# The effect of carvacrol on reducing bacterial translocation, liver and intestinal damage in obstructive jaundice models of rats

<sup>®</sup> Muhammet Fatih Keyıf,<sup>1</sup> <sup>®</sup> Ferdi Bolat,<sup>1</sup> <sup>®</sup> Mustafa Sıt,<sup>1</sup> <sup>®</sup> Songül Peltek Ozer,<sup>2</sup> <sup>®</sup> Mustafa Behcet,<sup>3</sup> <sup>®</sup> Oguz Catal,<sup>1</sup> <sup>®</sup> Bahri Ozer,<sup>1</sup> <sup>®</sup> Mehmet Hayri Erkol<sup>1</sup>

<sup>1</sup>Department of General Surgery, Abant Izzet Baysal University School of Medicine, Bolu-*Türkiye* <sup>2</sup>Department of Pathology, Abant Izzet Baysal University School of Medicine, Bolu-*Türkiye* <sup>3</sup>Department of Microbiology, Abant Izzet Baysal University School of Medicine, Bolu-*Türkiye* 

### ABSTRACT

**BACKGROUND:** Obstructive jaundice is a common surgical issue caused by obstruction in the bile ducts, which can result from factors such as stones or cancers in the main bile duct. This study aimed to investigate the effects of carvacrol, a compound known for its strong antioxidant properties, on intestinal damage, liver damage, and bacterial translocation in an animal model of obstructive jaundice.

**METHODS:** The study utilized six groups of six Wistar Albino rats each. Obstructive jaundice was induced in the rats through a surgical procedure, resulting in the enlargement of the common bile duct. Carvacrol was administered at a dose of 100 mg/kg to evaluate its therapeutic effects. Blood samples were collected for biochemical analysis, and tissue samples were obtained from the ileum and liver for histopathological examination. Additionally, samples from the spleen and mesenteric lymph nodes were collected for microbiological analysis.

**RESULTS:** The findings revealed that carvacrol did not have a significant therapeutic effect on liver and bowel damage or on bacterial translocation in the rats with obstructive jaundice. Despite carvacrol's known antioxidant properties, it failed to show benefits in this experimental model.

**CONCLUSION:** Carvacrol, while recognized for its antioxidant effects, did not demonstrate therapeutic efficacy in treating obstructive jaundice in rats. The study suggests that further research with a larger sample size may be necessary to potentially uncover positive effects and better understand carvacrol's potential role in managing obstructive jaundice.

Keywords: Bacterial translocation; carvacrol; liver damage; obstructive jaundice.

# INTRODUCTION

Obstructive jaundice (OJ) is the accumulation of bile in the liver cells and biliary tract due to the inability of bile to flow into the intestine as a result of obstruction in the bile ducts. <sup>[1]</sup> When bile is prevented from entering the intestine, entero-

hepatic circulation is disrupted, and substances excreted with bile begin to accumulate in the bloodstream. Consequently, some pathological changes begin to manifest. The primary ones include the inhibition of the detergent and antibacterial effects of bile, deterioration in the functions of the reticuloendothelial system, suppression of immunity, alterations in

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Bacterial translocation refers to the spread of intra-intestinal bacteria from the lumen to the liver, spleen, mesenteric lymph nodes, and systemic circulation due to the breakdown of intestinal barrier function.<sup>[4]</sup> Since bile cannot flow into the intestinal lumen in cases of obstructive jaundice, endotoxemia and bacterial translocation are facilitated.<sup>[5]</sup>

Currently, many studies are being conducted to explore treatments for bile duct obstructions. Carvacrol, an aromatic compound found in various plants, is known to possess multiple properties, including antioxidant, hepatoprotective, and anticancer effects.<sup>[6]</sup>

This study aimed to investigate the effects of carvacrol on liver damage, intestinal injury, and bacterial translocation in a model of obstructive jaundice.

# MATERIALS AND METHODS

This experimental study was conducted in 2020 with the approval of the Bolu Abant İzzet Baysal University Animal Research Local Ethics Committee (dated November 6, 2019 and decision number 2019/42). Sixty Wistar Albino female rats, aged 2-4 months and weighing between 200-250 grams, were used as experimental animals. A total of six groups, each consisting of six rats, were formed as follows:

• Group I: Sham (Control): The common bile duct was identified via laparotomy, but the abdomen was closed without inducing obstructive jaundice.

• **Group 2: Control + Carvacrol:** The common bile duct was identified via laparotomy, and the abdomen was closed after administering 100 mg/kg carvacrol dissolved in 5% dimethyl sulfoxide (DMSO) at a volume of 0.2 mL intraperitoneally (i.p.) without inducing obstructive jaundice. Feed and water were provided once daily for three days.

• Group 3: Control + DMSO: The common bile duct was identified via laparotomy, and 0.2 mL of 5% DMSO was administered i.p. without inducing obstructive jaundice. The abdomen was then closed. Feed and water were provided once daily for three days.

• Group 4: Obstructive Jaundice (OJ): Following laparotomy, the common bile duct was dissected and ligated with 4.0 silk to induce obstructive jaundice, and the abdomen was closed.

• Group 5: OJ + DMSO: Following laparotomy, the common bile duct was dissected, ligated with 4.0 silk, and cut to induce obstructive jaundice. Subsequently, 0.2 mL of 5% DMSO was administered i.p., and the abdomen was closed.

Feed and water were provided once daily for three days.

• Group 6: OJ + Carvacrol Treatment: Following laparotomy, the common bile duct was dissected and ligated with 4.0 silk to induce obstructive jaundice. Then, 100 mg/kg carvacrol dissolved in 5% DMSO at a volume of 0.2 mL was administered i.p., and the abdomen was closed. Feed and water were provided once daily for three days.

In the study, in addition to the Sham group (Group I) and the OJ group (Group 4), both the Control + Carvacrol group (Group 2) and the OJ + Carvacrol group (Group 6) were created to evaluate the effect of carvacrol independently of other factors. Dimethyl sulfoxide was also included in the study due to its ability to easily penetrate cell membranes and transport other molecules. To evaluate the isolated effect of DMSO and determine whether it enhanced the effect of carvacrol (interaction status), the Control group (Group 3) and the OJ + DMSO group (Group 5) were created, where only DMSO was administered. The results obtained were compared to determine the isolated effect of carvacrol.

General anesthesia was administered to all rats via intramuscular injection into the right hind leg, using 10 mg/kg xylazine hydrochloride and 90 mg/kg ketamine hydrochloride. The anterior abdominal wall was shaved, and the area was disinfected with 10% povidone-iodine. A midline incision was made to access the abdomen. In the first three groups, the main bile duct was identified and left intact, while in the other three groups, the main bile duct was identified, dissected, tied with silk sutures, and cut (Fig. 1). The incision layers were then closed primarily using silk in accordance with anatomical sutures. After recovering from anesthesia, the female rats were placed in warm environments and provided with food six hours post-procedure.

On the third day following surgery, sterile conditions were ensured for all rats in the experimental group. Under anesthesia, the previous incisions were reopened, and the abdominal cavity was accessed. In the groups where obstructive jaundice had been induced by ligating the main bile duct, severe dilation of the bile ducts was observed (Fig. 2).

Intracardiac blood samples were collected from all rats for biochemical analysis, after which the rats were sacrificed. Tissue samples were obtained from the liver, spleen, mesenteric lymph nodes, and ileum for microbiological examination. Additionally, samples were collected from the liver and ileum for pathological evaluation.

#### **Biochemical Evaluation**

Intracardiac blood samples from all groups were initially drawn for blood culture, followed by additional samples for biochemical analysis, given the risk of contamination associated with collecting approximately 8-10 mL using a syringe.

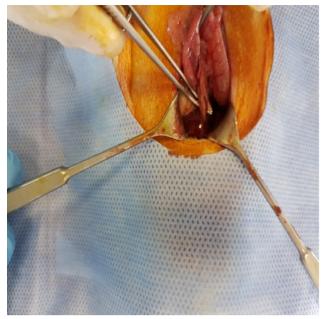


Figure 1. Dissection of the common bile duct.

The blood samples were placed in silicone tubes and centrifuged at 6500 rpm for 5 minutes to separate the serum. The blood samples were stored at -80°C until the day of measurement. The following biochemical parameters were analyzed: total antioxidant capacity (TAS), total oxidant capacity (TOS), oxidative stress index (OSI), malondialdehyde (MDA), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and lactate dehydrogenase (LDH). Additionally, two different devices were used to measure total protein (TP), albumin (Alb), total bilirubin (T.bil), direct bilirubin (D.bil), and alkaline phosphatase (ALP).

#### **Microbiological Evaluation**

Tissue samples from the liver, ileum, spleen, and mesenteric lymph nodes were collected from all rats under sterile conditions and weighed using a precision scale. The tissues were crushed, placed in tryptic soy broth medium, and diluted. Samples were planted on eosin methylene blue agar, 5% sheep blood agar, and chocolate agar media for aerobic cultures. These cultures were incubated at 35.5°C for 24-48 hours, and bacterial identification was performed. For anaerobic cultures, samples were cultivated in Schaedler agar medium.

#### **Histopathological Evaluation**

Liver and ileum tissue samples were fixed in 10% formaldehyde for 24 hours. After tissue processing, sections were prepared and stained with hematoxylin-eosin (H&E) and reticulin. Steatosis, portal inflammation, hepatocellular injury foci, congestion, cholestasis, and proliferative bile duct status were evaluated in the liver, while villous atrophy, crypt epithelial damage, and inflammation were assessed in the ileum.

### Statistical Analysis



Figure 2. Dilatation of the main bile ducts.

Statistical analyses were conducted using ready-to-use statistical software (IBM Statistical Package for the Social Sciences (SPSS) Statistics 25, SPSS Inc., IBM Co., Somers, NY). Homogenous distribution was evaluated using univariate analysis, and group comparisons were performed using Tukey and Bonferroni correction tests. Non-homogeneous distributions were analyzed with the Kruskal-Wallis test, and group comparisons were performed using the Mann-Whitney U test. A p value less than 0.05 was considered statistically significant.

### RESULTS

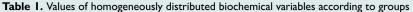
The samples collected for the study were thoroughly examined.

In the intergroup comparison of TAS, AST, ALT, GGT, T.bil, ALP, and MDA values, statistically significant differences were observed, with higher values in the groups exhibiting tissue stress (TS) (p<0.05). However, the OSI values were not statistically significant (p>0.05).

For total protein (TP) values, statistically significant differences were found between the following group comparisons: Group I and Group 5 (p=0.037), Group I and Group 6 (p=0.054), Group 2 and Group 4 (p=0.006), Group 2 and Group 5 (p=0.004), Group 2 and Group 6 (p=0.004), Group 3 and Group 5 (p=0.004), and Group 3 and Group 6 (p=0.004).

For D.bil values, statistically significant differences were identified in the following group comparisons: Group I to Group 4 (p=0.004), Group I to Group 5 (p=0.004), Group I to Group 6 (p=0.004), Group 2 to Group 3 (p=0.025), Group 2 to Group 4 (p=0.004), Group 2 to Group 5 (p=0.004), Group 2 to Group 6 (p=0.004), Group 3 to Group 4 (p=0.004),

	Group I mean (m) value	Group2 mean (m) value	Group3 mean (m) value	Group4 mean (m) value	Group5 mean (m) value	Group6 mean (m) value	р
TAS	0.97	0.85	0.97	1.83	2.01	1.94	0.000
OSI	0.71	0.76	0.98	0.40	0.63	0.59	0.052
AST	124.00	108.83	158.00	269.333	221.50	247.83	0.000
ALT	60.16	49.50	55.50	289.50	251.16	298.16	0.000
GGT	2.50	2.83	2.83	19.00	17.83	29.50	0.000
LDH	1239.00	1226.16	1188.83	1291.33	1632.00	1232.83	0.833
Alb	3.74	3.51	3.70	3.47	3.61	3.72	0.171
T.bil	0.38	0.30	0.47	9.32	12.32	11.83	0.000
ALP	291.16	238.66	217.16	468.00	554.33	525.66	0.000
MDA	0.20	0.53	0.22	1.59	2.22	1.85	0.000



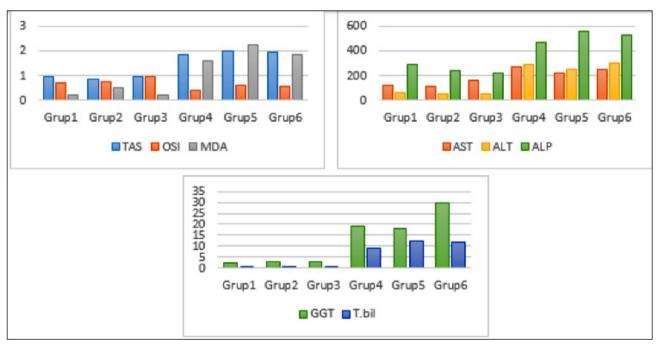


Figure 3. Comparative mean values of homogeneously distributed biochemical variables according to groups.

Group 3 to Group 5 (p=0.004), and Group 3 to Group 6 (p=0.004). A comparison of biochemical findings is presented in Table I and illustrated in Figure 3.

The effect on LDH (p=0.833), Alb (p=0.171), and TOS (p=0.325) values in the experimental groups was not statistically significant.

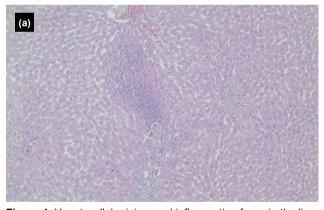
Similarly, growth in blood cultures did not demonstrate statistically significant results (p=0.094). The growth rates in ileum tissue cultures showed a marginal statistical effect (p=0.069), with the highest growth observed in six rats from Group 5 and Group 6. The growth rates in mesenteric lymph node (MLN) tissue cultures were statistically significant (p=0.018), with the highest growth observed in five rats from Group 6. In contrast, the growth rates in liver tissue cultures were not statistically significant (p=0.087). Growth in spleen tissue cultures was statistically significant (p=0.0001), with the highest growth observed in six rats from Group 4 (Table 2).

The bacterial growth per gram of tissue was determined for each group, yielding significant results regarding bacterial load in the MLN and spleen (Table 3).

	Group l n=6 (%)	Group2 n=6 (%)	Group3 n=6 (%)	Group4 n=6 (%)	Group5 n=6 (%)	Group6 n=6 (%)
Blood	0 (0)	0 (0)	0 (0)	2 (33.3)	2 (33.3)	3 (50)
İleum	2 (33.3)	4 (66.7)	4 (66.7)	5 (83.3)	6 (100)	6 (100)
MLN	0 (0)	l (16.7)	2 (33.3)	l (16.7)	4 (66.7)	5 (83.3)
Liver	0 (0)	0 (0)	0 (0)	3 (50)	2 (33,3)	l (16,7)
Spleen	0 (0)	0 (0)	0 (0)	6 (100)	l (16,7)	2 (33,3)

Table 3. Mean bacterial counts with growth per gram of tissue (cfu/g)

	Group I	Group 2	Group 3	Group 4	Group 5	Group 6	Р
İleum	8152.00	16362.67	14167.50	9514.83	37806.00	15203.33	0.126
MLN	0.00	2083.33	1700.50	183.00	45244.50	7987.00	0.014
Liver	0.00	0.00	0.00	11875.83	5557.33	396.67	0.078
Spleen	0.00	0.00	0.00	40101.50	3932.50	1441.67	0.0001



**Figure 4.** Hepatocellular injury and inflammation focus in the liver section in the treatment group (H&E x100).

**Figure 5.** Bile duct proliferation and inflammation focus in the liver section in the treatment group (H&Ex100 (A) H&E x200 (B)).

In terms of liver bacterial load, a marginal statistical effect was observed between Group I and Group 4 (p=0.059), Group 2 and Group 4 (p=0.059), and Group 3 and Group 4 (p=0.059). Statistically significant differences were found in spleen bacterial load between Group I and Group 4 (p=0.002), Group 2 and Group 4 (p=0.002), Group 3 and Group 4 (p=0.002), Group 4 and Group 5 (p=0.008), and Group 4 and Group 6 (p=0.009). In terms of ileum bacterial load, statistically significant differences were identified between Group I and Group 5 (p=0.022) and between Group 4 and Group 5 (p=0.055). For MLN bacterial load, statistically significant differences were observed between Group I and Group 5 (p=0.022),

Group 1 and Group 6 (p=0.007), Group 4 and Group 5 (p=0.05), and Group 4 and Group 6 (p=0.013).

Although bacterial growth in liver tissue was statistically insignificant, 50% growth was observed in Group 4, 33.3% in Group 5, and 16.7% in the treatment group, indicating proportionally less growth in the liver tissue of the treatment group.

It was observed that hepatocellular injury foci and proliferative bile ducts were significantly higher in the groups with OJ (p=0.004 and p=0.0001, respectively) (Figures 4 and 5).

# DISCUSSION

Obstructive jaundice occurs due to obstruction of the bile ducts and the inability of bile to pass into the duodenum, affecting multiple systems, particularly the reticuloendothelial, gastrointestinal, and immune systems.<sup>[7]</sup> Cholestasis, resulting from bile duct obstruction, suppresses immunity, impairs the reticuloendothelial system, and disrupts the intestinal barrier function, leading to oxidative damage to the intestinal wall and bacterial translocation.<sup>[8,9]</sup>

Opening the obstruction, reducing inflammation, and inhibiting hepatocyte apoptosis are critical in preventing hepatic damage. Free oxygen radicals generated during the proinflammatory process, along with an imbalance in the antioxidant defense system, are the main causes of tissue damage. Malondialdehyde, the end product of lipid peroxidation, increases as a marker of cellular damage.<sup>[10,11]</sup>

In the study of Alturfan et al., it was demonstrated that AST, ALT, and MDA levels were elevated, and hepatic damage increased in rats with obstructive jaundice.<sup>[12]</sup> Elevated levels of bilirubin, GGT, and ALP were also observed in cases of bile duct obstruction.<sup>[13]</sup> Furthermore, since chenodeoxycholic acid is converted into the bile acid betamuricolic acid in the liver when the common bile duct is ligated, the resulting bilirubin levels in the blood are more hepatotoxic in rats compared to humans.<sup>[14]</sup>

Dimethyl sulfoxide, an organic compound commonly used as a solvent, is also recognized for its various independent effects on biological systems. The effects of DMSO stem from its biochemical and pharmacological properties, which lend it a wide range of applications in both experimental and clinical fields.<sup>[15,16]</sup>

Dimethyl sulfoxide can suppress inflammation by reducing the production of prostaglandins and free radicals. This property helps prevent cellular damage caused by oxidative stress and protects cell membranes by minimizing lipid peroxidation in the cellular environment. Additionally, DMSO has protective effects on the central nervous system and can relieve pain due to its impact on nerve cells.<sup>[15]</sup>

The most significant and widely utilized feature of DMSO is its ability to easily penetrate the cell membrane and carry other molecules. This property enables its use as a drug carrier and makes it widely utilized as a solvent in pharmacological research.<sup>[15]</sup>

Dimethyl sulfoxide also exhibits direct bacteriostatic and antifungal effects. It can suppress the immune response in certain cases while enhancing it in others.<sup>[15,17,18]</sup> Furthermore, DMSO can improve microcirculation by reducing blood viscosity and prevent thrombosis by decreasing platelet aggregation.<sup>[15,17]</sup>

According to the literature, many agents have been explored for reducing liver damage and preventing bacterial transloca-

tion due to their antioxidant effects in cases of obstructive jaundice. In our study, we investigated the effect of carvacrol, which possesses antioxidant, antitumoral, antihepatotoxic, antimicrobial, and anti-inflammatory properties. A study by Canbek et al.<sup>[19]</sup> demonstrated that carvacrol has a protective effect against ischemia-reperfusion injury in the liver of rats and is not hepatotoxic. Additionally, it has been reported that carvacrol inhibits processes during the biofilm formation stage, a bacterial structure, and can reduce the risk of antibiotic resistance.<sup>[20]</sup>

In our study, biochemical parameters were analyzed by comparing Group 4 and Group 6 to evaluate the effect of carvacrol on TS. A significant difference in GGT levels was observed between these two groups (p=0.016). However, when carvacrol was administered to rats with TS, no changes in other biochemical values were noted, indicating that carvacrol had no role in preventing liver damage, regardless of the presence of TS.

In the development of jaundice, hepatocellular proliferation begins after 48 hours, peaks on the fifth day, and then remains at the same level. In this study, three days were deemed sufficient for developing a jaundice model with clinical follow-up, as the first symptoms of OJ typically appear within 24 hours, and laboratory findings manifest within 48 hours. Cholestasis, portal inflammation, bile duct proliferation, and hepatocellular injury foci were proportionally higher in the OJ groups, with significant differences observed compared to the non-OJ group (p=0.069, p=0.133, p=0.0001, and p=0.04, respectively).

For this purpose, Group 4 and Group 6 were compared, and no significant difference was observed. However, histopathological examination of parameters associated with hepatocyte damage showed that while the effect of carvacrol on liver damage in the treatment group was not statistically significant, it did reduce the damage. Furthermore, administering carvacrol alone, without OJ, was found to be non-toxic.

According to Parks et al.,<sup>[9]</sup> bacterial translocation in blood, liver, MLN, and spleen cultures increased seven days after TS was induced, compared to the control group. Similarly, in this study, it was observed that bacterial reproduction was higher in the TS groups. Considering the average number of bacteria growing per gram of tissue in the groups, significant results were observed in bacterial load for MLN (p=0.014) and spleen (p=0.0001).

Although bacterial growth in the liver was not statistically significant, proportional growth was lower in the treatment group compared to other groups.

In terms of bacterial load, significant effects were observed between: Group 2 and Group 4 (p=0.059) and Group 3 and Group 4 (p=0.002), Group 2 and Group 4 (p=0.002), and Group 3 and Group 4 (p=0.002) in the spleen; Group I and Group 5

(p=0.022) in the ileum; and Group I and Group 5 (p=0.022)and Group I and Group 6 (p=0.007) in MLN. These findings support the occurrence of bacterial translocation. Considering the growth observed in cultures from the OJ groups, bacterial translocation appeared to increase, consistent with findings in the literature.

According to our microbiological data, it was observed that bacterial translocation was not prevented when carvacrol was administered in OJ cases.

# CONCLUSION

Although the literature suggests that carvacrol prevents bacterial translocation in cases of OJ, our study found that while carvacrol did not statistically inhibit bacterial translocation, it did result in a decrease in bacterial load. Furthermore, although carvacrol is reported in the literature to prevent liver damage associated with OJ, our findings demonstrated that it was statistically ineffective in preventing liver damage but did contribute to its reduction. The small number of animals in the study groups is a limiting factor, and we believe that increasing the sample size may yield more meaningful results.

**Ethics Committee Approval:** This study was approved by the Bolu Abant İzzet Baysal University Animal Research Local Ethics Committee (Date: 06.11.2019, Decision No: 2019/42).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: M.F.K.; Design: F.B.; Supervision: M.F.K.; Resource: B.O.; Materials: S.P.O., M.B.; Data collection and/or processing: M.F.K.; Analysis and/or interpretation: O.C., M.H.E.; Literature review: M.F.K.; Writing: M.F.K., M.S.; Critical review: M.F.K., M.H.E.

Conflict of Interest: None declared.

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#### DENEYSEL ÇALIŞMA - ÖZ

# Sıçanlarda tıkanma sarılığı oluşturulan modelde karvakrolün karaciğer, bağırsak hasarı ve bakteriyel translokasyonun engellenmesi üzerine etkisi

AMAÇ: Obstrüktif sarılık, safra kanallarındaki tıkanmalardan kaynaklanan yaygın bir cerrahi sorundur ve bu tıkanmalar safra kesesindeki taşlar veya ana safra kanalı kanserleri gibi faktörlerden kaynaklanabilir. Bu çalışma, güçlü antioksidan özellikleri ile bilinen karvakrolün, obstrüktif sarılık modelinde bağırsak hasarı, karaciğer hasarı ve bakteriyel translokasyon üzerindeki etkilerini araştırmayı amaçlamıştır.

GEREÇ VE YÖNTEM: Çalışmada her biri altı Wistar Albino sıçan grubundan oluşan toplam altı grup kullanılmıştır. Obstrüktif sarılık, sıklıkla ortak safra kanalının genişlemesiyle sonuçlanan cerrahi bir prosedürle ratlarda indüklenmiştir. Karvakrol, terapötik etkilerini değerlendirmek için 100 mg/ kg dozunda uygulanmıştır. Kan örnekleri biyokimyasal analiz için toplanmış, ileum ve karaciğerden doku örnekleri histopatolojik inceleme için elde edilmiştir. Ayrıca, dalak ve mezenterik lenf düğümlerinden mikrobiyolojik analiz için örnekler alınmıştır.

BULGULAR: Sonuçlar, karvakrolün, obstrüktif sanlığı olan ratlarda karaciğer ve bağırsak hasarı veya bakteriyel translokasyon üzerinde anlamlı bir terapötik etki göstermediğini ortaya koymuştur. Karvakrolün bilinen antioksidan özelliklerine rağmen, bu deneysel modelde fayda sağladığı gösterilmemiştir.

SONUÇ: Karvakrol, antioksidan etkileriyle tanınmasına rağmen, sıçanlarda obstrüktif sarılığı tedavi etmede terapötik etkinlik göstermemiştir. Çalışma, daha büyük bir örneklem büyüklüğü ile yapılacak ileri araştırmaların, karvakrolün obstrüktif sarılığın yönetimindeki potansiyel rolünü daha iyi anlamak için gerekli olabileceğini önermektedir.

Anahtar sözcükler: Bakteriyel translokasyon; karvakrol; karaciğer hasarı; obstrüktif sarılık.

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