth group was OX+Artichoke (therapeutic group). In the fourth group, artichoke treatment was started seven days before OX application and continued for seven days, followed by 15 days after OX application. In the fifth group, the artichoke and OX giving were started simultaneously, and artichoke was applied for seven days and OX was applied for 15 days. While artichoke extract was prepared by dissolving it in distilled water, OX was prepared by dissolving it in 0.5% sodium carboxymethyl cellulose. The rats were decapitated 24 hours following the final administration, and their blood tissues were subsequently collected.

Preparation of Blood: Blood samples were subjected to centrifugation at 3.000 revolutions per minute (rpm) for a duration of 15 minutes in tubes containing Ethylenediaminetetraacetic acid (EDTA) to facilitate the extraction of plasma. Plasma samples were utilized to assess MDA levels, which serve as an indicator of LPO. Whole blood specimens were employed for the determination of GSH and GSH-Px levels. Three times, plasma separated blood samples were rinsed in 0.9% NaCl saline. Then, the activities of the SOD and CAT as well as the levels of erythrocyte hemoglobin (Hb) were measured.

Table 1. Experimental design

Groups	Applications
Control Group	No application was made to the rats in this group (n: 7)
Artichoke Group	Artichoke extract was administered to this group at a dose of 1.5 g/kg/day for 7 days by gavage needle, artichoke was prepared by dissolving in distilled water (n: 7)
OX Group	OX was administered to this group for 15 days at a dose of 100 mg/kg/day by gavage needle. OX was prepared by dissolving in 0.5% sodium carboxymethyl cellulose (n: 7)
Artichoke+OX Group *(Protective group)*	Artichoke treatment was started 7 days before the OX application and continued for 7 days, followed by 15 days of OX application (n: 7)
OX+Artichoke Group *(Therapeutic group)*	Artichoke and OX applications were started at the same time, and artichoke was applied for 7 days and OX was applied for 15 days (n: 7)

Assessment of LPO and Some Antioxidants: This study used a spectrophotometer and a modified Placer et al. (15) method to detect the levels of MDA in tissue samples. The process involves the interaction of MDA, an LPO byproduct, with thiobarbituric acid. The method described by Ellman et al. (16) was used to quantify the GSH levels. The method relies on spectrophotometric analysis of the yellow coloration produced when 5,5'-dithiobis (2-nitrobenzoic acid) is introduced to sulfhydryl groups. Since hydrogen peroxide (H_2O_2) can absorb light at 240 nm, the methodology established by Aebi in 1974 was employed to assess the activity of CAT (17). This method uses spectrophotometry to measure the rate of H_2O_2 breakdown by the CAT enzyme. The Beutler method (18) was used to calculate the GSH-Px activity. This method entails using H_2O_2 to catalyze. The conversion of GSH to its oxidized form, known as oxidized glutathione (GSSG), which is done by GSH-Px. The glutathione reductase (GR) reaction was used to calculate the rate at which GSSG formed. Using a modified version of Sun et al.'s (19) approach, the SOD activity was measured by measuring the color of the reduction product, which was obtained by reducing nitroblue tetrazolium with the superoxide anion (O_2^-) generated by the xanthine oxidase (XO) system. According to Frankel et al. (20), the drabkin method was used to measure hemoglobin concentrations.

Statistical Analysis: The evaluation of statistical significance among various groups was conducted utilizing the SPSS 22 software. The Shapiro-Wilk normality test was used to assess whether the raw values of all measured parameters showed a normal distribution. The outcomes of the test demonstrated that every parameter value did so. Based on the outcomes of this test, group differences were assessed utilizing *post hoc* Tukey testing and one-way analysis of variance (ANOVA), it was utilized to compare the groups. All values were derived using the mean and the standard error of the mean. The mean and standard error were used to illustrate the study's conclusions. *p*-values that fell below 0.05 were considered to be statistically significant.

Results

Compared to the control group, the OX applied group exhibited significantly elevated levels of MDA (P<0.001) and GSH (P<0.001), alongside reduced activities of CAT (P≤0.001), GSH-Px (P<0.01), and SOD (P<0.001). There were no statistically significant differences observed between the artichoke group and the control group for any of the parameters. While the values in all parameters in the fifth group (OX+Artichoke) reached the values of the control group, MDA levels in the fourth group could not reach the control group values. In addition, there was no statistical difference in CAT and GSH-Px activities between the OX-administered group and the fourth group (Artichoke+OX group) (Figure 1-5).

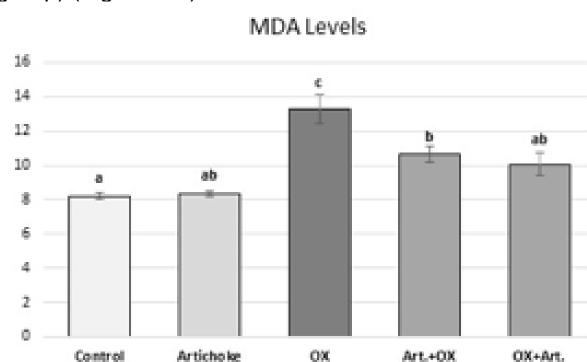

Figure 1. Effects of artichoke on plasma MDA levels in OX-applied rats

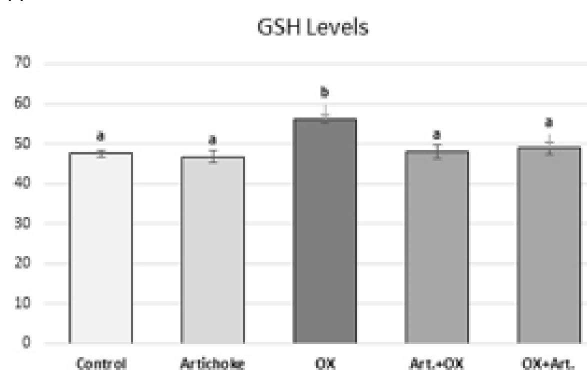

Figure 2. Effects of artichoke on erythrocyte GSH levels in OX-applied rats

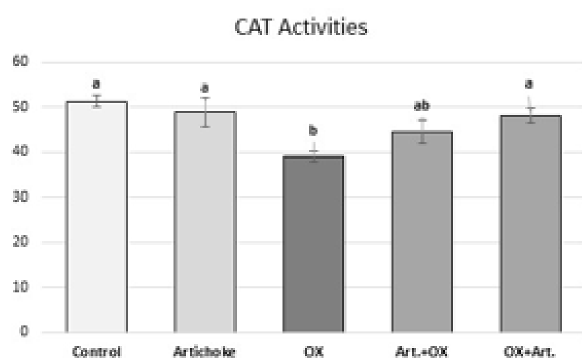

Figure 3. Effects of artichoke on erythrocyte CAT activities in OX-applied rats

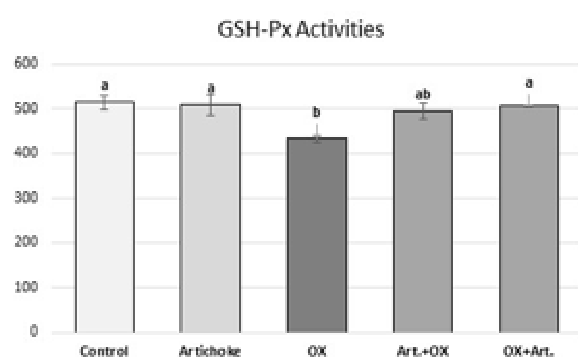

Figure 4. Effects of artichoke on erythrocyte GSH-Px activities in OX-applied rats

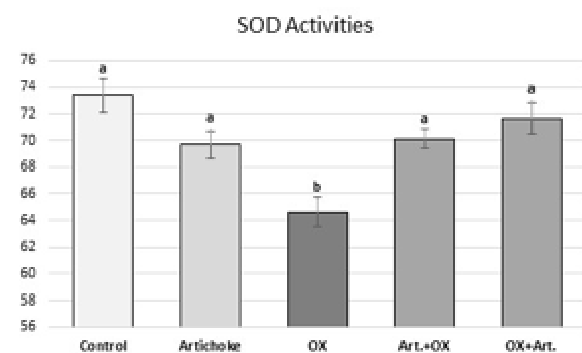

Figure 5. Effects of artichoke on erythrocyte SOD activities in OX-applied rats

Discussion

OX is a widely used broad-spectrum anthelmintic that is used to treat and prevent gastrointestinal parasites in livestock animals, such as pigs, sheep, and cattle. While it is effective against parasites, like many medications, it can also have unintended side effects and potential toxicities. Some of the potential adverse effects of OX include liver damage, gastrointestinal disturbances, and hypersensitivity reactions (21, 22).

The 38th session of the joint FAO/WHO expert committee on food additives (JECFA) reported that OX decreased the levels of connexin 32, a protein crucial for gap junctional intercellular communication, which serves as a biological marker for tissues that have been exposed to tumor-promoting agents. Furthermore, it was observed that it increased the number of hepatocellular foci that were positive for the placental variant of GST, a novel preneoplastic marker linked to chemical carcinogens (23, 24). The results suggest that OX facilitates tumor development in the rat liver through a non-genotoxic or indirectly genotoxic mechanism, as it does not demonstrate the mutagenic potential observed in short-term genotoxicity assessments (23); however, the exact molecular mechanism underlying this activity is still unknown (25).

Repeated administration of benzimidazole-derived anthelmintics, specifically mebendazole and albendazole, has been documented to induce an imbalance in glutathione homeostasis and liver toxicity in rat models (26). The results indicate that oxidative stress could be a contributing factor in the carcinogenesis of rats induced by FEN and OX. Although OX is not thought to have carcinogenic potential in rats and mice, it has been emphasized that OX may have tumor-promoting potential in rats. Thus, acceptable daily intake levels (0–7 µg/kg/gün) have been determined for OX and many other benzimidazole derivative anthelmintic drugs. However, although the mechanisms underlying the tumor-promoting activity of OX in rats have not yet been elucidated, administration of OX above the therapeutic dose and at a frequency exceeding the therapeutic dose may disrupt the oxidative balance and lead to lipid peroxidation (1, 3, 5, 26).

Oxygen is present in the liver due to enzymatic activities. Oxygen can cause oxidative stress during metabolism and activity, which can result in a disparity exists between the capacity of the body to resist ROS and the rate at which they are manufactured. The body has a sophisticated antioxidant defense system that comprises a number of antioxidant enzymes that are essential for preserving cellular redox balance in order to combat the damaging effects of ROS. In response to increased ROS production induced by OX, the body's defense mechanisms are triggered (22, 27, 28). Certain research indicates that OX may influence both the expression and functionality of antioxidant defence enzymes, either by promoting their synthesis or inhibiting their function, depending on the specific tissue and dosage. OX may interfere with the body's inherent mechanisms for antioxidant defense, depleting the levels of antioxidants like GSH, SOD and CAT. Reduced antioxidant capacity can lead to increased ROS accumulation and oxidative damage (27-29). The relationship between OX and antioxidants involves a complex interplay. OX has the potential to provoke oxidative stress, which in turn activates antioxidant response mechanisms and enhances the activity of various antioxidant defence enzymes (27, 28). However, the drug's impact on the activity of these enzymes and its tissue-specific effects require further investigation.

In the present study, the increase in MDA levels observed in the OX-treated group can be explained by the mechanism by which OX causes cell damage by

causing lipid peroxidation in cells. The present study also showed that a significant increase in oxidative stress was accompanied by a simultaneous decrease in the activities of enzymes involved in the removal of superoxide anions and peroxides, namely CAT and SOD, and their related enzymes (GSH-Px). The significant increase observed in plasma MDA levels in OX-treated animals showed that OX leads to the formation of high levels of free radicals that cannot be tolerated by the cellular antioxidant defense system. This significant decrease in enzyme activities can be explained by the consumption of free radicals during their conversion to less harmful or harmless metabolites. It can be explained as the increase in the activity of GSH-Px due to the insufficient conversion of GSH, which is the substrate, to GSSG.

These findings suggest that ROS production is involved in the cellular tumor promotion of OX and strongly support previous studies (28, 30).

Vegetable artichokes (*Cynara scolymus*) are well-known for their possible health advantages, which include liver support and antioxidant qualities. Artichoke contains compounds like cynarin and silymarin, which are believed to have hepatoprotective effects. However, there is no established evidence to suggest that artichoke can directly counteract or mitigate OX induced damage. The potential liver-protective properties of artichoke are more commonly studied in the context of liver disorders and toxicity caused by factors like alcohol consumption, drug use, and exposure to environmental toxins (9-14, 31).

Because artichokes are rich in antioxidants, including flavonoids, polyphenols, and cynarin, their potential effects on oxidative stress have been researched. Antioxidants are compounds that assist in neutralizing detrimental entities known as free radicals, which can lead to cellular oxidative stress and damage. Oxidative stress comes out when there is a disparity between the concentration of free radicals and the body's ability to neutralize them via antioxidants. It is associated with various health conditions, including inflammation, cardiovascular diseases, neurodegenerative disorders, and cancer. The potential effects of artichoke on oxidative stress have been investigated in both animal and human studies. Artichoke extracts have demonstrated strong antioxidant properties in vitro and animal studies. These antioxidants help scavenge free radicals, minimizing oxidative harm to cells and tissues (9-14, 31).

Artichoke extracts have been shown to protect the many tissues from oxidative stress and damage in animal models (9, 13, 14, 31). They may enhance the activity of antioxidant enzymes, leading to improved detoxification and reduced oxidative damage.

In the present study, it was observed that MDA levels were lower in the groups applied artichoke for both therapeutic and preventive purposes compared to the group applied OX, and this can be explained as artichoke eliminates the possibility of oxidative stress caused by OX application in rats. Artichoke as a treatment for rats treated with OX may be effective in significantly increasing CAT and GSH-Px activities. Artichoke reduced the increased GSH levels, caused an increase in the decreased SOD activity and thus prevented the harmful effects of superoxide radicals. When the results are examined, it was observed that some parameters (CAT and GSH-Px) in the artichoke group applied for preventive purposes did not change as much as in the artichoke group applied for therapeutic purposes. This can be explained as the oxidative effects of OX applied after artichoke occurred rapidly and were higher than the antioxidant effects of artichoke. It can be thought that artichoke achieves all of this by neutralizing harmful entities known as free radicals, which can cause cellular oxidative stress and damage, with antioxidants such as flavonoids, polyphenols and cynarin in its content. Artichoke can prevent free radical formation by directly cleaning free radicals and then converting antioxidant species into less toxic products.

In conclusion, OX, like many drugs, has the potential to induce oxidative stress, which can lead to cellular damage. While artichoke is known for its potential hepatoprotective properties, there is currently no scientific evidence to support its specific role in counteracting OX induced damage.

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