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Effect of Paclitaxel and Ferrostatin-1 administration on fecal short chain fatty acids

Efecto de la administración de Paclitaxel y Ferrostatina-1 sobre los ácidos grasos de cadena corta en las heces

Beyza Suvarikli-Alan[1]*, Zuhal Alkay[2], Göktuğ Şentürk[3], Avni Camgöz[1], Yunus Emre Tunçil[2], Tufan Keçeci[4], Feray Altan[5], Zafer Bulut[1,6]

[1]Selçuk University, Faculty of Veterinary, Department of Biochemistry, Türkiye
[2]Necmettin Erbakan University, Faculty of Engineering, Department of Food Engineering, Türkiye
[3]Aksaray University, Faculty of Veterinary Medicine, Department of Physiology, Türkiye
[4]Selçuk University, Faculty of Veterinary, Department of Physiology, Türkiye
[5]Dokuz Eylül University, Faculty of Veterinary Medicine, Department of Pharmacology and Toxicology, Türkiye
[6]Dokuz Eylül University, Faculty of Veterinary Medicine, Department of Biochemistry, Türkiye

ABSTRACT

Short-chain fatty acids are organic acids manufactured by the gut microbiota. The type and amount of microflora in the colon, the source of substrate and the transition period through the intestine affect the rate and amount of Short-chain fatty acids production. Ferrostatin-1, a synthetic compound and a potent inhibitor of ferroptosis, is an antioxidant capable of inhibiting ferroptosis. Paclitaxel is a type of chemotherapy called taxane and causes peripheral neuropathy as a side effect of cancer treatment. In this study, we researched the effect of paclitaxel and ferrostatin-1 administration on fecal Short-chain fatty acids. For this purpose, rats were divided into four groups as control (n = 6), paclitaxel (n = 8), ferrostatin (n = 9) and paclitaxel + ferrostatin (n = 9). Paclitaxel (10 mg/kg) and ferrostatin-1 (5 mg/kg) were administered intraperitoneally once a week for 4 weeks. At the end of the experiment, the amounts of Short-chain fatty acids (acetate, propionate and butyrate) and branched-chain fatty acids (iso-butyrate and iso-valerate) in the feces were determined by gas chromatography. According to the results obtained, acetate level increased significantly ($P < 0.05$) in Ferrostatin-1 treated group compared to control group and total Short-chain fatty acids level increased significantly ($P < 0.05$) in Ferrostatin-1group compared to Ferrostatin-1 + Paclitaxel group. Although statistically insignificant, it was observed that ferrostatin-1 increased all the Short-chain fatty acids except butyrate, while paclitaxel decreased all the Short-chain fatty acids. The findings of this study suggest that ferrostatin-1 and paclitaxel may affect the functions of microorganisms in the large intestine and thus the amount of microbial Short-chain fatty acids. In addition, it is clear that therapeutic targeting of these specific bacteria, and thus the produced Short-chain fatty acids, will be important for successful treatment regimens and improved quality of life, especially in cancer patients, and may improve treatment outcomes.

Key words: Ferrostatin; paclitaxel; rat; short-chain fatty acid; feces.

RESUMEN

Los ácidos grasos de cadena corta son ácidos orgánicos producidos por la microbiota intestinal. El tipo y la cantidad de microflora en el colon, la fuente de sustrato y el período de transición a través del intestino afectan la velocidad y la cantidad de producción de ácidos grasos de cadena corta. La ferrostatina-1, un compuesto sintético y un potente inhibidor de la ferroptosis, es un antioxidante capaz de inhibir la ferroptosis. El paclitaxel es un tipo de quimioterapia llamada taxano y causa neuropatía periférica como efecto secundario del tratamiento contra el cáncer. En este estudio, investigamos el efecto de la administración de paclitaxel y ferrostatina-1 sobre los ácidos grasos de cadena corta fecales. Para ello, se dividió a las ratas en cuatro grupos: control (n = 6), paclitaxel (n = 8), ferrostatina (n = 9) y paclitaxel + ferrostatina (n = 9). Se administraron paclitaxel (10 mg/kg) y ferrostatina-1 (5 mg/kg) por vía intraperitoneal una vez a la semana durante cuatro semanas. Al final del experimento, se determinaron mediante cromatografía de gases las cantidades de ácidos grasos de cadena corta (acetato, propionato y butirato) y ácidos grasos de cadena ramificada (isobutirato e isovalerato) en las heces. Según los resultados obtenidos, el nivel de acetato aumentó significativamente ($P < 0,05$) en el grupo tratado con ferrostatina-1 en comparación con el grupo control, y el nivel total de ácidos grasos de cadena corta aumentó significativamente ($P < 0,05$) en el grupo ferrostatina-1 en comparación con el grupo ferrostatina-1 + paclitaxel. Aunque no fue estadísticamente significativo, se observó que la ferrostatina-1 aumentó todos los ácidos grasos de cadena corta excepto el butirato, mientras que el paclitaxel disminuyó todos los ácidos grasos de cadena corta. Los resultados de este estudio sugieren que la ferrostatina-1 y el paclitaxel pueden afectar a las funciones de los microorganismos en el intestino grueso y, por lo tanto, a la cantidad de ácidos grasos de cadena corta microbianos. Además, está claro que la terapia dirigida a estas bacterias específicas y, por lo tanto, a los ácidos grasos de cadena corta producidos, será importante para el éxito de los regímenes de tratamiento y la mejora de la calidad de vida, especialmente en pacientes con cáncer, y puede mejorar los resultados del tratamiento.

Palabras clave: Ferrostatina; paclitaxel; rata; ácido graso de cadena corta; heces.

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INTRODUCTION

The gut microbiota plays a fundamental role in the normal physiological regulation of intestinal barrier functions, the maintenance of selective intestinal permeability, inflammation and innate immune response, repair mechanisms, apoptosis, and oxidative stress, plays a key role in the maturation of the immune system and health balance [1].

A primary function of the microbiota is the fermentation of host-indigestible complex carbohydrates and dietary fibers, yielding vital metabolites such as short-chain fatty acids (SCFAs). Acetate (C2), propionate (C3), and butyrate (C4) are the most abundant SCFAs [2, 3].

These compounds serve as the principal energy substrate for colonocytes and interact with host cellular pathways to regulate diverse physiological and pathological processes. Consequently, the physiological influence of the gut microbiota encompasses not only digestive health but also immune, metabolic, and neurological homeostasis, thereby shaping overall host well-being [2, 3].

A dynamic and mutually beneficial relationship exists between the microbiota and SCFA production. This relationship is mediated by specific bacterial groups, particularly those capable of fermenting nondigestible carbohydrates. Bacteria belonging to phyla such as Firmicutes and Bacteroides, located in the anaerobic colon, are the primary organisms that break down dietary fiber and maximize SCFA production [4].

Among these metabolites, the C4 is crucial for maintaining intestinal barrier integrity and regulating inflammatory responses. The C3 is metabolized in the liver, influencing gluconeogenesis and systemic metabolism, while the C2 serves as a metabolic substrate for various peripheral tissues [2]. This metabolic cross-talk is fundamental for maintaining intestinal homeostasis. Disruptions in SCFA-producing microbial communities are a hallmark of dysbiosis and have been linked to various pathological states [5].

Emerging evidence suggests a connection between SCFAs, the microbiota, and cancer, indicating that SCFA levels may serve as potential biomarkers and therapeutic targets to improve treatment quality for cancer patients [6].

Ferroptosis is a distinct type of non-apoptotic cell death driven by iron and lipotoxicity, and is considered a novel type of inflammatory cell death. The potential benefit of modulating the gut microbiota to regulate ferroptosis in treating intestinal diseases has recently been the subject of research. Promoting or reducing ferroptosis by regulating the gut microbiota is a promising approach for treating related diseases [7, 8].

Ferrostatin-1 is reported to eliminate lipid hydroperoxides in reduced iron and exhibit antiferroptotic effects [9]. Notably, Wang *et al.* [10] identified a regulatory mechanism whereby butyrate inhibits the mTOR pathway, sensitizing cells to ferroptosis and suppressing tumor growth [10].

Supporting this, He *et al.* [11] reported that butyrate supplementation could overcome ferroptosis resistance in colorectal cancer patients with deficient endogenous butyrate production, highlighting its therapeutic potential.

Paclitaxel is a chemotherapeutic drug that disrupts the division cycle of cancer cells, leading to cell death [12]. Thanks to this unique mechanism of action, paclitaxel has been successfully used as a standalone treatment or as part of a combination therapy with other agents in the treatment of cancers like breast, ovarian, and lung [13, 14, 15].

While potent chemotherapeutic drugs like paclitaxel target rapidly dividing cancer cells, they also harm the beneficial bacteria in the gut microbiota. This disrupts the microbial balance (dysbiosis), damaging the beneficial SCFA-producing bacteria in the gut microbiota, leading to decreased SCFA levels. This interaction paves the way for developing new microbiota-targeting strategies, including using paclitaxel in cancer treatment [13].

Current approaches to cancer treatment aim to prevent or mitigate the applicability and adverse effects of chemotherapeutic agents by targeting the microbiota. Maintaining the integrity of the microbiota through the anti-inflammatory, antioxidant, and protective effects of SCFAs has important implications for preventing adverse effects, such as gastrointestinal and hematological side effects, commonly observed in cancer treatment, and also for regulating treatment efficacy [16].

This study will examine the effects of paclitaxel and ferrostatin-1 on fecal short-chain fatty acid profiles.

MATERIAL AND METHODS

Animals

All animal experiments were performed in accordance with the guidelines and approved by the Selçuk University Experimental Medicine Research and Application Center. In the study, 32 healthy adult Wistar Albino rats (*Rattus norvegicus*), weighing 250-300 grams (g), were housed with unlimited access to food and water (*ad libitum*). All rats were entrained to a 12-hour (h) light/12-h dark cycle in polycarbonate cages at 24 ± 1 oC and 60 % atmospheric humidity.

Study design

The treatment period lasted 28 days (d). Animals were divided into 4 groups as control (C; n = 6), Paclitaxel (Pak; n = 8), Ferrostatin-1 (Fer-1; n = 9), Paclitaxel+Ferrostatin-1 (Fer-1+Pak; n = 9).

Group C: During the trial period, standard rat feed and drinking water were provided ad *libitum*. No interventions were performed.

Group Pak: During the trial period, standard rat feed and drinking water were provided ad *libitum*. Paclitaxel was administered intraperitoneal (i.p.) once a week at a dose of 10mg/kg for fourweeks in the Pak group.

Group Fer-1: During the trial period, standard rat feed and drinking water were provided ad *libitum*. Fer-1 was administered i.p. once a week at a dose of 5mg/kg for four week in the Fer-1 group.

Group Pak + Fer-1: During the trial period, standard rat feed and drinking water were provided ad *libitum*. Paclitaxel was

administered i.p. once a week at a dose of 10mg/kg for four weeks, at the same tıme Fer-1 was administered i.p. at a dose of 5mg/kg in the Fer-1+Pak group.

At the end of the study, fecal samples were taken from the animals and kept at -80 oC until analysis.

Gas chromatography system

The amount of SCFA was quantitatively and qualitatively determined on a fused silica capillary column (Restek® Stabilwax Column) in a Gas Chromatography (GC) (GC/FID, GC-2030, Shimadzu) connected to a flame ionization detector (FID) (Agilent GC6890) under the following conditions. GC conditions were as follows: Injector temperature 230 °C; initial oven temperature 100 °C; temperature was increased by 10 °C/min to 200 °C and kept at the final temperature for 6 min. Helium was used as carrier gas at a rate of 1.1 mL/min.

Determination of SCFA

Microbial SCFA in collected rat feces were extracted according to the method described by Bishehsari *et al.* [17]. The SCFA was analyzed by gas chromatography and mass spectrometry (GC, Shimadzu, GC-2030) using the method described by Lebet *et al.* [18] and modified by Tuncil *et al.* [19]. At the end of the analysis, the presence and concentrations of C2, C4, C3, and (Branched-chain fatty acids) BCFA (isovaleric and isobutyric acids) were determined. Briefly, samples collected for SCFA analysis were combined with 100 µL of internal standard mixture (IS).

The IS was adjusted to 25 mL with 157.5 µL of 4-methylvaleric acid, 1.47 mL of 85 % phosphoric acid, 39 mg of copper sulfate pentahydrate, and distilled water. Samples for analysis were held at room temperature. The supernatants (4 µL) were injected into a GC instrument equipped with a silica capillary column and flame ionization detector (GC-FID) after centrifugation (Hettich UNIVERSAL 320) at 13,000 rpm for 10 min.

Statistical analysis

The results were evaluated by the ANOVA statistical test (SPSS 22.0). $P < 0.05$ was accepted as the limit of statistical significance. Graphs were created with GraphPad Prism® Version 8.0 software program (GraphPad Software, La Jolla, CA, USA).

RESULTS AND DISCUSSION

As a result of this study, the distribution of short-chain fatty acids in the animals is given in FIG. 1. When the change in short-chain fatty acids between the groups was examined, no statistical difference ($P > 0.05$) was detected between C4, C3, isovalerate, isobutyrate, and BCFA. However, although no statistically significant, the group treated with Fer-1 compared to the control group, showed a nonsignificant ($P > 0.05$) increase and in C3, isovalerate, isobutyrate, SCFA and BCFA levels and a nonsignificant ($P > 0.05$) decrease in C4, C3, isovalerate, isobutyrate, SCFA and BCFA levels in the Pak treated group compared to the C group. In addition, column graphs were drawn to show the individual differences of the animals (FIG. 1).

When C2 was analyzed, it was determined that there was a statistically significant increase ($P < 0.05$) in the Fer-1-treated group compared to the C group (FIG. 2). There was a statistically significant decrease ($P < 0.05$) in the Pak and Pak + Fer-1 group compared to the Fer-1 group in the SCFA. There was a non-statistical ($P > 0.05$) increase in the Fer-1 group and a non-statistical ($P > 0.05$) decrease in the Pak and Pak + Fer-1 groups compared to the C group (FIG. 2).

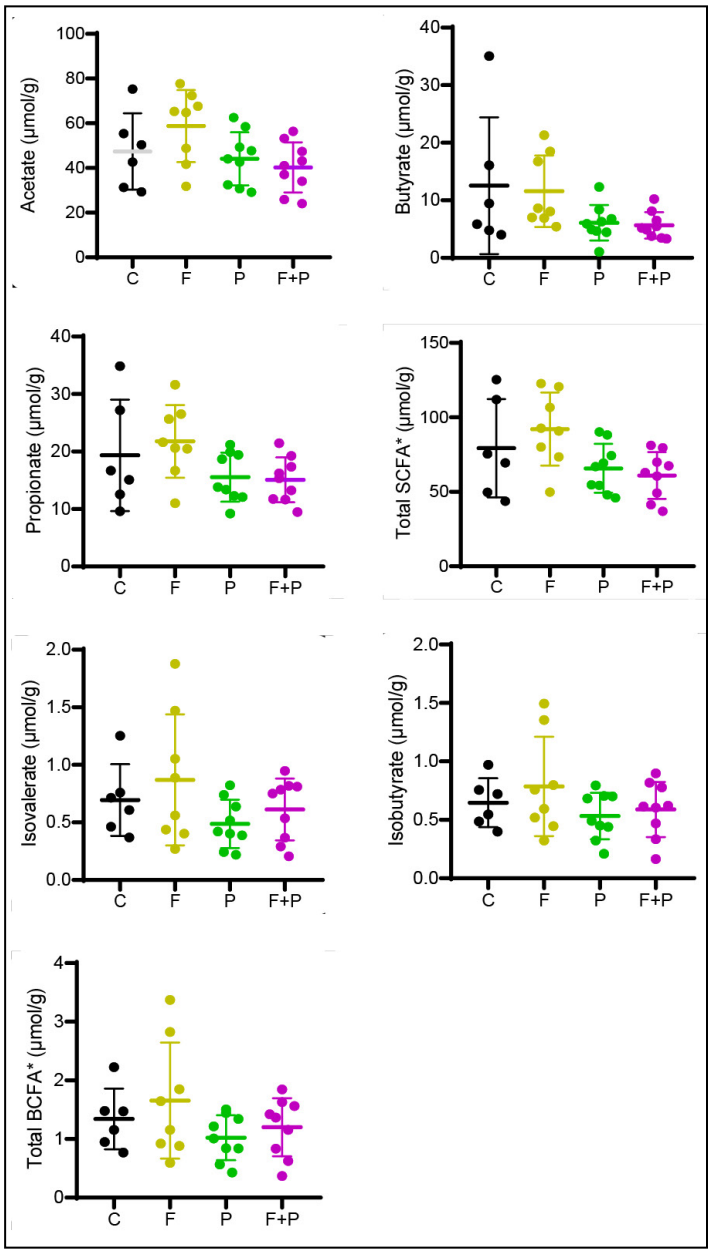

FIGURE 1. Column plots of short chain fatty acids in groups Control (C), Ferrostatin-1 (F), Paclitaxel (P), Paclitaxel+Ferrostatin-1 (F), short-chain fatty acids (SCFAs), Branched-chain fatty acids (BCFAs).

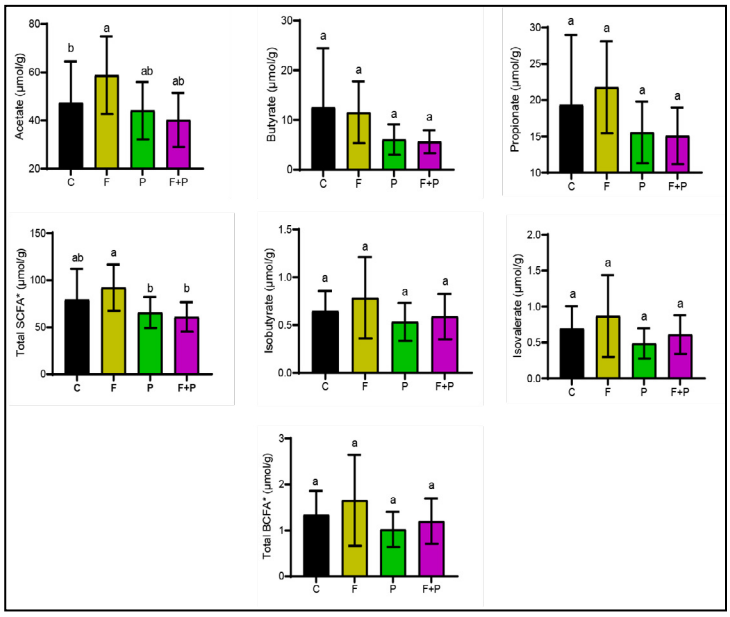

FIGURE 2. Inter-group variations of short chain fatty acids. Control (C), Ferrostatin-1 (F), Paclitaxel (P), Paclitaxel+Ferrostatin-1 (F), short-chain fatty acids (SCFAs), Branched-chain fatty acids (BCFAs).

Although the mechanisms of chemotherapy-induced gastrointestinal toxicities in cancer patients are becoming better understood, pharmacologic treatments are limited [1]. Diarrhea is a common problem in 50-80 % of cancer patients receiving chemotherapy [20]. In diarrhea caused by irinotecan, an anti-cancer drug, it has been reported that the toxicity of the drug used for treatment may increase, and intestinal bacteria may change [21]. Irinotecan causes severe colonic damage accompanied by excessive mucosal secretion in addition to the usual small intestinal damage caused by chemotherapy, such as villous atrophy and crypt hypoplasia. Increased levels of cell apoptosis and changes in goblet cell numbers, together with histopathologic changes in both jejunum and colon, cause changes in absorption rates, possibly leading to diarrhea [20].

It was also reported that fecal flora in rats changed quantitatively after 200 mg/kg irinotecan (a relatively new cytotoxic agent utilized in the treatment of solid tumors) treatment, *E*. coli, *Staphylococcus* spp., and *Clostridium* spp. increased, while *Lactobacillus* spp., *Bifidobacterium* spp. (both beneficial bacteria) and Bacteroides spp. decreased [21]. Loman *et al.* [22] reported that Pak-induced neuroinflammation in female BALB/c mice administered 30 mg/kg i.p. was associated with impaired colon and bacterial homeostasis. In this study, although statistically insignificant, it was observed that Pak decreased all SCFA. When compared with the study of Loman *et al.* [23] it was thought that the results found were due to differences in dose, duration of administration, and animal breed, and it is clear that paclitaxel negatively affects the intestinal microbiota.

Yuan *et al.* [24] demonstrated that Fer-1 straightly inhibits ferroptosis after liver transplantation and regulates the microbiota by reducing the pathogenicity of bacteria present in the recipient's gut after transplantation. In this study, when compared with the Fer-1 + Pak group, it was determined that the level of SCFA increased statistically significantly ($P < 0.05$) in the Fer-1 group. A non-statistical ($P > 0.05$) increase was determined in the Fer-1 group compared to the C group (TABLE II). C2, on the other hand, showed a statistically significant increase ($P < 0.05$) in the Fer-1-treated group compared to the C group (TABLE II). Accordingly, it was observed that ferrostatin-1 increased all SCFA except C4, although no statistically significant difference was found.

The C4 is produced by microorganisms such as *Roseburia intestinalis*, *Eubacterium rectale*, *Roseburia insulinivorans*, *Clostridiales bacterium*, *Anaerostripes hadrus*, *Coprococcus* spp., *Clostridium symbiosum*, *Faecalibacterium prausnitzii*, *Coprococcus* spp. [25]. Following administration of Fer-1 and Deferoxamine (DFO) to mice under acute stress conditions, C4 was associated with the regulation of ferroptosis and depression-like behavioral changes along the gut-brain axis [26].

Wang *et al.* [27] analyzed the diversity and composition of gut microbiota in C57BL/6J mice exposed to ionizing radiation by 16S rRNA gene sequencing and reported that Fer-1 restores gut structure and physiological function and protects intestinal injuries by suppressing apoptosis.

In another study, C4, a short-chain fatty acid, was reported to prevent morphine and Pak-induced peripheral hypersensitivity [28]. Cristiano *et al.* [29] reported that oral sodium butyrate (0.23 mg/mL concentration dissolved in drinking water daily for 44 d) supplementation to mice improved paclitaxel (4 doses of 8 mg/kg) induced intestinal dysfunction. As a result, they reported that C4 levels in feces decreased after four doses of Pak treatment, while there was no effect on acetic and C3 levels.

In this study, when the Pak-treated group was compared to the C group, it was observed that there was no statistically significant difference ($P > 0.05$) in C2, C4, and C3 levels. The lack of statistical difference was thought to be related to animal species and the administration dose. C4 level was observed that there was a decrease in the Pak-treated group compared to the C group, which was not statistically significant ($P > 0.05$). This supports that oral butyrate administration may be beneficial.

Chemotherapy causes enterotoxicity, compromises intestinal barrier function, bile acid absorption, and enteric microbial populations, and leads to bacterial translocation, hepatic endotoxemia, and cholestasis, resulting in impaired bile acid absorption and microbial metabolism. Loman *et al.* [23] reported that they administered 30 mg/kg Pak chemotherapy to mice by 100 µL intraperitoneal injection. They concluded that the development of therapies that utilize microbiota to protect against enterotoxicity while promoting bile acid metabolism may improve the quality of life and treatment outcomes of patients undergoing cancer treatment.

In this study, when compared with the Fer-1+Pak group, it was determined that the level of SCFA increased statistically significantly ($P < 0.05$) in the Fer-1 group. A non-statistical ($P > 0.05$) increase was determined in the Fer-1 group compared to the C group (TABLE II). It was also determined that acetate showed a statistically significant increase ($P < 0.05$) in the Fer-1-treated group compared to the C group (TABLE II). Although most of the results were statistically insignificant, Fer-1 increased all

short-chain fatty acids except C4, whereas Pak decreased all SCFA.

CONCLUSION

In general, when the change in SCFA between the groups was examined, no statistical difference was detected between C4, C3, isovalerate, isobutyrate, and BCFA. However, although no statistically significant, the group treated with Fer-1 compared to the C group, showed a nonsignificant increase and in C3, isovalerate, isobutyrate, SCFA and BCFA levels and a nonsignificant decrease in C4, C3, isovalerate, isobutyrate, SCFA and BCFA levels in the Pak treated group compared to the C group. The dose used may have contributed to these results. Based on all these results, it is recommended to evaluate the results of longer application and different doses in future studies. In addition to SCFA, it is thought that analyzing bacteria by 16S sequencing method will also be useful. In this way, it is clear that therapeutic targeting of these specific bacteria and the SCFA produced by them will be important for the realization of successful treatment regimens, especially in patients undergoing cancer treatment, to improve the quality of life and may improve treatment outcomes.

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Ethical Approval

This study ethical approval (Approval no: 2024/77, date 29.11.2024) was obtained from Selcuk University Experimental Medicine And Application Center Ethics Committee (SÜDAM).

Conflict of ınterest

The authors declare no conflict of interest.

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